Universidad Miguel Hernández de Elche
Programa de doctorado en Deporte y Salud

METHODOLOGICAL FACTORS IN MEASURING HEART RATE-BASED INDICES AND EFFECT OF EXERCISE-BASED CARDIAC REHABILITATION ON MORTALITY PREDICTORS: FROM ATHLETES TO PATIENTS

Doctoral thesis

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La presente tesis doctoral, titulada "*Methodological factors in measuring heart rate-based indices and effect of exercise-based cardiac rehabilitation on mortality predictors: from athletes to patients"*, es un compendio de cuatro artículos publicados en revistas indexadas en el *Journal Citation Reports* de la *Web of Science*:

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Además de los artículos previamente publicados, la presente tesis doctoral incluye un artículo que se encuentra en proceso de revisión en una revista indexada en *Journal Citation Reports* de la *Web of Science*:

- Manresa-Rocamora A, Sarabia JM, Guillen-Garcia S, Pérez-Berbel P, Miralles-Vicedo B, Roche E, Vicente-Salar N, Moya-Ramón M. Is heart rate variability-guided training superior to predefined training for improving mortality predictors in patients with coronary artery disease? Under review in *Med Sport*

El Dr. *Franscico José Vera García*, director, y el Dr. *Manuel Moya Ramón*, codirector de la tesis doctoral titulada **"***Methodological factors in measuring heart rate-based indices and effect of exercise-based cardiac rehabilitation on mortality predictors: from athletes to patients"*

INFORMA/N:

Que D. *Agustín Manresa Rocamora* ha realizado bajo nuestra supervisión el trabajo titulado **"***Methodological factors in measuring heart rate-based indices and effect of exercise-based cardiac rehabilitation on mortality predictors: from athletes to patients"* conforme a los términos y condiciones definidos en su Plan de Investigación y de acuerdo al Código de Buenas Prácticas de la Universidad Miguel Hernández de Elche, cumpliendo los objetivos previstos de forma satisfactoria para su defensa pública como tesis doctoral.

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INFORMA:

Que D. *Agustín Manresa Rocamora* ha realizado bajo la supervisión de nuestro Programa de Doctorado el trabajo titulado "*Methodological factors in measuring heart rate-based indices and effect of exercise-based cardiac rehabilitation on mortality predictors: from athletes to patients"* conforme a los términos y condiciones definidos en su Plan de Investigación y de acuerdo al Código de Buenas Prácticas de la Universidad Miguel Hernández de Elche, cumpliendo los objetivos previstos de forma satisfactoria para su defensa pública como tesis doctoral.

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Prof. Dr. *Francisco Javier Moreno Hernández*

Coordinador/a del Programa de Doctorado en Deporte y Salud

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List of abbreviations

AMI: Acute myocardial infarction.

ANS: Autonomous nervous system.

B: Regression coefficient.

bpm: Beats per minute.

CAD: Coronary artery disease.

CG: Control group.

CHF: Chronic heart failure.

CI: Confidence interval.

CR: Cardiac rehabilitation.

CRF: Cardiorespiratory fitness.

DFA-1 alpha: Detrended fluctuation analysis of heart rate variability and its short-term scaling exponent 1 alpha.

ES: Effect size.

F-OR: Functional overreaching.

HF: High frequency.

HIIT: High-intensity interval training.

HR: Heart rate.

HRR: Heart rate recovery.

HRR 1 min: The number of heart beats recovered within 1 min after exercise.

HRV: Heart rate variability.

HRV-G: Heart rate variability-guided training group.

k: Number of analysis units.

LnRMSSD: The log transformed root-mean-square difference of successive normal R-R intervals.

MCT: Moderate continuous training.

MD: Mean difference.

MD_+: Pooled mean difference.

n: Number of participants.

N-FOR: Non-functional overreaching.

non-OR: Non-overreached.

PNS: Parasympathetic nervous system.

PRED-G: Predefined training group.

RMSSD: The root-mean-square difference of successive normal R-R intervals.

SD: Standard deviation.

SD_1: The standard deviation of instantaneous beat-to-beat R-R interval variability.

SMD: Standardised mean difference.

SMD_+: Pooled standardised mean difference.

SNS: Sympathetic nervous system.

SWC: Smallest worthwhile change.

SWC_1: Smallest worthwhile change during the first three weeks of the study protocol.

SWC_2: Smallest worthwhile change during the first three weeks of the training period.

$\dot{V}O_2$ max: Maximum oxygen uptake.

$\dot{V}O_2$ peak: Peak oxygen uptake.

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Abstract

Background: Parasympathetic nervous system (PNS) activity can be indirectly assessed by heart rate (HR)-based indices (i.e., resting HR, resting vagal-related HR variability [HRV] indices, and post-exercise HR recovery 1 min [HRR 1 min]). Decreased PNS activity is considered an independent mortality predictor. In the same vein, cardiorespiratory fitness (CRF), assessed by peak oxygen uptake ($\dot{V}O_2$ peak), is also considered an independent mortality predictor. There is evidence showing the positive effect of exercise-based cardiac rehabilitation (CR) on mortality rates in patients with coronary artery disease (CAD). However, the results of previous studies of the effects of exercise-based CR on mortality predictors (i.e., HR-based indices and $\dot{V}O_2$ peak) are controversial. The sparse findings could be due to the influence of methodological factors (e.g., breathing pattern, use of averaged or isolated values, and assessment position) on the sensitivity of HR-based indices to detect PNS hyperactivity, which has mainly been investigated in endurance-trained athletes with functional overreaching (F-OR) symptoms. Moreover, controversial findings about the effects of exercise-based CR on mortality predictors could be explained by the influence of potential moderator variables (e.g., aerobic training method) on the training-induced effect. In this regard, previous systematic reviews with meta-analyses showed that high-intensity interval training (HIIT) enhances $\dot{V}O_2$ peak to a higher extent than moderate continuous training (MCT) in patients with CAD. Nonetheless, there is less evidence of the influence of other variables (e.g., training frequency) on the effect of exercise-based CR on CRF and PNS activity. Finally, high heterogeneity in the individual response to the same predefined training programme has also been previously reported. Therefore, the effects of individualised training programmes based on daily HRV measurements (i.e., HRV-guided training) have been tested in healthy people (i.e., sedentary or physically active people and endurance-trained athletes) and in patients with chronic heart failure, showing optimistic findings for improving CRF. However, the effects of HRV-guided training on HR-based indices have been less studied, and it has not been tested in patients with CAD.

Therefore, the main objectives of this doctoral thesis were: a) to study the influence of methodological factors on the sensitivity of HR-based indices for inferring increased PNS activity; and b) to know the effect of exercise-based CR (i.e., predefined training and HRV-guided training) on mortality predictors (i.e., HR-based indices and $\dot{V}O_2$ peak) in patients with CAD.

Methods: Systematic reviews with meta-analyses and experimental methods were used to address the aims of this doctoral thesis. Regarding the systematic reviews with meta-analyses, electronic searches were conducted in at least two databases. Selected terms were established based on the PICOS (*participants, intervention, comparison, outcomes, and study design*) guideline. Random-effects models of standardised mean difference or mean difference were estimated. On the other hand, in the experimental study, male and female adult patients diagnosed

with CAD were randomly allocated to the HRV-guided training group (HRV-G = 11) or the predefined training group (PRED-G = 12). All the participants measured their HRV daily at home after waking up and trained three times a week for six weeks. Patients allocated to the HRV-G performed HIIT sessions based on their daily HRV measurements, while those patients allocated to the PRED-G followed a predefined training programme. HR-based indices and $\dot{V}O_2$ peak were assessed before and after the exercise-based CR programme. Regarding vagal-related HRV indices, isolated values were obtained in the time-domain (the root-mean-square difference of successive normal R-R intervals [RMSSD]) and frequency-domain (high frequency [HF]), as well as by using the Poincaré plot method (the standard deviation of the instantaneous beat-to-beat R-R interval variability [SD_1]). In addition, daily RMSSD values measured at home across one week were pooled to obtain weekly averaged RMSSD before and after the intervention. Comparisons between the two groups were reported as difference in mean or median changes with 95% confidence interval. Moreover, the effect of exercise-based CR, regardless of the training group, on mortality predictors was also estimated if there was no difference between the two training prescription methods.

Results: The first systematic review with meta-analysis showed an increase in averaged vagal-related HRV values (i.e., weekly averaged RMSSD) in F-OR athletes, while no changes in isolated vagal-related HRV indices were noticed. In addition, the results showed increased HRR 1 min in F-OR athletes. The second and third systematic review with meta-analysis showed that exercise-based CR enhances HRR 1 min and $\dot{V}O_2$ peak, respectively, in patients with CAD. The findings also confirmed that HIIT is more effective than MCT for improving $\dot{V}O_2$ peak. Regarding heterogeneity analyses, the training-induced effect on HRR 1 min was higher in studies which included younger patients. The improvement in $\dot{V}O_2$ peak after MCT was larger in studies which performed training sessions on a bicycle, as well as in studies which included patients with worse prognosis (e.g., increased risk of a new event) or lower CRF at baseline. In contrast, the results of the included studies of the effect of exercise-based CR programmes on vagal-related HRV indices (i.e., RMSSD or HF) were controversial. The findings showed an increase in RMSSD after an exercise-based CR programme. Nonetheless, there were no changes in HF, and the results of the included studies were sparse (i.e., high heterogeneity). In addition, no influence of potential moderator variables on the training-induced effect on HF was found. The fourth systematic review with meta-analysis showed that, accounting for methodological factors, HRV-guided training is more effective than predefined training for improving vagal-related HRV indices (i.e., RMSSD and SD_1) in healthy people (i.e., sedentary or physically active people and endurance-trained athletes). Nonetheless, no differences were found between HRV-guided training and predefined training for improving CRF. In the same line, the fifth study showed that, taking methodological factors into account, HRV-guided training increases vagal-

related HRV indices (i.e., weekly averaged RMSSD) to a greater extent than predefined training in patients with CAD. Regardless of the training prescription method used, the results showed that exercise-based CR enhances resting HR and $\dot{V}O_2$ peak, but not HRR 1 min, in patients with CAD.

Conclusions: PNS hyperactivity found in F-OR athletes can be identified by means of HRR 1 min and weekly averaged RMSSD. On the other hand, exercise-based CR is effective for improving PNS tone (i.e., HRR 1 min) and CRF in patients with CAD. Nonetheless, the training-induced effect on PNS modulation is more controversial. Finally, accounting for methodological factors, HRV-guided training seems to be more effective than predefined training for enhancing PNS modulation (e.g., weekly averaged RMSSD) in patients with CAD, as well as in healthy people. The results of this doctoral thesis show the importance of considering methodological factors in measuring vagal-related HRV indices to detect increased PNS modulation, as well as the beneficial effect of exercise-based CR programmes on mortality predictors in patients with CAD.

Keywords: *Coronary artery disease, heart rate variability, resting heart rate, heart rate recovery, cardiorespiratory fitness, HRV-guided training.*

Resumen

Antecedentes: La actividad parasimpática se puede estimar a partir de los índices basados en la frecuencia cardiaca (HR) (i.e., HR de reposo, índices vagales de la variabilidad de la HR [HRV] en reposo y recuperación de la HR durante el primer minuto post ejercicio [HRR 1 min]). La actividad parasimpática baja se considera un predictor independiente de mortalidad. Igualmente, el fitness cardiorrespiratorio (CRF), medido a través del consumo de oxígeno pico ($\dot{V}O_2$ pico), también se considera un predictor independiente de mortalidad. Existen evidencias acerca del efecto positivo de la rehabilitación cardiaca (CR) basada en el ejercicio físico sobre la mortalidad de pacientes con enfermedad arterial coronaria (CAD). Sin embargo, los resultados de estudios previos sobre el efecto de la CR basada en el ejercicio físico en los predictores de mortalidad (i.e., índices basados en la HR y $\dot{V}O_2$ pico) no son concluyentes. Los resultados contradictorios podrían ser debidos a la influencia de los factores metodológicos (p. ej., frecuencia respiratoria, utilización de valores promediados o puntuales, y posición en la que se lleva a cabo la valoración) sobre la sensibilidad de los índices basados en la HR para detectar los cambios de la actividad parasimpática, lo que ha sido estudiado principalmente en deportistas de resistencia con síntomas de sobrecarga funcional (F-OR). Además, la influencia de potenciales variables moderadoras (p. ej., método de entrenamiento aeróbico) sobre el efecto de la CR basada en el ejercicio físico en los predictores de mortalidad también podría explicar la falta de congruencia de los estudios previos. En relación con esto, revisiones sistemáticas y metaanálisis previos han mostrado que el entrenamiento interválico de alta intensidad (HIIT) es más efectivo que el entrenamiento continuo de moderada intensidad (MCT) para la mejora del $\dot{V}O_2$ pico en pacientes con CAD. Sin embargo, existen menos evidencias acerca de la influencia de otras variables de entrenamiento (p. ej., frecuencia de entrenamiento semanal) sobre el efecto de la CR basada en ejercicio físico en el CRF y la actividad parasimpática. Finalmente, debido a la alta heterogeneidad encontrada en la respuesta individual a un mismo programa de entrenamiento predefinido, estudios previos han analizado el efecto de programas de entrenamiento individualizados en función de los valores diarios de HRV (i.e., entrenamiento guiado por la HRV) en sujetos sanos y pacientes con insuficiencia cardiaca, mostrando resultados positivos para la mejora del $\dot{V}O_2$ pico. Sin embargo, el efecto del entrenamiento guiado por la HRV en los índices basados en la HR ha sido menos estudiado. Además, no se han llevado a cabo estudios que analicen el efecto del entrenamiento guiado por la HRV en los predictores de mortalidad en pacientes con CAD.

Por tanto, los principales objetivos de esta tesis doctoral fueron: a) estudiar la influencia de los factores metodológicos sobre la sensibilidad de los índices basados en la HR para detectar los incrementos de actividad parasimpática; y b) conocer el efecto de los programas de CR basados en el ejercicio físico (i.e., entrenamiento predefinido y entrenamiento guiado por la HRV) en los predictores de mortalidad (i.e., índices basados en la HR y $\dot{V}O_2$ pico) en pacientes con CAD.

Métodos: Para abordar los objetivos planteados en esta tesis doctoral se utilizaron métodos de revisiones sistemáticas con metaanálisis y métodos experimentales. Respecto a las revisiones sistemáticas con metaanálisis, las búsquedas electrónicas se llevaron a cabo en, al menos, dos bases de datos. Los términos utilizados para llevar a cabo las búsquedas se establecieron según la estrategia PICOS (*participants, intervention, comparison, outcomes, and study design*). Se utilizó un modelo de efectos aleatorios para la ponderación de la diferencia de medias estandarizada o la diferencia de medias. Respecto al estudio experimental, varones y hembras adultos que habían sido diagnósticos con CAD fueron distribuidos de forma aleatoria en el grupo de entrenamiento guiado por la HRV (HRV-G = 11) o en el grupo de entrenamiento predefinido (PRED-G = 12). Todos los pacientes registraron diariamente su HRV en casa al despertar y entrenaron tres días a la semana durante seis semanas. Los pacientes incluidos en el HRV-G realizaron sesiones de HIIT en función de sus valores diarios de HRV, mientras que aquellos que fueron asignados al PRED-G siguieron un programa de entrenamiento previamente establecido. Antes y después de la intervención se realizaron valoraciones de los índices basados en la HR y el $\dot{V}O_2$ pico. En cada una de las valoraciones se registraron valores puntuales (un registro) de los índices vagales de la HRV en el dominio del tiempo (raíz cuadrada de la media del cuadrado de las diferencias entre intervalos R-R adyacentes [RMSSD]) y de la frecuencia (alta frecuencia [HF]), así como por el método de Poincaré plot (desviación estándar instantánea de la variabilidad del intervalo R-R latido a latido [SD_1]). Además, los valores diarios de RMSSD registrados en casa durante una semana se promediaron para obtener el promedio semanal de RMSSD antes y después de la intervención. Las comparaciones entre los dos grupos se reportaron como la diferencia de los cambios medios o medianos con un intervalo de confianza al 95%. Además, en el caso de no encontrar diferencias entre ambos grupos, se estimó el efecto de la CR basada en el ejercicio físico, independientemente del grupo de entrenamiento, en los predictores de mortalidad.

Resultados: La primera revisión sistemática con metaanálisis mostró un incremento del promedio semanal de RMSSD en atletas con F-OR. Sin embargo, no se encontraron cambios de los valores puntuales de los índices vagales de la HRV. Además, los resultados de los estudios incluidos mostraron un incremento de la HRR 1 min en atletas con F-OR. La segunda y tercera revisión sistemática con metaanálisis mostraron que la CR basada en el ejercicio físico mejora la HRR 1 min y el $\dot{V}O_2$ pico, respectivamente, en pacientes con CAD. Los resultados confirmaron que el HIIT es más efectivo que el MCT para mejorar el $\dot{V}O_2$ pico. Respecto al análisis de la heterogeneidad, el efecto del entrenamiento sobre la HRR 1 min fue mayor en los estudios que incluyeron pacientes más jóvenes. Por otro lado, el efecto del MCT sobre el $\dot{V}O_2$ pico fue mayor en los estudios en los que las sesiones de entrenamiento se llevaron a cabo en bicicleta, así como en los estudios que incluyeron pacientes con peor pronóstico (p. ej., mayor riesgo de sufrir un nuevo evento) o menor CRF al inicio del estudio. Por el contrario, el efecto de la CR basada en

el ejercicio físico sobre los índices vagales de la HRV (i.e., RMSSD o HF) es más controvertido. Los resultados mostraron un incremento de RMSSD tras un periodo de entrenamiento. Sin embargo, no se encontraron cambios en HF y los resultados de los estudios incluidos fueron contradictorios (i.e., alta heterogeneidad). Además, las variables moderadoras analizadas no mostraron influencia en el efecto inducido por el ejercicio físico en HF. La cuarta revisión sistemática con metaanálisis mostró que, considerando factores metodológicos, el entrenamiento guiado por la HRV es más efectivo que el entrenamiento predefinido para la mejora de los índices vagales de la HRV (i.e., RMSSD o SD_1) en personas sanas (i.e., sujetos sedentarios, físicamente activos y atletas entrenados en resistencia). Sin embargo, no se encontraron diferencias entre ambos métodos de prescripción del entrenamiento en la mejora del CRF. En la misma línea, el quinto estudio mostró que, considerando factores metodológicos, el entrenamiento guiado por la HRV incrementa los índices vagales de la HRV (i.e., promedio semanal de RMSSD) en mayor medida que el entrenamiento predefinido en pacientes con CAD. Independientemente del método de prescripción del entrenamiento utilizado, los resultados mostraron que la CR basada en el ejercicio físico mejora la HR de reposo y el $\dot{V}O_2$ pico, pero no la HRR 1 min, en pacientes con CAD.

Conclusión: Los deportistas con F-OR mostraron un incremento de actividad parasimpática que puede ser identificado a partir de la HRR 1 min y del promedio semanal de RMSSD. Por otra parte, la CR basada en el ejercicio físico es efectiva para la mejora del tono parasimpático (i.e., HRR 1 min) y el CRF en pacientes con CAD. Sin embargo, el efecto de la CR basada en el ejercicio físico sobre la modulación parasimpática es más controvertido. Por último, considerando factores metodológicos, el entrenamiento guiado por la HRV parece ser más efectivo que el entrenamiento predefinido para la mejora de la modulación parasimpática (p. ej., promedio semanal de RMSSD) en pacientes con CAD, así como en sujetos sanos. Los resultados de esta tesis doctoral muestran la importancia del control de los factores metodológicos para incrementar la sensibilidad de los índices vagales de la HRV para detectar los cambios en la modulación parasimpática, como también el efecto positivo de la CR basada en el ejercicio físico en los predictores de mortalidad en pacientes con CAD.

Palabras clave: *Enfermedad arterial coronaria, variabilidad de la frecuencia cardiaca, frecuencia cardiaca de reposo, frecuencia cardiaca de recuperación, fitness cardiorrespiratorio, entrenamiento guiado por la HRV.*

CHAPTER 1

GENERAL INTRODUCTION

Chapter 1. General introduction

1.1. Heart rate-based indices

1.1.1. Autonomous nervous system and heart rate-based indices

The autonomous nervous system (ANS) plays an important role in the modulation of heart rate (HR). The ANS is divided into two branches, the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS), which exert opposing effects on the HR [1] (Figure 1). The heart is under tonic inhibitory control by PNS influences, which has been pharmacologically shown by using atropine and propranolol blockade [2-5]. Thus, resting HR (e.g., 60 – 70 beats per minute [bpm]) is lower than intrinsic HR (e.g., 95 – 110 bpm) and can be used as a cardiac vagal index.

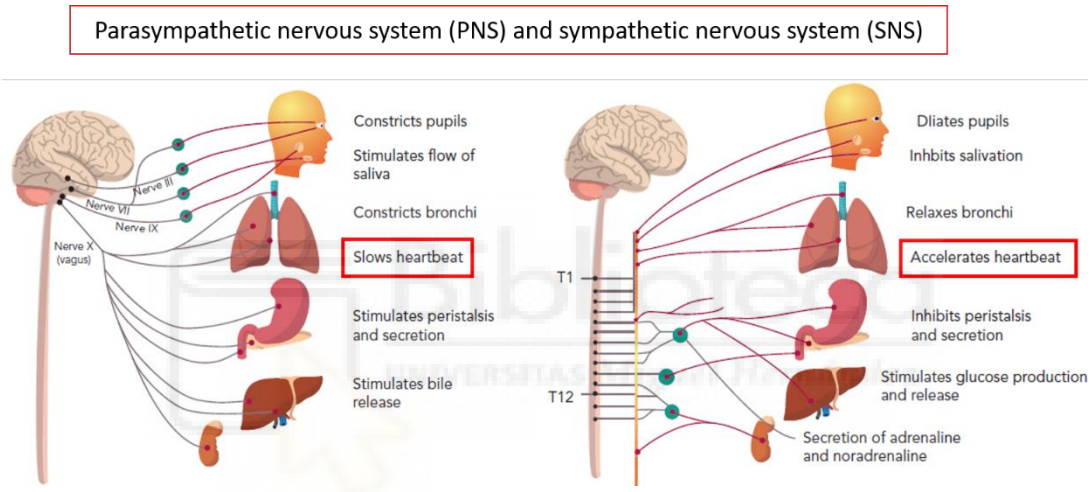

Figure 1. Anatomy and functions of the autonomous nervous system branches. Adapted from: Singh et al. [6]

Resting HR time series are characterised by beat-to-beat lability (i.e., HR variability [HRV]) [7, 8], which occurs due to complex interactions between the two branches of the ANS on the HR [9, 10]. Several HRV indices can be obtained from linear (i.e., time- and frequency-domain) and non-linear methods [11, 12] (Table 1). Power spectral density methods, such as fast-Fourier transform or auto-regressive, are used to obtain frequency-domain indices [13]. During resting conditions, the root-mean-square difference of successive normal R-R intervals (RMSSD), the high frequency (HF), and the standard deviation of the instantaneous beat-to-beat R-R interval variability (SD_1) from Poincaré plot analysis are predominantly modulated by the PNS branch of the ANS. Nonetheless, other HRV indices are influenced by the two branches of the ANS, and their interpretation is more complicated [11, 14-20].

During exercise, PNS activity decreases and SNS activity increases (i.e., HR increases and HRV decreases) [21-24]. Nowadays, based on the fractal correlation properties of HRV, detrended fluctuation analysis of HRV and its short-term scaling exponent 1 alpha (DFA-1 alpha) is used

for establishing training zones in endurance-trained athletes [25-28]. In the same line, HRV threshold based on DFA-1 alpha and first ventilatory threshold were found to be correlated in a group of cardiac patients [29]. Even though optimistic findings have been reported, more evidence is necessary about the use of HRV changes during exercise for setting training zones, mainly in clinical population.

Table 1. Linear and non-linear heart rate variability indices

Method	Variable	Description
Linear method. Time-domain indices	RMSSD	The root-mean-square difference of successive normal R-R intervals
	Mean R-R	Mean R-R intervals
	SDNN	The standard deviation of R-R intervals
	pNN50	The mean number of times an hour in which the change in successive normal sinus intervals exceeds 50 ms
Linear method. Frequency-domain indices	VLF	Very low frequency (0.00-0.04 Hz)
	LF	Low frequency (0.04-0.15 Hz)
	HF	High frequency (0.15-0.40 Hz)
	LF/HF	Ratio LF to HF
Non-linear method. Poincaré plots	SD_1	The standard deviation of the instantaneous beat-to-beat R-R interval variability
	SD_2	The standard deviation of the continuous long-term R-R intervals
	SD_1/ SD2	Ratio SD_1 to SD_2
Other non-linear indices	SampEn	Sample entropy
	LE	Lyapunov exponent
	HE	Hurst exponent
	CD	Correlation dimension
	DFA-1 alpha	Detrended fluctuation analysis of HRV and its short-term scaling exponent 1 alpha
	DFA-2 alpha	Detrended fluctuation analysis of HRV and its long-term scaling exponent 2 alpha

Finally, after exercise, PNS activity increases and SNS activity decreases (i.e., HR decreases and HRV increases) [30]. The recovery of HR after exercise, known as HR recovery (HRR) [31], presents a first order exponential decay function with a fast HR fall immediately after exercise, followed by a slow decay of HR [30] (Figure 2). Studies using pharmacological blockade showed that the HR decrease during the first minute of recovery is mainly due to PNS reactivation, while further HR decrease seems to be attributed to PNS reactivation and SNS withdrawal [32-36]. The long-term recovery of the ANS status (i.e., from 24 to 48 hours to return to pre-exercise values) [37, 38] depends on the progressive removal of metabolites from the skeletal muscles after

exercise, which allows the restoration of baroreflex activity [39]. Heightened SNS tone during long-term recovery allows to restore homeostasis and muscle glycogen [40, 41].

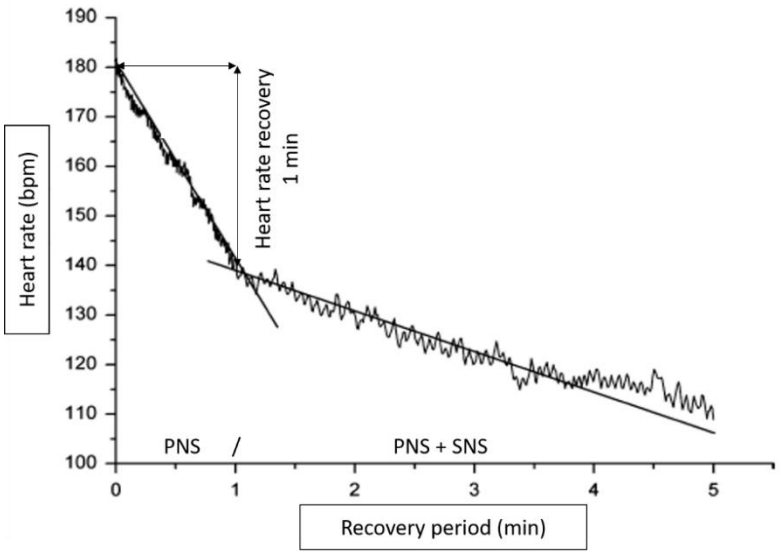

Figure 2. Slow and fast phases of heart rate recovery. *PNS*, parasympathetic nervous system; *SNS*, sympathetic nervous system. Adapted from: Peçanha et al. [31]

Assessment of HRV requires stationary conditions, mainly with frequency-domain indices, which are easier to attain in resting condition than after exercise, to assume that HR data series are stationary [11, 42, 43]. In this regard, time-varying analysis of RMSSD (i.e., RMSSD obtained on consecutive 30-s windows) [30] and time-frequency techniques [42, 44, 45] are used to study PNS reactivation by means of vagal-related HRV indices. Nevertheless, the use of post-exercise HRV is less common than the use of resting HRV, and HRR is the common measurement used to assess ANS restoration after exercise. Additionally, both indices do not seem to be interchangeable [46]. On the other hand, even though other HRR indices have been proposed for assessing PNS reactivation during the fast phase of HRR (e.g., the negative reciprocal of the slope of regression line between the natural logarithm of HR from the first 30 s after exercise), the number of heart beats recovered within the first minute after exercise (HRR 1 min) is the most used index to assess PNS reactivation. Its ability to provide diagnostic information has been widely reported [31, 34]. In the same vein, several HRR indices are also used for evaluating the slow phase of HRR (e.g., the number of heart beats recovered within 2 min after exercise and the time constant of the first order exponential fitting curve of the HRR) [31, 32]. Nevertheless, as it has been commented above, their interpretation is more difficult because the two branches of the ANS are implicated in the slow HRR phase.

Based on this previous evidence, HR-based indices (i.e., resting HR, resting vagal-related HRV indices, and HRR 1 min) have been used specifically to evaluate PNS activity. Nonetheless, the underlying physiological determinants of these indices are different [47-49]. Resting HR and HRR 1 min are predominantly influenced by PNS tone, while vagal-related HRV indices are

generated by respiratory modulation of the PNS efferent outflow (i.e., PNS modulation) instead of the PNS tone per se. In this regard, Goldberger et al. [50], who pharmacologically increased PNS tone by phenylephrine infusion, reported a marked reduction in both resting HR and resting vagal-related HRV indices (Figure 3). In the same line, there is evidence that shows that increased blood plasma volume induces increased post-exercise vagal-related HRV indices (i.e., PNS modulation) [37, 51-53], while no changes were found in HRR indices (i.e., PNS tone) [53]. The difference between the underlying physiological determinants of HR-based indices should be taken into consideration to understand the influence of methodological factors (e.g., breathing pattern and assessment position) on the sensitivity of these indices to detect PNS changes [54, 55], which is presented below (see Section 1.2).

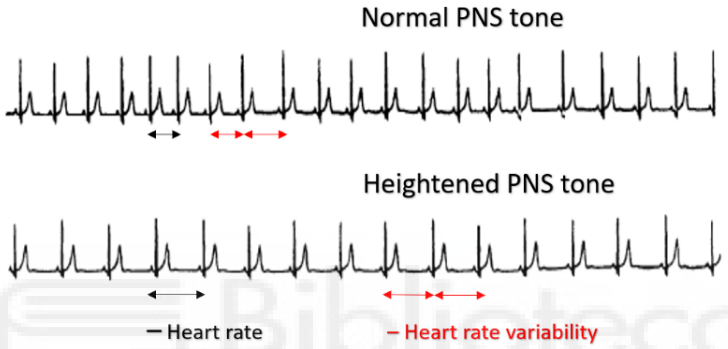

Figure 3. Effect of increased parasympathetic tone on heart rate and heart rate variability. *PNS*, parasympathetic nervous system. Adapted from: Goldberger et al. [50]

1.1.2. Prognostic value of heart rate-based indices

A wide body of evidence has shown a relationship between decreased PNS activity, assessed by HR-based indices, and increased mortality risk, even after controlling for a wide range of confounders [56-72]. For instance, Chen et al. [59] found a two-fold increase in risk of all-cause mortality in 50-year-old males with high resting HR (i.e., > 75 bpm) compared with males with low resting HR (i.e., ≤ 55 bpm). Regarding resting HRV, Tsuji et al. [65] reported that, in cardiac patients, both time- and frequency-domain HRV indices were significantly associated with the risk of a cardiac event. For instance, these authors reported that the adjusted risk of a new cardiac event was multiplied by 1.4 for each one standard deviation (*SD*) decrement in RMSSD. On the other hand, Cole et al. [60], who followed 2428 adult patients for six years, also found a two-fold increase in relative mortality risk in patients with reduced HRR 1 min (i.e., ≤ 12 bpm) compared with those patients with normal HRR 1 min (i.e., > 12 bpm). Therefore, high resting HR, low vagal-related HRV and delayed HRR 1 min are used as independent mortality predictors. This evidence makes the PNS branch of the ANS a valid target for pharmacological and non-pharmacological (e.g., exercise training) therapies aimed to reduce mortality in both healthy and diseased people.

Though the exact mechanisms are not fully understood yet, the tonic control of the PNS branch of the ANS on the inhibition processes of the allostatic systems has been used to explain the relationship between decreased PNS activity and increased mortality risk [7, 73]. Moreover, the anti-inflammatory response is also under tonic PNS control (i.e., cholinergic anti-inflammatory pathway). Thus, diminished PNS activity promotes a lower anti-inflammatory response, which induces macrophage activation and increased blood cytokine concentrations (i.e., TNF-alpha, interleukin 1, and interleukin 18), leading to the development and/or rupture of the atherosclerotic plaque [74].

1.2. Methodological factors in measuring heart rate-based indices

Before addressing the methodological factors in measuring HR-based indices, it should be noted that ANS modulation is highly sensitive to environmental influences (e.g., noise, temperature, humidity, light, and time of the day) and daily physical activity [11, 53, 75, 76]. Therefore, it is of importance to control the conditions that affect ANS activity to reach conclusive findings about the status of this physiological system. Apart from that, even though HR-based indices are cardiac vagal indices, methodological factors in measuring these indices, which are exposed beneath, should also be considered to attain conclusive findings [76].

1.2.1. Vagal-related heart rate variability indices

As it has been commented above, HRV reflects the influence of respiration on the cardiac efferent PNS discharge [47, 48]. HR increases and decreases during inspiration and expiration, respectively, known as respiratory sinus arrhythmia [54]. Respiratory sinus arrhythmia is measured by the decomposition of the HRV spectrum, corresponding to the HF band (0.15 to 0.40 Hz), which is associated to respiration [77]. Lower respiratory rates (e.g., < 0.15 Hz) diminish respiratory sinus arrhythmia and consequently HF [78]. Thus, the control of the breathing pattern is paramount to increase the validity of spectral indices of HRV (e.g., HF) to reflect PNS modulation, which has been previously reported [77, 79]. Besides that, there is evidence showing that the sensitivity of RMSSD and SD_1 to different breathing rates is lower than the sensitivity of HF [80, 81], which increases the validity of RMSSD and SD_1 [79].

Another important methodological consideration to assess vagal-related HRV indices properly is the position used to capture R-R intervals (e.g., supine, standing, and sitting). Previous studies found decreased HR (i.e., bradycardia) along with decreased vagal-related HRV indices (e.g., RMSSD) when HR-based indices were assessed in the supine position [82], which seems to be a limitation of vagal-related HRV indices due to its inability to detect changes in PNS modulation in this position [83]. Differences between resting HR and vagal-related HRV indices could be explained by the underlying physiological determinant of the two HR-based indices [47, 48]. Heightened PNS tone (i.e., low HR) could induce saturation of acetylcholine receptors in myocytes, which eliminates respiratory modulation and, therefore, decreases vagal-related HRV

indices [50, 82, 84, 85], leading to a bell-shaped relationship between PNS tone and PNS modulation. Nevertheless, in this scenario, the standing position is used for inducing orthostatic stress, which causes baroreflex-mediated autonomic and hemodynamic adjustments, and counteracts the effect of heightened PNS tone [86].

The importance of using averaged HRV values instead of isolated HRV values for inferring PNS modulation has also been highlighted in methodological studies [87-90]. In this regard, averaged HRV values (e.g., seven-day averaged RMSSD values) are more suitable than isolated HRV values (e.g., single-day RMMSD values) for reflecting PNS modulation due to the high day-to-day variability of HRV. For instance, Plews et al. [87] and Buchheit et al. [88] found a large correlation between performance and PNS modulation changes only when averaged HRV values were used for inferring PNS modulation. The use of averaged HRV values allows to control the influence of environmental conditions and previous physical activity on a single-day HRV value [11, 53, 75, 76]. In this regard, Buchheit et al. [53] reported that enhanced baroreflex-mediated PNS activity due to increased blood plasma volume (i.e., hypervolemia) within the following 48 hours after exercise [91, 92] could be the main source of day-to-day HRV lability. In addition, the use of averaged HRV values seems to be more important when HF is used as vagal-related HRV index because its day-to-day variability seems to be higher than the lability of other HRV indices (i.e., RMSSD and SD_1) [79]. In this regard, Saboul et al. [80] demonstrated that RMSSD and SD_1 provide that same variation regardless of the breathing pattern, which could explain the lower day-to-day variability of these vagal-related HRV indices.

There are other methodological factors that should not be overlooked when PNS modulation is inferred by vagal-related HRV indices. For instance, ectopic beats, artefacts, and noise should be removed before performing HRV analyses [11]. Apart from that, different interpolation methods are normally used to replace ectopic beats and artefacts from R-R interval series (e.g., lineal interpolation) [11, 93]. Furthermore, R-R intervals must be stable for HRV analysis in the frequency domain, which is mandatory to ascertain that those spectral components represent the true HRV [43, 76, 94].

Therefore, considering this previous evidence, it seems that the influence of methodological factors on the sensitivity of vagal-related HRV indices for inferring PNS activity is lower on RMSSD and SD_1 than on HF, which has been also previously reported [79].

1.2.2. Heart rate recovery

The most important determinant of ANS restoration after exercise is metaboreflex stimulation, which increases SNS activity and decreases PNS activity [49, 95]. Greater intensity promotes higher concentration of metabolites (i.e., lactate, K^+, and H^+) and, therefore, increased metaboreflex stimulation, that induces slower PNS reactivation and/or SNS withdrawal [14].

Thus, HRR indices are intensity dependent. Nevertheless, the influence of metaboreflex stimulation on ANS restoration seems to be phase dependent [31]. In this regard, PNS reactivation at the beginning of the recovery (i.e., fast phase) is due to central and peripheral (i.e., mechanoreflex) deactivation, that reduces the impact of the exercise intensity on the fast phase of HRR (i.e., HRR 1 min) [31, 34]. Nonetheless, some studies found that HRR 1 min is also slower after supramaximal exercise [96, 97], showing controversial findings about the effect of the test intensity on the fast phase of PNS reactivation. In contrast, a wide body of evidence shows that the slow phase of HRR is workload dependent [31, 32, 34, 35, 97].

Other methodological factors that affect PNS reactivation are the recovery mode (i.e., active and passive) and the assessment position (e.g., standing and sitting). In this regard, active recovery periods induce slower HRR 1 min than passive recovery periods due to increased mechanoreflex stimulation [98, 99]. HRR 1 min is also slower in the standing position than in sitting or supine positions [100]. Activated postural muscles in the standing position induce increased and decreased SNS and PNS activity, respectively [101]. Therefore, the recovery mode and the assessment position should also be considered for inferring PNS reactivation.

1.3. Heart rate-based indices as a tool for monitoring exercise training

An altered PNS status (i.e., decreased PNS tone and/or PNS modulation) coincides with several hormonal changes in endurance-trained athletes [102]. Additionally, as it has been commented above, there is evidence showing the relationship between HR-based indices and PNS status [103]. Thus, HR-based indices have been proposed as tools for inferring training-induced status (i.e., adaptation and maladaptation) and guiding endurance training (i.e., HRV-guided training) [14, 104].

1.3.1. Sensitivity of heart rate-based indices for inferring training-induced status

There is evidence showing increased PNS activity along with decreased performance capacity in endurance-trained athletes after an overload training period [105-107]. The decrease in performance after an overload training period is known as functional overreaching (F-OR) status [108]. After a proper short recovery period or tapering (e.g., from several days to weeks), performance capacity increases above pre-overload training period values (i.e., supercompensation). Nonetheless, if overload training continues, it may induce a state of non-functional overreaching (N-FOR), which diminishes performance capacity for a long time (e.g., from several weeks to months) despite a recovery period or a tapering [108-110]. Even though performance assessment is the gold standard method used to identify F-OR athletes, this is fatiguing and may be contraindicated for F-OR athletes, who are at risk of developing N-FOR. Therefore, it is mandatory to use other tools to infer the training-induced fatigue status of athletes who perform an overload training period to avoid symptoms of N-FOR.

HR-based indices (i.e., resting HR, vagal-related HRV indices, and HRR 1 min) have been proposed to assess PNS hyperactivity in athletes at risk of developing N-FOR [14, 111-114]. Even though resting HR has been used for inferring training-induced fatigue status, nowadays, vagal-related HRV and HRR 1 min are more used than resting HR due to technology developments [11, 115], which have allowed researchers and coaches to monitor these HR-based indices daily. Besides, the sensitivity of vagal-related HRV indices and HRR 1 min for inferring changes in PNS activity seems to be higher than the sensitivity of resting HR [87]. Nevertheless, the results of previous studies of the sensitivity of HR-based indices to detect PNS hyperactivity are controversial. While some studies found increased PNS activity, inferred by faster HRR 1 min or higher vagal-related HRV indices, in athletes suspected of being F-OR [107, 116], other studies did not find changes in these HR-based indices [117-119]. Nevertheless, it should be noted that endurance-trained athletes could also maintain or increase their performance capacity after an overload training period despite high levels of perceived fatigue, which is known as acute fatigue [108]. Thus, other training-induced fatigue status (e.g., acute fatigue) could explain the controversial findings of previous studies, which highlights the relevance of knowing the training-induced fatigue status to reach conclusive findings about the sensitivity of HR-based indices to detect PNS hyperactivity in F-OR athletes. To achieve this, other tools such as biochemical parameters (e.g., epinephrine, haemoglobin, and lactate concentration levels) [117, 120] and questionnaires (e.g., profile of mood states, daily analysis of life demands for athletes, and recovery stress questionnaire for athletes) [116, 121, 122] are also used. Besides this, methodological factors (e.g., isolated vagal-related HRV values, breathing patterns, the vagal-related HRV index used, test intensity, and assessment position) could also explain the lack of sensitivity of HR-based indices (i.e., vagal-related HRV indices and HRR 1 min) to detect PNS hyperactivity in F-OR athletes [105].

1.3.2. Heart rate variability-guided training

Traditional exercise prescription methodologies, in which endurance training variables (i.e., intensity, volume, frequency, and timing) are programmed in advance (i.e., predefined training), stimulate training adaptations efficiently (e.g., endurance performance, fitness, and PNS modulation) [123, 124]. Nevertheless, large heterogeneity has been found in individual training adaptations in response to a predefined training programme [88, 125-131]. Therefore, individualised training prescription methodologies in which training characteristics (e.g., intensity) are modulated according to the participant status are necessary to reduce the heterogeneity found in the response to predefined training. In this regard, the short-term recovery (e.g., within 48 hours after exercise) of PNS modulation, assessed by vagal-related HRV indices, seems to be related to the recovery of thermoregulatory, metabolic, and hemodynamic processes that are altered by physical exertion [95]. Moreover, the association between PNS modulation and

endurance training has been widely reported [83, 132, 133]. In this regard, the PNS status seems to play a paramount role in the response to endurance training (e.g., higher vagal-related HRV indices at baseline correlate with higher improvements in cardiorespiratory fitness [CRF]) [129, 134-140]. Thus, HRV has been also used as a tool for carrying out endurance training prescription on a daily basis (i.e., HRV-guided training) [141-143]. The basic idea behind this training prescription method is to adjust training (i.e., low intensity or rest) when HRV values are altered [144, 145]. Therefore, high-intensity training sessions are only performed when optimal PNS conditions are found before training sessions.

Previous studies have investigated whether HRV-guided training enhances PNS activity and/or CRF to a higher extent than predefined training in healthy people (e.g., sedentary people and endurance-trained athletes) [141-148]. Some of these studies showed greater enhancements in selected endpoints with similar or lower volume of high-intensity training [141, 143, 145, 146]. Moreover, less heterogeneity in the response at individual level in participants who carried out HRV-guided training has been also reported [141, 143]. In addition, some recent systematic reviews and meta-analyses have been carried out to compare the effectiveness of the two training prescription methods [149-151]. Granero-Gallegos et al. [149] found that HRV-guided training is superior to predefined training for improving CRF, assessed by maximum oxygen uptake ($\dot{V}O_2$ max), in endurance athletes. However, Düking et al. [150] and Medellin Ruiz et al. [151] reported no differences between the two training prescription methods for improving $\dot{V}O_2$ max in trained and untrained people, even though a trend was found in favour of HRV-guided training. Therefore, the superiority of HRV-guided training for improving CRF is still controversial. Nonetheless, different methodological approaches in measuring vagal-related HRV indices (e.g., time of the day, vagal-related HRV index used, breathing control, and assessment position), criteria (e.g., isolated vs. averaged HRV values and strict limit vs. individual smallest worthwhile change [SWC]), and rationale for HRV guidance have been used to carry out HRV-guided training interventions, which could explain the controversial findings previously reported [149-151].

Apart from that, whether HRV-guided training increases PNS activity to a greater extent than predefined training has not been addressed in the previous systematic reviews and meta-analyses [149-151]. However, as it has been commented above, HR-based indices are considered independent mortality predictors [56, 60, 64]. In this regard, da Silva et al. [144] found an increase in PNS modulation (i.e., RMSSD) in the group which carried out an HRV-guided training programme, while a trend in favour of this training prescription method was also found for enhancing PNS tone (i.e., HRR 1 min). Nonetheless, Kiviniemi et al. [141] reported HRV improvements regardless of the training prescription method used to perform endurance training. The enhancement of HR-based indices could reduce the mortality risk [152], being mandatory to

confirm whether HRV-guided training is better than predefined training for improving HR-based indices in healthy subjects. If this finding is confirmed, the efficacy of HRV-guided training for improving PNS activity should also be tested in patients (e.g., patients with coronary artery disease [CAD]), who have shown decreased PNS activity and, therefore, an increased mortality risk [153, 154].

1.3.3. Effect of exercise-based cardiac rehabilitation on mortality predictors

The beneficial effects of traditional exercise-based cardiac rehabilitation (CR) programmes, in which training variables are established in advance (i.e., predefined training), on mortality risk and/or adverse events have been widely reported [155-158]. These clinical benefits may be explained in part by the effect of exercise training on PNS activity [159]. Therefore, exercise training is considered a cornerstone within CR programmes [160]. Nevertheless, the results of previous studies of the effect of exercise-based CR programmes on HR-based indices are sparse. While some studies found increased vagal-related HRV indices and/or enhanced HRR 1 min after an exercise-based CR programme [161-163], other studies did not find changes in these indices [164, 165]. Methodological factors (e.g., breathing control, use of isolated HRV values, assessment position, and test intensity) could affect the sensitivity of HR-based indices for inferring changes in PNS activity in patients with CAD after an exercise-based CR programme [31, 76, 166]. For instance, Plews et al. [89] explicitly reported that the use of isolated HRV indices could explain contradictory findings about the effect of exercise training on PNS modulation, assessed by vagal-related HRV indices. Though high heterogeneity has been found in the results of previous meta-analyses, the influence of methodological factors on the sensitivity of HR-based indices to detect increased PNS activity in patients with CAD has not been addressed.

The effect of exercise-based CR on CRF, assessed by peak oxygen uptake ($\dot{V}O_2$ peak; the term used to refer to $\dot{V}O_2$ max in patients), has also been widely investigated because it is considered another independent mortality predictor [167, 168]. Epidemiological studies have shown that a better CRF is associated with lower mortality risk and/or adverse events (e.g., acute myocardial infarction [AMI]) [169, 170], even in the presence of traditional risk factors for cardiovascular disease. For instance, Laukkanen et al. [171] found that, in patients with CAD, an increase of 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ in $\dot{V}O_2$ peak was associated with a risk factor-adjusted decrease of 13% and 31% in non-fatal and fatal cardiac events, respectively. This finding showed the greater prognostic utility of $\dot{V}O_2$ peak in patients with CAD and emphasises the need to identify patients with low $\dot{V}O_2$ peak to take preventive measurements. Furthermore, CRF is lower in clinical-based population than in healthy people, which might be due to central (e.g., cardiac output) and/or peripheral (e.g., endothelial or mitochondrial dysfunction) alterations [169]. Thus, the improvement of CRF is one of the most important aims to reach after an exercise-based CR programme.

There is evidence showing that exercise-based CR is appropriate for improving $\dot{V}O_2$ peak in patients with CAD [172, 173]. Nevertheless, the results of previous studies are also controversial [173], which could be explained by the influence of potential moderator variables (e.g., exercise characteristics) on the effect of exercise-based CR programmes on $\dot{V}O_2$ peak. In this regard, most of the previous systematic reviews and meta-analyses were carried out to study the influence of the aerobic training method (i.e., moderate continuous training [MCT] and high-intensity interval training [HIIT]) on the effect of exercise-based CR on $\dot{V}O_2$ peak [174-180]. It should be noted that aerobic training is the common term used to refer to endurance training in patients. All these meta-analyses showed that HIIT is more suitable than MCT for improving CRF. Nevertheless, the influence of other training variables (e.g., frequency, session length, and intervention length) and participant characteristics (e.g., gender, age, and risk of a new event) on the effect of CR programmes based on MCT or HIIT on $\dot{V}O_2$ peak has been less studied.

In the same line as in healthy people, even though there is evidence that shows that exercise-based CR programmes are suitable for improving $\dot{V}O_2$ peak and HR-based indices in patients with CAD [181, 182], wide individual heterogeneity has been found in the response to traditional exercise-based CR programmes (i.e., predefined training) [183]. Therefore, it is also mandatory to design individualised exercise programmes, in which training characteristics are modulated based on the patient status (e.g., HRV-guided training), to diminish individual heterogeneity in the response to training. Nevertheless, whether HRV-guided training enhances mortality predictors (i.e., HR-based indices and $\dot{V}O_2$ peak) to a greater extent than predefined training in patients with CAD has not been investigated [153]. It should be noted that prescription (e.g., training frequency) and response to training (e.g., recovery of ANS activity) in patients with CAD may be different from that of healthy population (i.e., sedentary or physically active people and endurance-trained athletes) [144, 146]. Furthermore, even though HIIT seems to be more effective than MCT for improving $\dot{V}O_2$ peak in patients with CAD [178], PNS reactivation and SNS withdrawal after HIIT are slower than after MCT [184], increasing the stress of patients with high mortality risk unnecessarily. If HRV-guided training were more effective than predefined training for improving PNS activity and/or CRF, the former training prescription method should be used to design exercise-based CR programmes and diminish mortality risk in patients with CAD. Additionally, the developments of new methodologies (e.g., shorter recordings) [185] and field-based technologies capable of tracking HR-based indices [115, 186, 187] have allowed the use of HRV-guided training in clinical settings. In this regard, Behrens et al. [188] tested the efficacy of HRV-guided training and predefined training for improving CRF in patients with chronic heart failure (CHF). Authors found an improvement in $\dot{V}O_2$ peak after an HRV-guided training programme, while no change in this variable was noticed after a predefined training programme. However, whether HRV-guided training and predefined training enhance HR-based indices was not tested.

Therefore, the fact of studying the suitability of HRV-guided training for enhancing mortality predictors in patients with CAD is of highest importance.

As it has been commented throughout this chapter, HR-based indices (i.e., resting HR, vagal-related HRV indices, and HRR 1 min) and $\dot{V}O_2$ peak are considered independent mortality predictors. There is evidence showing that exercise-based CR programmes reduce mortality rates in patients with CAD, which could be explained in part by enhancement of HR-based indices and/or $\dot{V}O_2$ peak. Nonetheless, the results of previous studies of the effect of exercise-based CR on mortality predictors are controversial, which could be due to the influence of methodological factors on the sensitivity of HR-based indices, as well as to the influence of potential moderator variables (e.g., aerobic training method [i.e., HIIT vs. MCT]) on the training-induced effect on mortality predictors. Moreover, high heterogeneity has been found in the individual response to traditional exercise-based CR programmes (i.e., predefined training). In this regard, HRV-guided training seems to be better than predefined training for improving CRF (i.e., more effective and with less heterogeneity of individual responses) in healthy people and in patients with CHF. However, whether HRV-guided training enhances mortality predictors (i.e., HR-based indices and $\dot{V}O_2$ peak) to a greater extent than predefined training in patients with CAD has not been studied. Therefore, further research is needed to clarify the influence of methodological factors on the sensitivity of HR-based indices to detect changes in PNS activity and the effect of exercise-based CR programmes (i.e., predefined training and HRV-guided training) on mortality predictors in patients with CAD.

CHAPTER 2

RESEARCH OBJECTIVES AND HYPOTHESES

Chapter 2. Research objectives and hypotheses

2.1. General objectives

Based on the limitations and inconsistencies found in the scientific literature, mainly in measuring vagal-related HRV indices and HRR 1 min, and the heterogeneity found in the response to exercise-based CR programmes in patients with CAD, the general objectives of the current doctoral thesis were: a) *to study the influence of methodological factors on the sensitivity of HR-based indices for inferring changes in PNS activity*; and b) *to know the effect of exercise-based CR (i.e., predefined training and HRV-guided training) on mortality predictors (i.e., HR-based indices and $\dot{V}O_2$ peak) in patients with CAD.*

Five studies (four systematic reviews with meta-analyses and one experimental study) were carried out to attain the established aims. In the first systematic review with meta-analysis, the sensitivity of HR-based indices (i.e., vagal-related HRV indices and HRR 1 min) for inferring PNS hyperactivity in F-OR athletes was studied while accounting for methodological factors. In the second and third systematic review with meta-analysis, the effect of exercise-based CR on HR-based indices (i.e., vagal-related HRV indices and HRR 1 min) and $\dot{V}O_2$ peak, respectively, in patients with CAD was investigated. Moreover, the influence of potential moderator variables (e.g., patient characteristics and aerobic training method) on the training-induced effect on mortality predictors was analysed. In the fourth systematic review with meta-analysis and in the experimental study (fifth study), the effectiveness of HRV-guided training and predefined training for improving mortality predictors in healthy people (i.e., sedentary or physically active people and endurance-trained athletes) and patients with CAD, respectively, was studied while taking methodological factors into account.

The titles of the five studies included in this doctoral thesis are the following:

Study 1. Heart rate-based indices to detect parasympathetic hyperactivity in functionally overreached athletes. A meta-analysis.

Study 2. Exercise-based cardiac rehabilitation and parasympathetic function in patients with coronary artery disease: a systematic review and meta-analysis.

Study 3. Are the current cardiac rehabilitation programs optimized to improve cardiorespiratory fitness in patients? A meta-Analysis.

Study 4. Heart rate variability-guided training for enhancing cardiac-vagal modulation, aerobic fitness, and endurance performance: A methodological review with meta-analysis.

Study 5. Is heart rate variability-guided training superior to predefined training for improving mortality predictors in patients with coronary artery disease?

2.2. Specific objectives

The specific objectives have been structured according to the studies included in this doctoral thesis:

Study 1

1) To know whether vagal-related HRV indices and HRR 1 min are sensitive to detect PNS hyperactivity in F-OR athletes while taking methodological factors into account.

Study 2

2) To know whether exercise-based CR programmes enhance vagal-related HRV indices (i.e., RMSSD and HF) and HRR 1 min in patients with CAD.
3) To study the influence of potential moderator variables (e.g., aerobic training method) on the training-induced effect on HR-based indices in patients with CAD.

Study 3

4) To know whether CR programmes based on MCT or HIIT improve $\dot{V}O_2$ peak in patients with CAD.
5) To compare the effectiveness of MCT and HIIT for enhancing $\dot{V}O_2$ peak in patients with CAD.
6) To study the influence of potential moderator variables on the effect of MCT and HIIT on $\dot{V}O_2$ peak in patients with CAD.

Study 4

7) To know whether HRV-guided training increases $\dot{V}O_2$ max and HR-based indices to a greater extent than predefined training in healthy people (i.e., sedentary or physically active people and endurance-trained athletes) while accounting for methodological factors in measuring HR-based indices.

Study 5

8) To study whether HRV-guided training is better than predefined training for enhancing $\dot{V}O_2$ peak and HR-based indices in patients with CAD while taking methodological factors in measuring vagal-related HRV indices into account (i.e., isolated RMSSD vs. weekly averaged RMSSD).
9) To study the effect of exercise-based CR programmes on mortality predictors in patients with CAD regardless of the training prescription method.

2.3. Hypotheses

The following hypotheses were established in the studies included in this doctoral thesis according to the previous evidence:

Study 1

1) Accounting for methodological factors (e.g., vagal-related HRV index used [105], breathing control [80], and assessment position [50, 100]), vagal-related HRV indices and HRR 1 min will be sensitive to detect increased PNS activity in F-OR athletes [105, 107, 118].

Study 2

2) Exercise-based CR will enhance vagal-related HRV indices (i.e., RMSSD and HF) and HRR 1 min in patients with CAD [182, 189].
3) The effect of exercise-based CR on HR-based indices (i.e., vagal-related HRV indices and HRR 1 min) will be influenced by potential moderator variables (e.g., patient age [189], wait time to start exercise-based CR [190], and aerobic training method [178-180]).

Study 3

4) MCT and HIIT will induce enhancements in $\dot{V}O_2$ peak in patients with CAD [191].
5) The effect of HIIT on $\dot{V}O_2$ peak will be higher than the effect of MCT [178-180].
6) The effect of MCT and HIIT on $\dot{V}O_2$ peak will be influenced by potential moderator variables (e.g., patient age [192] and training characteristics [193]).

Study 4

7) HRV-guided training will be more effective than predefined training for improving $\dot{V}O_2$ max and HR-based indices in healthy people (i.e., sedentary or physically active people and endurance-trained athletes) [144, 149] when taking methodological factors in measuring HR-based indices into account (e.g., breathing control [80], vagal-related HRV index [105], and use of averaged vs. isolated HRV values [90]).

Study 5

8) HRV-guided training will be superior to predefined training for enhancing $\dot{V}O_2$ peak and HR-based indices in patients with CAD [144, 188] when accounting for methodological factors in measuring vagal-related HRV indices (i.e., weekly averaged RMSSD) [90, 107].
9) Exercise-based CR will enhance $\dot{V}O_2$ peak and HR-based indices in patients with CAD [182, 191].

CHAPTER 3

SUMMARY OF THE METHODS

Chapter 3. Summary of the methods

Systematic reviews with meta-analyses and experimental methods were used to address the objectives of this doctoral thesis. The summary of both research methods will be presented separately below.

3.1. Systematic reviews with meta-analyses

The systematic reviews with meta-analyses were conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines [194], and the protocols were registered in the PROSPERO database.

3.1.1. Data search and sources

At least two electronic databases (biomedical [e.g., PubMed] and multidisciplinary [e.g., Web of Science]) were consulted to select the studies that fulfilled the inclusion criteria. Moreover, the reference lists of previous systematic reviews, as well as the articles included in the systematic reviews, were manually checked to find further studies that fulfilled the inclusion criteria. Besides that, correspondence authors of the included studies were emailed in an attempt to identify unpublished or ongoing studies. Other electronic searches were also performed to try to retrieve unpublished studies (e.g., conference proceedings on the Web of Science).

3.1.2. Study selection

The eligibility criteria were established according to the PICOS (*participants, intervention, comparison, outcomes, and study design*) guideline. The specific inclusion criteria of each systematic review with meta-analysis were the following:

Study 1

Male and female endurance-trained athletes (*participants*); overload training period (*intervention*); control group (CG) composed by non-overreached (non-OR) athletes (i.e., athletes with acute fatigue or athletes who maintained their training load) (the inclusion of a CG was not mandatory) (*comparison*); vagal-related HRV indices (i.e., RMSSD, HF, and/or SD_1) and/or HRR 1 min (*outcomes*); and randomised, non-randomised, controlled, and uncontrolled trials (*study design*).

Study 2

Male and female adult patients diagnosed with CAD (*participants*); supervised or home-based CR programmes based on aerobic training, resistance training, or combined aerobic and resistance training (*intervention*); usual care interventions without performing an exercise-based CR programme (*comparison*); vagal-related HRV indices (i.e., RMSSD and/or HF) and/or HRR 1 min assessed after a maximal test (*outcomes*); and randomised and non-randomised controlled trials (*study design*).

Study 3

Male and female adult patients diagnosed with CAD (*participants*); supervised CR programmes based on MCT or HIIT (*intervention*); usual care interventions without performing an exercise-based CR programme (the inclusion of a CG was not mandatory) (*comparison*); $\dot{V}O_2$ peak directly measured (outcome); and randomised, non-randomised, controlled, and uncontrolled trials (*study design*).

Study 4

Sedentary or physically active people and endurance-trained athletes regardless of the sex (*participants*); HRV-guided training (*intervention*); predefined training (*comparison*); HR-based indices (i.e., resting HR, vagal-related HRV indices [i.e., RMSSD, HF, and/or SD_1] and/or HRR 1 min) and/or $\dot{V}O_2$ max (*outcomes*); and randomised and non-randomised controlled trials (*study design*).

3.1.3. Data extraction, coding study characteristics, and potential moderator variables

Information regarding study characteristics (e.g., publication year), participant characteristics (e.g., age), intervention characteristics (e.g., aerobic training method), methodological conditions used for measuring HR-based indices (e.g., breathing control), and statistical information (e.g., mean ± *SD*) were coded. In study 3, the risk of a new event was established based on $\dot{V}O_2$ peak and left ventricular ejection fraction values at baseline [195]. Some coded characteristics were considered as potential moderator variables and, therefore, their influence on the training-induced effect on mortality predictors was analysed by carrying out heterogeneity analyses, which are presented below.

3.1.4. Risk of bias/methodological quality

The Cochrane Collaboration's core risk of bias [196] and PEDro scale [197] were used to assess the risk of bias or methodological quality, respectively. Selection, detection, attrition, and reporting bias were classified as low, unclear, or high risk of bias.

Two authors carried out the study selection, data extraction, and risk of bias/methodological quality assessment for validation processes. Disagreements between both reviewers were settled by consensus. When consensus was not achieved, a third author checked the information to reach an agreement.

3.1.5. Computation of effect sizes and statistical analyses

The standardised mean difference (SMD) and mean difference (MD) were used as effect size (ES) indices [198-201]. The group was the analysis unit in studies 1 and 3 and, therefore, within-group comparisons were performed to calculate SMD and MD, respectively. Besides, in studies 1 and 3, ES were estimated in the CG, and pooled analyses were carried out based on the training-

induced status (i.e., F-OR athletes and non-OR athletes) and the CR group (i.e., MCT, HIIT, and CG), respectively. In contrast, controlled trials were included in studies 2 and 4. Therefore, between-group comparisons were carried out to estimate SMD (i.e., vagal-related HRV indices) and MD (i.e., HRR 1 min) in study 2, as well as SMD in study 4. In the multi-intervention studies with a shared CG (i.e., predefined training) included in study 4, the number of participants in the CG was split-up to avoid inflation of the sample size [202]. Positive SMD and MD values showed an improvement of mortality predictors after the intervention/control situation (within-group comparisons) or an enhancement in favour of the experimental group (between-group comparisons). Random-effects models with the inverse variance as weighted factor were used to carry out pooled analyses [203]. A value of 0.7 was used to calculate the variance when pre- and post-intervention correlation values were not disclosed [204]. Meta-analyses to obtain pooled SMD (SMD_+) and pooled MD (MD_+) were performed based on the outcome measure to avoid statistical dependence. In addition, to avoid statistical dependence in the results of study 1, preferential measurements (e.g., maximal tests instead of submaximal tests) [205], assessment positions (e.g., standing position instead of supine position) [50], and vagal-related HRV indices (e.g., RMSSD instead of HF) [80] were established for selecting outcomes which were obtained from the same athletes. Finally, absolute values of vagal-related HRV indices were logarithmically transformed before calculating the SMD [206].

All analyses comprised calculating the pooled ES with its 95% confidence interval (CI), a heterogeneity statistical test, chi-square, and the I^2 index to evaluate the degree of homogeneity of the individual ES around the pooled ES [207-209]. The SMD magnitude was classified as trivial (< 0.2), small (0.2 – 0.6), moderate (0.61 – 1.2), large (1.21 – 2.0), or very large (> 2.0) [210]. Heterogeneity was interpreted depending on I^2 index magnitude as low, moderate, or high at 25%, 50%, and 75%, respectively [207, 208, 211]. In case of substantial inconsistency ($p \leq$ 050 and/or $I^2 \geq 50\%$) [211], heterogeneity analyses were carried out by using subgroup analysis or simple meta-regression based on the variable scale (i.e., categorial or continuous variable) [212]. In study 4, RMSSD and SD_1 were considered the same index ($RMSSD/SD_1$) to carry out the subgroup analysis based on the vagal-related HRV index used [213].

Several strategies were used to carry out sensitivity analyses (e.g., impact of including/excluding non-randomised trials). Moreover, funnel plots and Egger tests were used to carry out publication bias analyses [204, 214], while the trim-and-fill method was used for imputing missed ES in case of suspected publication bias [215]. Review Manager (RevMan) 5.3, Comprehensive Meta-Analysis 3.3, macros for SPSS, and STATA software were used to carry out the statistical analyses. Specific methodological aspects which were carried out on each systematic review with meta-analysis are summarised in Table 2.

Table 2. Specific methodological aspects of each systematic review

Study	Protocol registration	Unpublished studies search	Risk of bias/ methodological quality analyses	Sensitivity analyses	Publication bias analyses
Study 1	Yes	Yes	No	No	No
Study 2	Yes	Yes	Yes	Yes	Yes
Study 3	No	Yes	Yes	Yes	Yes
Study 4	Yes	Yes	Yes	Yes	Yes

3.2. Experimental study

3.2.1. Participants

Male and female adult patients diagnosed with CAD (e.g., AMI and angina pectoris) were included. Patients with other pathologies (e.g., unstable angina) and/or symptom-limited cardiopulmonary exercise test at baseline were excluded.

3.2.2. Study design

Study 5 was a parallel-group, double-blind, randomised controlled trial. Patients were interviewed and instructed to carry out daily HRV measurements at home. Daily HRV assessments were performed for 90 s in the supine position with spontaneous breathing immediately after waking up, and the last 60 s were used to calculate HRV [185]. A photoplethysmography smartphone application (HRV4Training) was used to measure daily HRV at home [187]. The study protocol was divided into two periods: a two-week baseline period and a six-week training period. After the baseline and training periods, a baseline assessment week and a final assessment week were conducted, respectively. After the baseline assessment week, patients were randomly allocated to the predefined training group (PRED-G) or to the HRV-guided training group (HRV-G) (Figure 4). Patients and assessors were blinded to the group allocation.

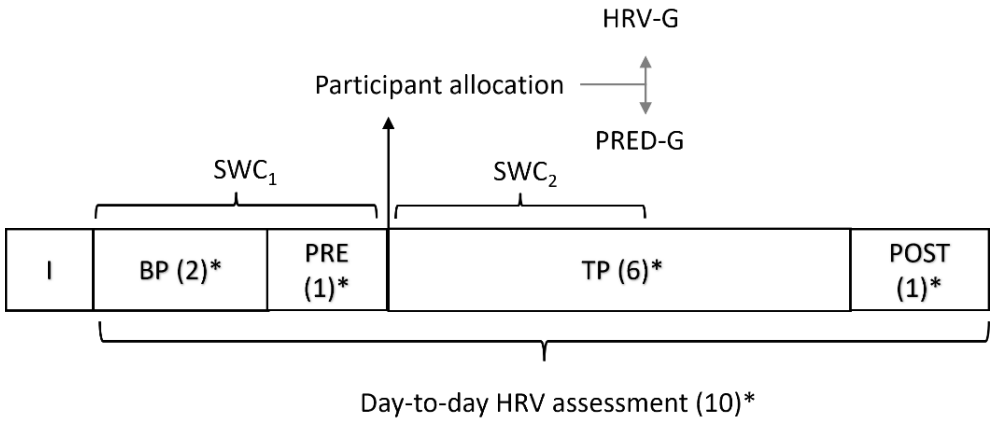

Figure 4. Experimental design. *BP*, baseline period; *HRV*, heart rate variability; *HRV-G*, heart rate variability-guided training group; *I*, interview; *POST*, final assessment week; *PRE*, baseline assessment week; *PRED-G*, predefined training group; SWC_1, smallest worthwhile change during the first three weeks of the study protocol; SWC_2, smallest worthwhile change during the first three weeks of the training period; *TP*, training period; *refers to the number of weeks

3.2.3. General procedures

All patients performed two low-intensity sessions per week during the baseline period (i.e., two weeks). Later, patients allocated to the PRED-G carried out a predefined exercise-based CR programme which combined MCT (i.e., 30 – 40 min between the first and second ventilatory threshold) and HIIT sessions (i.e., four × 4 min work bouts above the second ventilatory threshold interspersed with 4 min of active recovery below the first ventilatory threshold). Patients assigned to the HRV-G carried out training sessions based on their daily HRV measurements (i.e., HRV-guided training) following a decision schema (Figure 5). All patients trained three days a week during the training period (i.e., six weeks). RMSSD, which was logarithmically transformed (LnRMSSD), was selected as the vagal-related HRV index to perform HRV-guided training [14, 87]. The seven-day rolling average of RMSSD was also calculated [89]. During the first three weeks of the study protocol (i.e., baseline period and baseline assessment week), the SWC of the LnRMSSD was calculated (SWC_1). SWC was updated after the first three weeks of the training period (SWC_2). SWC_1 and SWC_2 were used to carry out training prescription for the first and the last three weeks of the training period, respectively (Figure 4).

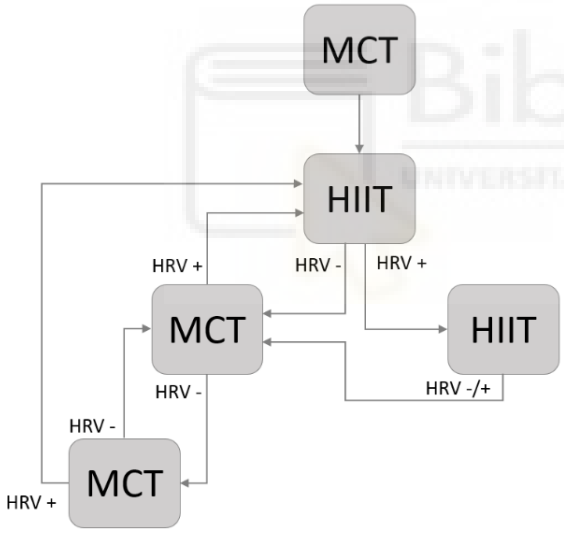

Figure 5. Heart rate variability-guided training schema. *HIIT*, high-intensity interval training; *HRV*, heart rate variability; *HRV -*, the log transformed seven-day rolling average of the root-mean-square difference of successive normal R-R intervals fell outside the smallest worthwhile change; *HRV +*, the log transformed seven-day rolling average of the root-mean-square difference of successive normal R-R intervals fell inside the smallest worthwhile change; *MCT*, moderate continuous training

Laboratory-based measurements of mortality predictors (i.e., HR-based indices and $\dot{V}O_2$ peak) were carried out during the assessment weeks (i.e., baseline and final assessment weeks). The procedures which were carried out for measuring mortality predictors are briefly explained below:

Peak oxygen uptake

$\dot{V}O_2$ peak was evaluated using a medically supervised maximal graded cycle ergometer exercise test (Excite Bike Med, Technogym, Cesena, Italy). A 1-min stage incremental exercise test to volitional exhaustion with 10 W work increments was performed. Respiratory gas exchange was measured by MasterScreen CPX (Jaeger, Hoechberg, Germany) and HR was monitored using a 12-lead electrocardiogram (Jaeger, Hoechberg, Germany). Breath by breath gas exchange

measurements were averaged every 15 s. The $\dot{V}O_2$ peak was defined as the maximum value of oxygen uptake reached at the end of the test.

Heart rate-based indices

Polar H7 chest strap (Polar Electro OY, Kempele, Finland) and Elite HRV app [216] were used to assess isolated vagal-related HRV indices. HRV assessments lasted 20 min, and the last 5 min were captured to calculate HRV indices. Measurements were performed in the supine position and patients were asked to control their breathing rate at ~ 12 breaths per min throughout the HRV assessments. Kubios HRV Software 2.0 for Windows (The Biomedical Signal Analysis Group, Kuopio, Finland) was used to obtain vagal-related HRV indices (i.e., RMSSD, HF, and SD_1). Fast-Fourier transform was used to calculate power spectral density. Apart from that, day-to-day RMSSD values measured at home across baseline and final assessment weeks (see 3.2.2 section for details) were averaged to obtain weekly averaged RMSSD. Finally, resting HR and HRR 1 min were assessed before and after the cycle ergometer exercise test, respectively, in the seated position. HRR 1 min was assessed during a low-intensity recovery period (i.e., 10 W).

3.2.4. Statistical analyses

G*Power was used to estimate the required sample size a priori (α = .050, 1 - β = .080). Statistical and graphical tools were used to check normality assumption before performing data analyses. The Fisher's exact test was used to carry out between-group comparisons in categorical variables at pre-intervention. Based on the normality assumption, parametrical (i.e., Student's *t* test) and non-parametrical (i.e., Wilcoxon's signed rank test and Mann-Whitney *U* test) tests were used to perform between- and within-group comparisons in continuous variables. The significance level was established at $p \leq .050$. In addition, comparisons between the two experimental groups were reported as differences in mean or median changes with 95% CI (PRED-G was used as the reference group). Finally, the effect of exercise-based CR, regardless of the training group, on mortality predictors was also estimated (i.e., mean or median change with 95% CI) if there was statistically non-significant between-group difference in the mean or median change ($p > .050$). The intention-to-treat principle was applied to perform data analyses. STATA software was used to carry out the statistical analyses.

CHAPTER 4

SUMMARY OF THE RESULTS

Chapter 4. Summary of the results

This chapter summarises the main results of this doctoral thesis, which will be presented according to the aims previously established.

4.1. Heart rate-based indices in functionally overreached athletes

4.1.1. Study selection and characteristics

Fifteen studies were included in the qualitative synthesis, of which, three were excluded from the quantitative synthesis [107, 217, 218]. Therefore, 12 studies were selected to carry out pooled analyses [116-118, 120-122, 219-224].

Out of all the studies included in the systematic review, 12 measured vagal-related HRV indices, of which, 10 reported RMSSD [107, 116, 118, 121, 122, 218-221, 223], eight HF [107, 117, 121, 217-221], and one SD_1 [221]. Five studies carried out laboratory-based measurements [117, 121, 122, 220, 223], four performed daily HRV assessments at home after waking up, mostly by using seven-day averaged HRV values (i.e., weekly averaged HRV) [107, 116, 118, 219], and three carried out nocturnal HRV assessments [217, 218, 221]. HRV assessments were performed in the supine position [121, 122, 220], in the standing position [118], as well as in standing and supine positions [107, 116, 219]. Only one study disclosed that the breathing rate was controlled during HRV assessments [117]. On the other hand, eight studies assessed PNS reactivation, of which, six measured HRR 1 min after a maximal test [107, 120, 220, 221, 223, 224], one after a submaximal test [222], and one after maximal and submaximal tests [118]. All studies carried out a passive recovery, mostly in the seated position, while one study carried out the recovery in the supine position [224].

4.1.2. Pooled and heterogeneity analyses for vagal-related heart rate variability indices

There was no increase in vagal-related HRV indices for F-OR athletes (p = .990). Moreover, there was no difference in changes in vagal-related HRV indices between F-OR and non-OR athletes (p = .600; I^2 = 0%). Nevertheless, the included studies' results for F-OR athletes were highly inconsistent (p < .001; I^2 = 83%). The subgroup analysis showed that there was a moderate increase in averaged vagal-related HRV indices (i.e., weekly averaged RMSSD) (number of analysis units [k] = 3; SMD_+ = 0.81 [95% CI = 0.35, 1.26]), and a small, statistically non-significant decrease in isolated vagal-related HRV indices (k = 5; SMD_+ = −0.45 [95% CI = −0.96, 0.06]) for F-OR athletes.

4.1.3. Pooled and heterogeneity analyses for heart rate recovery

There was a moderate increase in HRR 1 min for F-OR athletes (k = 6; SMD_+ = 0.65 [95% CI = 0.44, 0.87]) and no change for non-OR athletes (k = 4; SMD_+ = 0.10 [95% CI = −0.15, 0.34]). In addition, there was no inconsistency in changes in HRR 1 min for F-OR (p = .620; I^2 = 0%) and non-OR athletes (p = .730; I^2 = 0%). The subgroup analysis showed that there was difference in

changes in HRR 1 min between F-OR and non-OR athletes ($p < .001$; $I^2 = 91\%$). Even though there was no inconsistency in changes in HRR 1 min for F-OR athletes, subgroup analyses showed that there was a small, statistically non-significant increase in HRR 1 min after submaximal tests (k = 2; $SMD_+ = 0.36$ [95% CI = −0.33, 1.04]), and a moderate increase after maximal tests (k = 5; $SMD_+ = 0.64$ [95% CI = 0.39, 0.89]).

4.2. Exercise-based cardiac rehabilitation and heart rate based-indices

4.2.1. Study selection and characteristics

Twenty-five studies were included in the qualitative synthesis, of which, four were excluded from the quantitative synthesis [225-228]. Therefore, 21 studies were selected to carry out pooled analyses [229-249].

All the studies included in the systematic review carried out aerobic training, of which, three also performed resistance training (i.e., combined aerobic and resistance training) [229, 233, 239]. Regarding the aerobic training method, 23 studies applied MCT and two performed HIIT [240, 244], hindering the possibility of analysing changes in HR-based indices based on the aerobic training method. In regard to vagal-related HRV indices, 15 studies used HF [225, 226, 228, 230, 234-238, 240, 241, 243-246] and five reported RMSSD [237, 240, 241, 243, 244]. All the included studies used isolated vagal-related HRV indices. Four studies performed 24-hour ambulatory HRV monitoring [225, 226, 240, 244] and 11 carried out laboratory-based measures [228, 230, 234-238, 241, 243, 245, 246], mainly in the supine position, of which, seven did not control the breathing rate throughout HRV assessments [230, 234, 236-238, 243, 246], three controlled the breathing rate [228, 235, 241], and one did not explicitly disclose this information [245]. Regarding PNS reactivation, 10 studies assessed HRR 1 min after a maximal test [227, 229, 231-233, 239, 242, 247-249], of which, five carried out an active recovery [233, 239, 247-249], one performed a passive recovery while patients were seated [242], and four did not report this information [227, 229, 231, 232].

4.2.2. Effect of exercise-based cardiac rehabilitation on vagal-related heart rate variability indices

There was no difference between the exercise-based CR group and the CG for improving HF (k = 12; $SMD_+ = 0.14$ [95% CI = −0.12, 0.40]), though the results of the included studies showed moderate to high heterogeneity ($p < .001$; $I^2 = 70\%$). Nonetheless, there was no influence of any of the analysed moderator variables on the training-induced effect on HF ($p > .050$). On the other hand, there was a small increase in RMSSD in the exercise-based CR group compared with the CG (k = 5; $SMD_+ = 0.30$ [95% CI = 0.12, 0.49]), and the results of the included studies showed no inconsistency ($p = .430$; $I^2 = 0\%$).

4.2.3. Effect of exercise-based cardiac rehabilitation on heart rate recovery

There was an increase in HRR 1 min in the exercise-based CR group compared with the CG (k = 9; MD_+ = 5.35 bpm [95% CI = 4.08, 6.61]). Nonetheless, the results of the included studies showed high heterogeneity ($p < .001$; I^2 = 85%). Meta-regressions showed that the effect of exercise-based CR on HRR 1 min was higher in studies which included younger patients (k = 8; regression coefficient [*B*] = −0.33; $p = .008$).

4.2.4. Sensitivity analyses and publication bias

There was no influence of the study design (i.e., randomised vs. non-randomised studies), outliers, and imputed correlation values on the findings. In addition, there was no evidence of publication bias.

4.3. Exercise-based cardiac rehabilitation and peak oxygen uptake

4.3.1. Study selection and characteristics

Twenty-nine studies were included in the qualitative and quantitative syntheses [191, 231, 241, 245, 250-274], of which, 27 were randomised trials and two were non-randomised [271, 272]. The included studies allowed us to define 26, 14, and 14 analysis units (i.e., groups) in which patients performed MCT, HIIT, or did not carry out exercise training (i.e., CG), respectively. Out of all the HIIT groups, nine performed long intervals of high intensity (i.e., ≥ 3 min) [191, 250, 253, 262, 264, 265, 267, 268, 270], two combined long and short intervals [263], and three carried out short intervals [252, 254, 273].

4.3.2. Effect of exercise-based cardiac rehabilitation on peak oxygen uptake

There were improvements in $\dot{V}O_2$ peak after MCT (k = 26; MD_+ = 3.36 $ml \cdot kg^{-1} \cdot min^{-1}$ [95% CI = 2.96, 3.76]) and HIIT (k = 14; MD_+ = 4.61 $ml \cdot kg^{-1} \cdot min^{-1}$ [95% CI = 4.02, 5.19]), while no changes were found in the CG (k = 14; MD_+ = 0.12 $ml \cdot kg^{-1} \cdot min^{-1}$ [95% CI = −0.31, 0.55]). Furthermore, the enhancement in $\dot{V}O_2$ peak was higher after HIIT than after MCT ($p < .001$). The results of the included studies of the effect of MCT on $\dot{V}O_2$ peak showed moderate inconsistency ($p < .001$; I^2 = 67%). Table 3 summarises the influence of the analysed categorical variables on the MCT-induced on $\dot{V}O_2$ peak. Briefly, there were higher improvements in $\dot{V}O_2$ peak in studies in which patients carried out training sessions on a bicycle and in those studies including patients with worse prognosis (i.e., patients with higher risk of a new event, patients with AMI, and patients who waited less time to start exercise-based CR). Meta-regressions showed that there were higher improvements in $\dot{V}O_2$ peak in studies which included patients with lower CRF at baseline ($B = −0.10$; $p = .025$). Finally, the effect of MCT on $\dot{V}O_2$ peak was higher in non-randomised studies than in randomised studies ($p = .002$; I^2 = 90%).

4.3.3. Sensitivity analyses and publication bias

There was lower MCT-induced effect on $\dot{V}O_2$ peak after removing the two non-randomised studies (k = 24; MD_+ = 3.23 ml·kg^{-1}·min^{-1} [95% CI = 2.81, 3.65]). Regarding publication bias, the Egger test reached statistical significance (p = .022) for the effect of MCT on $\dot{V}O_2$ peak. Nevertheless, the trim-and-fill method imputed no ES.

Table 3. Influence of categorical variables on the effect of moderate continuous training on peak oxygen uptake

					Subgroup analyses	
Moderator variable	**Category**	***k***	**MD_+**	**95% CI**	***p***	**I^2 (%)**
Training mode	Treadmill	6	1.63	0.82, 2.44	< .001	90
	Cycling	16	3.71	3.32, 4.09		
	Mixed	3	3.42	1.72, 5.15		
Risk of a new event	Low	5	2.40	1.26, 3.54	.010	77
	Moderate	14	3.04	2.40, 3.67		
	High	7	3.96	3.46, 4.46		
Type of cardiovascular event	AMI	15	3.82	3.42, 4.22	.009	85
	Mixed	10	2.60	1.76, 3.44		
Wait time to start exercise-based CR	≤ 3 weeks	10	4.05	3.68, 4.42	.010	77
	4 – 12 weeks	7	3.10	2.16, 4.04		
	> 12 weeks	4	2.04	0.46, 3.62		

95% CI, 95% confidence interval; *AMI*, acute myocardial infarction; *CR*, cardiac rehabilitation; I^2, heterogeneity index; *k*, number of analysis units; MD_+, pooled mean difference; *p*, probability level associated to the chi-square statistic

4.4. Heart rate variability-guided training in healthy people

4.4.1. Study selection and characteristics

Eight studies fulfilled our inclusion criteria and were selected to perform the qualitative and quantitative syntheses [141-148]. Kiviniemi et al. [146] included three experimental groups and two CG, allowing us to define 10 analysis units. Seven studies were randomised and one was non-randomised [143]. Most of the included studies exclusively recruited males. Out of all the selected studies, one included sedentary females [144], one recruited physically active adults [146], and six included endurance-trained athletes [141-143, 145, 147, 148]. RMSSD was used in five studies to carry out HRV-guided training [142-145, 147], while SD_1 and HF were used in one [146] and two studies [141, 148], respectively. Regarding the assessment of cardiac-vagal activity, one study measured HRR 1 min after a maximal test [144], four measured resting HR [141, 146-148], and five assessed resting vagal-related HRV indices, of which, two used HF as HRV index [141, 148] and three used RMSSD [144, 147] or SD_1 [146]. Out of all the studies which assessed changes in resting HR-based indices, only two explicitly disclosed that participants breathed spontaneously during measurements [144, 146], while the remaining studies did not report this information. Four studies used averaged values (e.g., three – seven values) [141, 144, 146, 147] and one used isolated and 21-day averaged values at pre- and post-intervention [148], respectively. Four studies assessed resting HR-based indices in the standing position [141, 144, 146, 148]. Therefore, even though other positions were also used (e.g., supine

and sitting positions) [141, 148], only standing HR-based indices were pooled. Regarding $\dot{V}O_2$ max, seven studies performed an incremental cardiopulmonary exercise test for assessing CRF [141-143, 145-148].

4.4.2. Effect of heart rate variability-guided training on heart rate-based indices

There was no difference between HRV-guided training and predefined training for improving vagal-related HRV indices (p = .590) or resting HR (p = .820). Nonetheless, there was moderate inconsistency for vagal-related HRV indices (p = .040; I^2 = 58%). The subgroup analysis showed that there was a small enhancement in RMSSD/SD_1 (k = 4; SMD_+ = 0.50 [95% CI = 0.09, 0.91]) and a small decrement in HF (k = 2; SMD_+ = −0.60 [95% CI = −1.15, −0.05]) after an HRV-guided training programme compared with a predefined training programme. Additionally, there was no inconsistency for RMSSD/SD_1 (p = .710; I^2 = 0%) and HF (p = .660; I^2 = 0%).

4.4.3. Effect of heart rate variability-guided training on maximum oxygen uptake

There was no difference between HRV-guided training and predefined training for enhancing $\dot{V}O_2$ max (k = 9; SMD_+ = 0.13 [95% CI = −0.12, 0.39]). Besides, the results of the included studies were homogeneous (p = .890; I^2 = 0%), showing no influence of the participant characteristics or methodological approaches/criteria on the effect of HRV-guided training on $\dot{V}O_2$ max.

4.5. Heart rate variability-guided training in exercise-based cardiac rehabilitation

4.5.1. Study participants

Twenty-three patients, of which 21 were male and two were female, were randomly allocated to the HRV-G (number of participants [n] =11) or to the PRED-G (n = 12) after the baseline assessment week, of which, two dropped out the study. Finally, a total of 10 and 11 patients completed the study in the HRV-G and PRED-G, respectively. The percentage of diabetic patients was lower in the HRV-G (0%) than in the PRED-G (46%) (p = .035).

4.5.2. Effect of heart rate variability-guided training on mortality predictors

Table 4 summarises the effect of HRV-guided training and predefined training on mortality predictors. Accounting for methodological factors, the results showed that there was difference between the two experimental groups in weekly averaged RMSSD (p = .034), finding an increase in weekly averaged RMSSD in favour of the HRV-G compared with the PRED-G (mean change difference = 10.36 ms [95% CI = 0.80, 19.92]). There was an increase in weekly averaged RMSSD in the HRV-G (n = 10; mean change = 7.57 ms [95% CI = 0.48, 14.64]), while there was no change in the PRED-G (n = 11; mean change = −2.79 ms [95% CI = −10.13, 4.55]). In contrast, there were no differences between HRV-guided training and predefined training for improving isolated vagal-related HRV indices (i.e., RMSSD, HF, and SD_1), resting HR, HRR 1 min, and $\dot{V}O_2$ peak (p > .050).

4.5.3. Effect of exercise-based cardiac rehabilitation on mortality predictors

Regardless of the training prescription method, there were improvements in resting HR (n = 21; mean change = −4.10 bpm [95% CI = −6.37, −1.82]) and $\dot{V}O_2$ peak (n = 21; mean change = 3.04 $ml \cdot kg^{-1} \cdot min^{-1}$ [95% CI = 1.70, 4.37]) after exercise-based CR, but there was no change in HRR 1 min (n = 21; mean change = 0.81 bpm [95% CI = −0.36, 1.98]), in patients with CAD.

Table 4. Effect of heart rate variability-guided training and predefined training on mortality predictors

Variable	Group	Pre	Post	MCD (95% CI)	*p*
RMSSD (ms)	HRV-G	41.9 ± 34.0	39.1 ± 29.1	−3.86 (−13.93, 6.21)	.431
	PRED-G	28.4 ± 11.8	29.4 ± 10.2		
HF (ms^2)	HRV-G	649.5 (190.3, 1269.0)	353.5 (197.5, 627.0)	−84.50[#] (−649.75, 480.75)	.770
	PRED-G	272.0 (151.3, 663.0)	480.5 (188.5, 670.3)		
SD_1 (ms)	HRV-G	29.7 ± 24.1	27.5 ± 20.7	−2.77 (−9.99, 4.45)	.430
	PRED-G	20.1 ± 8.3	20.7 ± 7.1		
Averaged RMSSD (ms)	HRV-G	49.7 ± 16.0	57.3 ± 18.3	10.36 (0.80, 19.92)	.034
	PRED-G	57.6 ± 20.0	54.8 ± 19.8		
Resting HR (bpm)	HRV-G	63.0 ± 9.1	57.2 ± 10.6	−3.25 (−7.68, 1.17)	.140
	PRED-G	64.7 ± 5.0	62.2 ± 7.3		
HRR 1 min (bpm)	HRV-G	22.7 ± 12.3	22.8 ± 11.8	−1.35 (−3.67, 0.96)	.235
	PRED-G	17.6 ± 6.8	19.1 ± 5.7		
$\dot{V}O_2$ peak ($ml \cdot kg^{-1} \cdot min^{-1}$)	HRV-G	24.9 ± 5.3	28.0 ± 6.4	−0.25 (−3.01, 2.51)	.851
	PRED-G	25.0 ± 5.7	28.1 ± 6.0		

95% CI, confidence interval; *HF*, high frequency; *HR*, heart rate; *HRR 1 min*, heart rate recovery 1 min; *HRV-G*, heart rate variability-guided training group; *MCD*, mean change difference; *PRED-G*, predefined training group; *RMSSD*, the root-mean-square difference of successive normal R-R intervals; *SD_1*, the standard deviation of instantaneous beat-to-beat R-R interval variability; *$\dot{V}O_2$ peak*, peak oxygen uptake

Data at pre- and post-intervention are shown as mean ± standard deviation or median (25th and 75th percentiles); *p* values refer to between-group difference in mean or median changes

[#]Indicates median change difference instead of mean change difference

CHAPTER 5

SUMMARY OF THE DISCUSSIONS

Chapter 5. Summary of the discussions

The studies included in this doctoral thesis were aimed a) to investigate the influence of methodological factors (e.g., assessment position and breathing rate) on the sensitivity of HR-based indices (i.e., vagal-related HRV indices and HRR 1 min) for detecting changes in PNS activity, and b) to study the effect of exercise-based CR (i.e., predefined training and HRV-guided training) on mortality predictors (i.e., HR-based indices and $\dot{V}O_2$ peak) in patients with CAD.

5.1. Sensitivity of heart rate-based indices

The current results show that weekly averaged RMSSD is sensitive for detecting increased PNS modulation in F-OR athletes after an overload training period, while isolated vagal-related HRV indices are insensitive (i.e., high heterogeneity). These findings agree with the results reported in previous studies [87-90]. The use of averaged HRV values allows to control day-to-day HRV lability, which seems to be mainly generated by enhanced PNS outflow after exercise [53]. On the other hand, it should be noted that all the included studies which used averaged vagal-related HRV indices also captured resting HR-based indices in the standing position, which limits the scope of the subgroup analysis based on the assessment position. Nevertheless, based on previous evidence, the standing position instead of other positions should be used to avoid saturation of acetylcholine receptors in people with heightened PNS tone (e.g., endurance athletes). Saturation of these receptors diminishes PNS modulation and, therefore, could reduce the sensitivity of vagal-related HRV indices to detect increased PNS modulation [50, 82, 84, 85]. In this regard, Le Meur et al. [107] and Bellenger et al. [116], who directly compared averaged vagal-related HRV indices based on the assessment position, found PNS hyperactivity only when HRV measurements were carried out in the standing position.

Previous systematic reviews and meta-analyses also investigated the sensitivity of vagal-related HRV indices to detect increased PNS modulation in F-OR athletes [105, 106]. Bellenger et al. [105] found an increase of vagal-related HRV indices after performing a subgroup analysis based on the vagal-related HRV index used. These authors reported increased RMSSD values in F-OR athletes, while no changes were noticed in HF or SD_1. These findings should be interpreted with caution due to statistical dependence problems. Nonetheless, the higher sensitivity of RMSSD to detect increased PNS modulation could be due to the lower influence of breathing patterns on this vagal-related HRV index [275]. In the present study, a subgroup analysis based on the vagal-related HRV index used was not performed to avoid statistical dependence problems since some studies reported several vagal-related HRV indices (e.g., RMSSD and HF) obtained from the same athletes. In summary, our findings (study 1), as well as previous evidence, seem to support the use of averaged RMSSD values obtained in the standing position for detecting PNS hyperactivity in F-OR athletes. Nonetheless, there is evidence that shows that the response of PNS modulation to overload training in F-OR athletes is not uniform (e.g., decreased PNS activity)

[89, 276-279]. Therefore, no increased or decreased PNS modulation in F-OR athletes could also help to explain the controversial findings of previous studies about the sensitivity of vagal-related HRV indices to detect PNS hyperactivity.

Regarding PNS reactivation, the current findings show that HRR 1 min is sensitive for inferring increased PNS tone in F-OR athletes. This finding agrees with the results reported in a previous systematic review with meta-analysis [105]. In addition, the results of the included studies did not show inconsistency, which exhibits no influence of methodological factors on the sensitivity of HRR 1 min for inferring PNS hyperactivity. Nonetheless, most of the included studies (83%) performed a maximal test before measuring HRR 1 min, which may help to explain the low heterogeneity. Therefore, even though no inconsistency was found, heterogeneity analyses were performed based on the previously established potential methodological factors in measuring HRR 1 min (e.g., exercise requirement and training variable increased). Interestingly, although subgroup comparisons were not performed to avoid statistical dependence, the findings showed that HRR 1 min measured after carrying out a submaximal test is insensitive to detect PNS hyperactivity in F-OR athletes. Nonetheless, only two pooled studies carried out a submaximal test for measuring HRR 1 min [118, 222]. Hammes et al. [222] and Le Meur et al. [280], who were excluded from the quantitative synthesis because they reported insufficient data, found that HRR 1 min assessed after a submaximal test (e.g., 60% of maximal aerobic speed) is sensitive to detect PNS hyperactivity in F-OR athletes. In contrast, Bellenger et al. [118] only found that HRR 1 min is sensitive to detect increased PNS activity in F-OR athletes after a maximal test. However, the intensity of submaximal tests was prescribed in absolute values (i.e., 160 W and 200 W), and the relative intensity was not reported. Therefore, the prescribed intensity could be lower than the minimal intensity required for inferring PNS hyperactivity, which requires future studies. Furthermore, HRR 1 min was measured in the seated position in most of the included studies (75%) and, therefore, the influence of the assessment position on the sensitivity of HRR 1 min was not analysed. In this regard, Thomson et al. [224], who assessed PNS reactivation in the supine position, also reported increased HRR 1 min in F-OR athletes. Therefore, HRR 1 min measured after a maximal test in the seated position seems to be sensitive for inferring increased PNS tone in F-OR athletes, while the sensitivity of HRR 1 min after a submaximal test should be addressed in future studies to determine the minimal intensity required to detect increased PNS tone.

The data provided above seem to support the hypothesis of increased PNS activity in F-OR athletes [107, 111, 281, 282]. Furthermore, the sensitivity of vagal-related HRV indices to detect increased PNS modulation seems to be affected by methodological factors in measuring these indices, which should be considered to infer training-induced fatigue status after an overload training period in F-OR athletes properly.

5.2. Effect of exercise-based cardiac rehabilitation on mortality predictors

5.2.1. Exercise-based cardiac rehabilitation

The present findings show that CR, based mainly on aerobic training (i.e., MCT), is a non-pharmacological treatment for improving PNS tone (i.e., HRR 1 min) in patients with CAD, which is in line with the results obtained in patients with CHF [283]. Additionally, patient characteristics (e.g., age) seem to be related to the training-induced effect on HRR 1 min, which is discussed below. However, the effect of exercise-based CR programmes on PNS modulation, based on the vagal-related HRV index used (i.e., RMSSD or HF), was controversial. While increased RMSSD was found after exercise-based CR, no changes were noticed in HF. In addition, the results of the included studies of the training-induced effect on HF were inconclusive. Nonetheless, none of the analysed moderator variables were related to the training-induced effect on HF. The qualitative synthesis revealed that all included studies used isolated vagal-related HRV indices for inferring PNS modulation. Based on our findings with F-OR athletes (study 1) and previous evidence [87-90], the use of isolated vagal-related HRV indices could diminish the sensitivity of vagal-related HRV indices for inferring changes in PNS activity. In addition, only two studies, which used HF as vagal-related HRV index, disclosed that the breathing rate was controlled during HRV assessments [235, 241]. In this regard, spontaneous breathing could increase day-to-day HRV lability [80]. Therefore, the use of isolated HRV values and the lack of breathing control during HRV assessments in studies which used HF may help to explain the controversial findings of the included studies about the training-induced effect on PNS modulation. On the other hand, there is evidence showing that the effect of exercise training on vagal-related HRV indices could be affected by the PNS status at baseline [129, 138], which may also explain the controversial findings. Therefore, solid conclusions could not be drawn about the effect of exercise-based CR on PNS modulation. Nonetheless, improvements in RMSSD after exercise-based CR seem to support enhanced PNS modulation in patients with CAD, which has been also previously reported in diseased [182, 283] and healthy individuals [189].

Concerning CRF, CR programmes based on either MCT or HIIT enhanced $\dot{V}O_2$ peak in patients with CAD, which agrees with previous evidence [172, 173]. Moreover, HIIT was more effective than MCT for enhancing $\dot{V}O_2$ peak in patients with CAD, which has already been widely reported [174-180]. The superiority of this aerobic training method for increasing $\dot{V}O_2$ peak could be due to higher improvement in contractility and hypertrophy of the cardiomyocyte after HIIT than after MCT [284]. Interestingly, the results of the included studies of the effect of HIIT on $\dot{V}O_2$ peak were conclusive (i.e., no heterogeneity). However, most of the studies performed long HIIT intervals (e.g., four bouts of 4 min at high intensity [e.g., > 85% of maximal HR] interspersed with 3-min recovery periods), while the effect of other HIIT protocols (e.g., short intervals) on $\dot{V}O_2$ peak has been less investigated. In addition, the effect of HIIT on $\dot{V}O_2$ peak was not tested

in patients with worse prognosis at baseline (e.g., patients with high risk of a new event or patients with low CRF), which could also explain the low heterogeneity of the effect of HIIT on this mortality predictor. In contrast, the results of the included studies of the effect of MCT on $\dot{V}O_2$ peak were inconclusive (i.e., moderate heterogeneity). As it has been aforementioned, inconclusive findings were also observed about the training-induced effect on HRR 1 min in patients with CAD. It should be remarked that all the included studies which analysed the effect of exercise-based CR on HRR 1 min also used MCT as aerobic training method, alone or combined with resistance training. These findings show the influence of potential moderator variables (e.g., patient and training characteristics) on the MCT-induced effect on mortality predictors, which is discussed beneath.

There is evidence that shows that participant characteristics (e.g., wait time to start exercise-based CR [190, 285, 286], participant age [189, 287], and CRF at baseline [192]) are related to the training-induced effect on mortality predictors in healthy and diseased people. In agreement with this previous evidence, our heterogeneity analyses showed that the effect of MCT on $\dot{V}O_2$ peak was higher in studies which included patients who had to wait less time to start exercise-based CR. The greater training-induced effect of earlier CR programmes on CRF could be due to a faster clearance of dead cells from the infarcted zone at the beginning of the recovery period [288]. In the same line, even though statistical significance was not reached (p = .080), heterogeneity analyses also showed that the training-induced effect on HRR 1 min was higher in those patients who had to wait less than three months to start exercise-base CR. It should be noted that the wait time to start exercise-based CR was dichotomised, which reduces the statistical power of the test to reach statistical significance [289]. In addition, our findings showed that the improvement in HRR 1 min after exercise-based CR seems to be higher in younger patients with CAD. Sandercock et al. [189] also reported smaller changes in R-R interval in older participants. The lower training-induced effect on PNS activity could be due to cardiovascular and ANS alterations as a result of ageing [290], which may limit the ANS response to training in old people compared with young people. Furthermore, the improvement in $\dot{V}O_2$ peak was higher in those studies which included patients with lower CRF or worse prognosis at baseline (e.g., patients with higher risk of a new event or patients with AMI). In this regard, Støren et al. [192] also found higher improvement in $\dot{V}O_2$ max in sedentary healthy people with worse training status at pre-intervention. Therefore, based on this evidence, MCT should be used as aerobic training method in exercise-based CR programmes aiming to improve $\dot{V}O_2$ peak in patients with worse prognosis.

On the other hand, previous studies pointed out that, regarding participant characteristics, genetics is the main contributor of exercise training response variability. Thus, modifiable methodological factors like training characteristics (e.g., type of exercise, intensity, and training prescription method [i.e., HRV-guided training or predefined training]) should be properly managed to reduce

the heterogeneity in the response to exercise-based CR programmes [131, 153]. In this regard, our analyses showed higher $\dot{V}O_2$ peak improvements in studies in which patients performed training sessions on a bicycle, which has also been previously reported [291]. Nonetheless, bicycle tests require patient adaptation to avoid muscular limitations that would not allow patients to reach their maximum cardiovascular capacity at baseline. Thus, adaptation to cycle ergometer throughout the intervention period may help to explain the higher enhancement in $\dot{V}O_2$ peak when exercise tests and training sessions are performed on a bicycle. On the other hand, the influence of the aerobic training method (i.e., HIIT vs. MCT) on the training-induced effect on HRR 1 min was not analysed because all the included studies carried out a CR programme based on MCT. Pattyn et al. [178] included in their meta-analysis studies which directly compared the effect of MCT and HIIT on HRR 1 min in patients with CAD or patients with CHF. These authors did not find differences between the two aerobic training methods for enhancing HRR 1 min.

Regarding other training characteristics (e.g., training frequency and intervention length), the analysed training variables showed no influence on the effect of exercise-based CR on mortality predictors, which is line with previous evidence [173, 292]. Nonetheless, Vanhees et al. [293] showed that a proper manipulation of the training variables (e.g., volume, training frequency, and intervention length) may help to reach long-term adaptations. In this regard, Sarabia et al. [294] highlighted that training prescription in exercise-based CR programmes was not properly performed in previous studies, which could limit the influence of the training variables on the training-induced effect on mortality predictors. Additionally, other limitations regarding training prescription have been previously reported. For instance, Conraads et al. [191] found differences between the prescribed and performed aerobic training intensity in patients who took part in HIIT sessions. Therefore, the performed intensity instead of the prescribed intensity should be reported to carry out dose-response analyses properly. Finally, the influence of the training prescription method on the training-induced effect on mortality predictors will be discussed in the next section, when HRV-guided training is taken into consideration to carry out exercise-based CR programmes in patients with CAD.

5.2.2. Heart rate variability-guided training

Taking methodological factors into account, the current results show that HRV-guided training seems to be superior to predefined training for improving PNS modulation, assessed by averaged RMSSD/SD_1, in healthy people (i.e., sedentary or physically active people and endurance-trained athletes). Nonetheless, there were controversial findings based on the vagal-related HRV index used for inferring PNS modulation (i.e., increased RMSSD/SD_1 and decreased HF after HRV-guided training compared with predefined training). It should be noted that RMSSD and SD_1 were averaged across three – seven days [144, 146], which enhances the validity of these vagal-related HRV indices [90]. Besides, regarding studies which used HF as vagal-related HRV index, isolated

values at pre-intervention were used [148], and the control of the breathing pattern throughout HRV assessments was not explicitly disclosed [141, 148], which could decrease the validity of HF [80, 275]. This evidence supports the idea that HRV-guided training enhances PNS modulation to a greater extent than predefined training. Interestingly, the results of our experimental study also showed that there is difference between the two training prescription methods for increasing PNS modulation, assessed by weekly averaged RMSSD, in patients with CAD. HRV-guided training enhanced weekly averaged RMSSD, while no changes in this variable were noticed after a predefined training programme. These findings agree with those reported by da Silva et al. [144], who used three-day averaged RMSSD as vagal-related HRV index. In this regard, Plews et al. [90] reported that a minimum of three values should be averaged for a valid assessment. Our systematic reviews showed that most of the included studies, as well as our experimental study, used weekly averaged RMSSD as vagal-related HRV index. Therefore, whether less than seven values are suitable to reflect changes in PNS modulation requires future study. On the other hand, our findings showed that there were no differences between the two training prescription methods for improving PNS modulation in patients with CAD when isolated vagal-related HRV indices were used (i.e., RMSSD, HF, or SD_1), which could be due to the influence of environmental conditions or hypervolemia on a single-day HRV value [53, 76]. Therefore, based on our findings with F-OR athletes (study 1) and previous evidence, which support the use of averaged RMSSD as vagal-related HRV index [36, 80, 87-90, 295], HRV-guided training seems to be more suitable than predefined training for improving PNS modulation and, therefore, for reducing mortality risk in patients with CAD. Interestingly, as it has been commented above, the status of the PNS could affect the response to exercise training [129, 138]. In this regard, as it has been found in this doctoral thesis, HRV-guided training, which considers the PNS status to carry out training prescription, could overcome the limitations of predefined CR programmes for enhancing PNS modulation.

In contrast, there were no differences between HRV-guided training and predefined training for enhancing HRR 1 min and resting HR, regardless of the population. It should be noted that only one study, which included sedentary healthy females, compared the effect of the two training prescription methods on HRR 1 min [144]. Nonetheless, in contrast to vagal-related HRV indices, the results of our meta-analysis (study 2) and previous studies [283] showed that predefined CR programmes enhance HRR 1 min, which may help to explain the absence of differences between HRV-guided training and predefined training for increasing PNS tone. Surprisingly, the results of our experimental study showed that predefined and HRV-guided training did not enhance HRR 1 min in patients with CAD. Nonetheless, patients included in the experimental study showed high HRR 1 min (mean ± *SD* = 20.0 ± 9.9 bpm) before starting the exercise-based CR programme, even though PNS reactivation was assessed during an active recovery period, which

diminishes HRR 1 min [98, 99]. Finally, in agreement with previous evidence [296, 297], there was a reduction in resting HR after exercise-based CR programmes, which shows increased PNS tone [50].

Regarding CRF, the effect of exercise training on this variable was not related to the training prescription method used, which is in line with previous evidence [150, 151]. However, Granero-Gallegos et al. [149] reported that HRV-guided training is more effective than predefined training for improving $\dot{V}O_2$ max in endurance-trained athletes. Nonetheless, comparison between the two training prescription methods was not performed, which limits the scope of their findings. In the same line, Behrens et al. [188], who included patients with CHF, only found improvements in $\dot{V}O_2$ peak after a four-week CR programme based on HRV-guided training, while no changes were noticed after a predefined training programme. In the same line as in patients with CAD, there is evidence that shows that predefined CR programmes enhance $\dot{V}O_2$ peak in patients with CHF [298, 299]. Nevertheless, in contrast to what happened with patients with CAD, Rees et al. [300] reported lower enhancements in $\dot{V}O_2$ peak after shorter interventions in patients with CHF. Therefore, based on the results reported by Behrens et al. [188] and Rees et al. [300], HRV-guided training could induce faster improvements in $\dot{V}O_2$ peak in patients with CHF, who seem to need longer intervention periods to boost $\dot{V}O_2$ peak. Finally, the findings of our current experimental study showed that exercise-based CR programmes enhance $\dot{V}O_2$ peak in patients with CAD, which agrees with the results of our meta-analysis (study 3) and previous evidence [172, 173].

Concerning the individual response to exercise-based CR, as Figure 6 shows, the number of patients who increased weekly averaged RMSSD was higher in the HRV-G (70%) than in the PRED-G (27%), showing less heterogeneity of the individual changes in response to HRV-guided training than in response to predefined training. These findings agree with those previously reported of the effect of HRV-guided training on endurance performance [143] and $\dot{V}O_2$ max [141] in endurance-trained athletes. However, the heterogeneity of individual changes in other mortality predictors (i.e., resting HR, HRR 1 min, and $\dot{V}O_2$ peak) was similar after HRV-guided training and predefined training. Therefore, it seems that HRV-guided training could enhance vagal-related HRV indices and reduce the heterogeneity of individual changes to a higher extent than predefined training. Nonetheless, future studies should be carried out to confirm these findings.

In conclusion, the results of the current systematic reviews show that the control of methodological factors in measuring vagal-related HRV indices is of highest importance to increase the validity of these HR-based indices. In this regard, the control of the breathing rate throughout HRV measurements is not common in both athletes and patients with CAD. Moreover, most of the studies carried out with patients with CAD used HF as vagal-related HRV index, as well as basing their findings on isolated vagal-related HRV indices, which could limit their

results. In contrast, the use of RMSSD and averaged vagal-related HRV indices (i.e., weekly averaged RMSSD) is more common in studies performed with athletes, which could overcome limitations of vagal-related HRV indices due to spontaneous breathing during HRV assessments. Moreover, our findings (study 2 and 3) and previous evidence showed that predefined CR programmes enhance PNS tone (i.e., HRR 1 min) and CRF (i.e., $\dot{V}O_2$ peak) in patients with CAD, while the training-induced effect on PNS modulation (i.e., vagal-related HRV indices) seems to be more limited or at least controversial. In this regard, HRV-guided training could be a useful training prescription method for overcoming the limitations of predefined CR programmes and improving PNS modulation in patients with CAD.

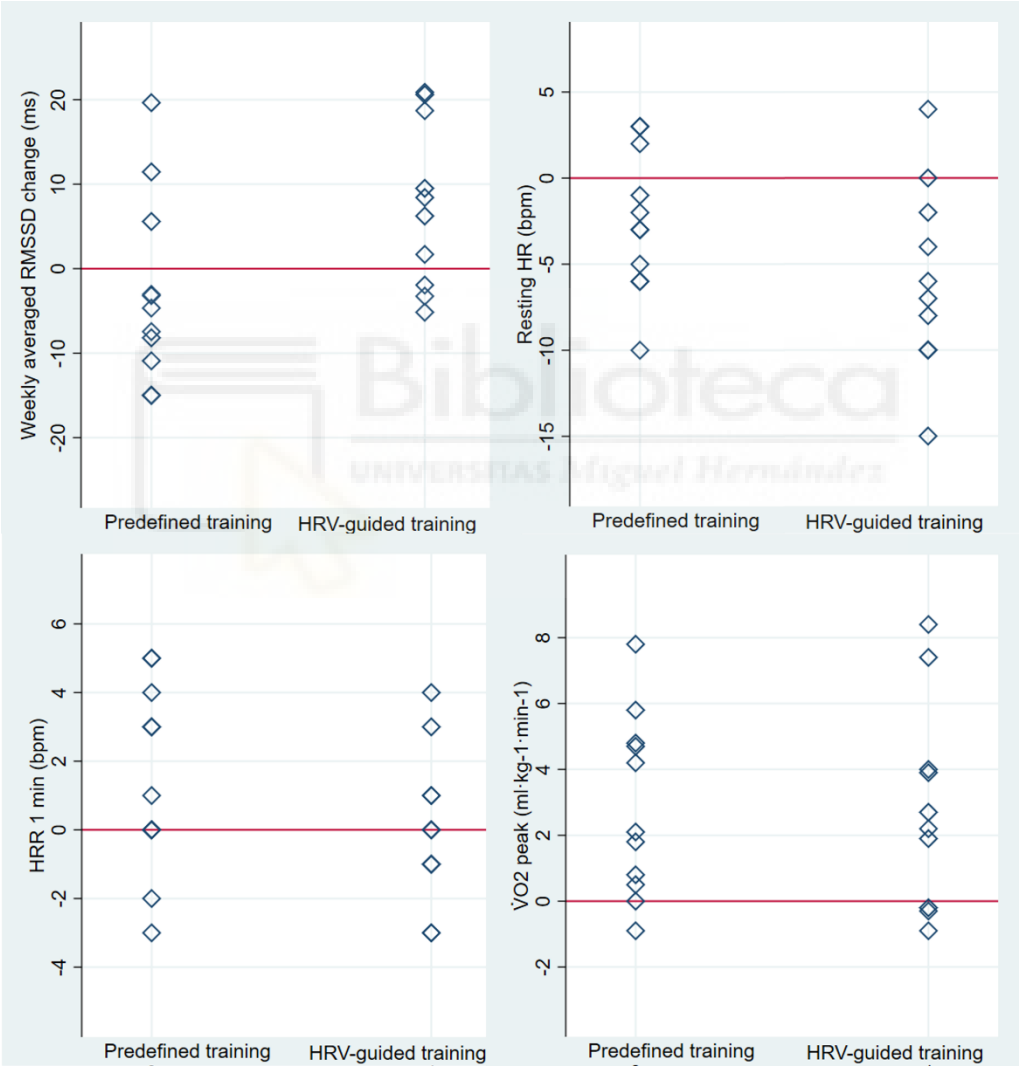

Figure 6. Individual changes, based on the training prescription method, in the averaged root-mean-square difference of successive normal R-R intervals (*RMSSD*), resting heart rate (resting HR), heart rate recovery 1 min (*HRR 1 min*), and peak oxygen uptake ($\dot{V}O_2$ *peak*). *HRV*, heart rate variability

CHAPTER 6

CONCLUSIONS OF THE THESIS

Chapter 6. Conclusions of the thesis

6.1. General conclusions

The studies included in this doctoral thesis show: a) the influence of methodological factors on the sensitivity of HR-based indices to detect increased PNS activity; and b) the effect of exercise-based CR (i.e., predefined training and HRV-guided training) on mortality predictors (i.e., HR-based indices and $\dot{V}O_2$ peak) in patients with CAD.

In the first systematic review with meta-analysis, the sensitivity of vagal related-HRV indices and HRR 1 min to detect PNS hyperactivity in F-OR athletes was investigated while accounting for methodological factors. In the second and third systematic review with meta-analysis, the effects of exercise-based CR programmes on HR-based indices (i.e., vagal-related HRV indices and HRR 1 min) and $\dot{V}O_2$ peak, respectively, in patients with CAD were investigated. In addition, in these two systematic reviews with meta-analyses, the influence of potential moderator variables on the effect of exercise-based CR on mortality predictors was tested. In the fourth systematic review with meta-analysis, the effect of HRV-guided training and predefined training for improving HR-based indices and $\dot{V}O_2$ max in healthy people (i.e., sedentary or physically active people and endurance-trained athletes) were compared while taking methodological factors into account. Finally, in the fifth study, the effects of HRV-guided training and predefined training for enhancing mortality predictors in patients with CAD were also compared.

The results of the current doctoral thesis should be used by coaches and clinicians to properly assess HR-based indices (i.e., vagal-related HRV indices), which may allow them to detect training-induced changes in PNS activity. On the other hand, exercise-based CR programmes should be used for improving PNS tone (i.e., resting HR and HRR 1 min) and CRF in patients with CAD. Even though HIIT enhances $\dot{V}O_2$ peak to a higher extent than MCT, the influence of the participant characteristics on the MCT-induced effect on HRR 1 min and $\dot{V}O_2$ peak should be considered to effectively apply exercise-based CR programmes. Furthermore, HRV-guided training should be considered as an alternative to predefined training for improving PNS modulation, which should be assessed by weekly averaged RMSSD.

The main conclusions of this doctoral thesis are summarised below:

Study 1

1) HRR 1 min assessed after a maximal test and weekly averaged RMSSD measured in the standing position are sensitive to infer increased PNS activity in F-OR athletes.

Study 2

2) In contrast to our hypothesis, the effect of exercise-based CR on vagal-related HRV indices (i.e., RMSSD and HF) in patients with CAD was controversial. Exercise-based CR only increased RMSSD.
3) In contrast to our hypothesis, there was no influence of the analysed moderator variables on the training-induced effect on vagal-related HRV indices (i.e., HF).
4) Exercise-based CR enhanced HRR 1 min in patients with CAD.
5) The training-induced effect on HRR 1 min was greater in studies which were performed with younger patients.

Study 3

6) MCT and HIIT enhanced $\dot{V}O_2$ peak in patients with CAD.
7) The effect of HIIT on $\dot{V}O_2$ peak was greater than the effect of MCT.
8) In contrast to our hypothesis, the effect of HIIT on $\dot{V}O_2$ peak was not influenced by potential moderator variables (i.e., low heterogeneity).
9) The effect of MCT on $\dot{V}O_2$ peak was mainly related to the patient characteristics (i.e., patient prognosis, CRF at baseline, and wait time to start exercise-based CR).

Study 4

10) Accounting for methodological factors, HRV-guided training was superior to predefined training for improving PNS modulation (assessed by standing averaged RMSSD or SD_1) in healthy people (i.e., sedentary or physically active people and endurance-trained athletes).
11) In contrast to our hypothesis, no differences were found between HRV-guided training and predefined training for improving $\dot{V}O_2$ max in healthy people.

Study 5

12) Taking methodological factors into account, HRV-guided training was more effective than predefined training for improving PNS modulation (assessed by weekly averaged RMSSD) in patients with CAD.
13) In contrast to our hypothesis, there were no differences between HRV-guided training and predefined training for improving resting HR, HRR 1 min, and $\dot{V}O_2$ peak in patients with CAD.
14) Regardless of the training prescription method, exercise-based CR enhanced resting HR and $\dot{V}O_2$ peak in patients with CAD but, in contrast to our hypothesis, it did not increase HRR 1 min.

6.2. Conclusiones generales

Los estudios incluidos en esta tesis doctoral muestran: a) la influencia de los factores metodológicos en la sensibilidad de los índices basados en la frecuencia cardiaca (HR) para detectar los incrementos de actividad parasimpática; y b) el efecto de la rehabilitación cardiaca (CR) basada en el ejercicio físico (i.e., entrenamiento predefinido y entrenamiento guiado por la variabilidad de la HR [HRV]) sobre los predictores de mortalidad (i.e., índices basados en la HR y consumo de oxígeno pico [$\dot{V}O_2$ pico]) en pacientes con enfermedad arterial coronaria (CAD).

En la primera revisión sistemática con metaanálisis se analizó la sensibilidad de los índices vagales de la HRV y la recuperación de la HR durante el primer minuto post ejercicio (HRR 1 min) para detectar los incrementos de actividad parasimpática en atletas con síntomas de sobrecarga funcional (F-OR) considerando factores metodológicos. En la segunda y tercera revisión sistemática con metaanálisis se estimó el efecto de la CR en los índices basados en la HR (i.e., índices vagales de la HRV y HRR 1 min) y el $\dot{V}O_2$ pico, respectivamente. Además, en estas dos revisiones sistemáticas con metaanálisis se analizó la influencia de las potenciales variables moderadoras sobre el efecto de la CR basada en el ejercicio físico en los predictores de mortalidad. En la cuarta revisión sistemática con metaanálisis se estudió el efecto del entrenamiento guiado por la HRV, comparado con el entrenamiento predefinido, sobre los índices basados en la HR y el consumo de oxígeno máximo ($\dot{V}O_2$ máx) en personas sanas (i.e., sujetos sedentarios, físicamente activos y entrenados en resistencia). Finalmente, en el quinto estudio se comparó el efecto del entrenamiento guiado por la HRV y el entrenamiento predefinido para la mejora de los predictores de mortalidad en pacientes con CAD.

Los resultados de esta tesis doctoral podrían ser utilizados por entrenadores y clínicos para medir los índices basados en la HR (i.e., índices vagales de la HRV), lo que les permitiría detectar los cambios producidos por el entrenamiento en la actividad parasimpática. Por otra parte, la CR basada en el ejercicio físico debería de ser utilizada para mejorar el tono parasimpático (i.e., HRR 1 min) y el CRF en pacientes con CAD. Aunque el HIIT produce mayores mejoras del $\dot{V}O_2$ pico que el MCT, la influencia de las características de los pacientes sobre el efecto del MCT en la HRR 1 min y el $\dot{V}O_2$ pico se debería tener en cuenta para aplicar los programas de CR basados en el ejercicio físico de forma efectiva. Además, el entrenamiento guiado por la HRV debería ser considerado como una alternativa al entrenamiento predefinido para la mejora de la modulación parasimpática, que debería ser evaluada a partir del promedio semanal de la raíz cuadrada de la media del cuadrado de las diferencias entre intervalos R-R adyacentes (RMSSD).

Las principales conclusiones de esta tesis doctoral se resumen a continuación:

Estudio 1

1) La HRR 1 min evaluada después de un test máximo y el promedio semanal de RMSSD medido de pie son índices sensibles para detectar los incrementos de actividad parasimpática en atletas con F-OR.

Estudio 2

2) En contra de nuestra hipótesis inicial, el efecto de la CR basada en el ejercicio físico en los índices vagales de la HRV (i.e., RMSSD y alta frecuencia [HF]) en pacientes con CAD fue controvertido. La CR basada en el ejercicio físico sólo incrementó RMSSD.
3) En contra de nuestra hipótesis inicial, ninguna de las variables analizadas se relacionó con el efecto del entrenamiento en los índices vagales de la HRV (i.e., HF).
4) La CR basada en el ejercicio físico mejoró la HRR 1 min en pacientes con CAD.
5) El efecto del entrenamiento en la HRR 1 min fue mayor en los estudios llevados a cabo con pacientes más jóvenes.

Estudio 3

6) Tanto el MCT como el HIIT mejoraron el $\dot{V}O_2$ pico en pacientes con CAD.
7) El efecto del HIIT sobre el $\dot{V}O_2$ pico fue mayor que el efecto del MCT.
8) En contra de nuestra hipótesis inicial, los resultados de los estudios previos que analizaron el efecto del HIIT en el $\dot{V}O_2$ pico fueron homogéneos.
9) El efecto del MCT sobre el $\dot{V}O_2$ pico se relacionó principalmente con las características de los pacientes (p. ej., pronóstico, CRF antes de la intervención y tiempo de espera para empezar la CR basada en el ejercicio físico).

Estudio 4

10) Considerando factores metodológicos, el entrenamiento guiado por la HRV fue más efectivo que el entrenamiento predefinido para mejorar la modulación parasimpática en reposo (medida a través de los valores promediados de RMSSD o la desviación estándar instantánea de la variabilidad del intervalo R-R latido a latido [SD_1] obtenidos de pie) en personas sanas (i.e., sujetos sedentarios, físicamente activos y entrenados en resistencia).
11) En contra de nuestra hipótesis inicial, no se encontraron diferencias entre el efecto del entrenamiento guiado por la HRV y el efecto del entrenamiento predefinido en el $\dot{V}O_2$ máx en personas sanas.

Estudio 5

12) Considerando factores metodológicos, el entrenamiento guiado por la HRV fue más efectivo que el entrenamiento predefinido para mejorar la modulación parasimpática en reposo (evaluada a partir del promedio semanal de RMSSD) en pacientes con CAD.

13) En contra de nuestra hipótesis inicial, el entrenamiento guiado por la HRV no produjo mayores mejoras que el entrenamiento predefinido en la HR de reposo, la HRR 1 min y el $\dot{V}O_2$ pico en pacientes con CAD.
14) Independientemente del método de prescripción del entrenamiento utilizado, la CR basada en el ejercicio físico mejoró la HR de reposo y el $\dot{V}O_2$ pico en pacientes con CAD. Sin embargo, en contra de nuestra hipótesis inicial, la CR basada en el ejercicio físico no incrementó la HRR 1 min.

6.3. Limitations and future directions

The studies included in this doctoral thesis show some constraints that could limit the scope of our findings. The main limitations of our studies are the following:

1) All the systematic reviews with meta-analyses were performed by using aggregated information at trial level (e.g., participant characteristics), which could induce spurious relationships between participant characteristics (e.g., participant age and CRF at baseline) and the training-induced effect on mortality predictors [301]. For this reason, heterogeneity analyses in studies 1 and 4 did not include the influence of individual characteristics on the training-induced effect.
2) The wait time to start exercise-based CR was categorised in studies 2 and 3 because most of the included studies did not specifically disclose this information (e.g., less than one month). Nevertheless, there is evidence that shows that dichotomisation of continuous variables diminishes the statistical power of the test [289].
3) The number of included studies in some categories of subgroup analyses was low, limiting the scope of these results.
4) Within-group comparisons were performed in studies 1 and 3 to increase the number of analysis units and investigate the influence of potential moderator variables on the training-induced effect on $\dot{V}O_2$ peak properly. Nonetheless, internal validity of within-group comparisons is lower than that of between-group comparisons [200, 302].
5) Isolated and daily HRV assessments were carried out in the supine position, which increases PNS tone and could reduce the sensitivity of vagal-related HRV indices to detect PNS changes [107]. Nonetheless, heightened PNS tone is more common in endurance-trained athletes than in patients.
6) Daily HRV measurements were performed while patients breathed spontaneously, which could reduce the validity of vagal-related HRV indices. However, RMSSD was used as vagal-related HRV index to carry out HRV-guided training and obtain weekly averaged RMSSD. As it has been commented, the influence of the breathing rate is lower on RMSSD than on HF [80].

Considering our findings and previous evidence, the future research purposes that may be addressed are the following:

1) To analyse the influence of patient characteristics on the effect of exercise-based CR on mortality predictors by performing systematic reviews with meta-analyses at individual level.
2) To study the influence of methodological factors on the sensitivity of HR-based indices to detect increased PNS activity in patients with CAD. There is evidence showing the influence of methodological factors on the sensitivity of HR-based indices. However,

most of the studies have been performed with athletes and we cannot confirm that the influence of methodological factors on the sensitivity of these indices for inferring PNS hyperactivity is the same in other populations (e.g., patients with CAD).

3) To investigate the effect of exercise-based CR on PNS modulation while accounting for methodological factors. We found that the effects of exercise-based CR on vagal-related HRV indices are controversial, which may be explained in part by the use of isolated HF values, measured while patients breathed spontaneously. Therefore, the effect of exercise-based CR programmes on PNS modulation should be analysed by using weekly averaged RMSSD.
4) To study the effect of different HIIT protocols (e.g., short intervals) on $\dot{V}O_2$ peak in patients with CAD. The magnitudes of the HIIT-induced effect on $\dot{V}O_2$ peak in the studies included in our systematic review (study 3) were similar. However, most of the studies used long intervals to carry out HIIT sessions, and we cannot claim that the effects of other HIIT programmes on $\dot{V}O_2$ peak are the same.
5) To study the effect of HIIT on HR-based indices (i.e., vagal-related HRV indices and HRR 1 min) in patients with CAD. Most of the studies included in our systematic review (study 2) used MCT as aerobic training method. There is evidence that shows that HIIT is more suitable than MCT for improving $\dot{V}O_2$ peak, and the effect of HIIT on HR-based indices could also be greater than the effect of MCT.
6) To investigate the effect of resistance training, alone or combined with aerobic training, on HR-based indices in patients with CAD disease. Aerobic training is considered a sufficient stimulus for improving PNS activity. Nevertheless, the effect of including resistance training on exercise-based CR for improving PNS activity requires further research.
7) To study the influence of different methodological approaches or criteria (e.g., mobile SWC instead of fixed) on the effectiveness of HRV-guided training for improving mortality predictors in patients with CAD. Our meta-analysis (study 4) showed no heterogeneity and, therefore, no influence of different methodological approaches or criteria for carrying out HRV-guided training on the effectiveness of this training prescription method for enhancing mortality predictors (i.e., $\dot{V}O_2$ max) in healthy people. Nonetheless, we cannot confirm that other methodological approaches or criteria used to perform HRV-guided training may induce the same response to training in patients with CAD.
8) To study the influence of different intervention characteristics (e.g., intervention length and training frequency) on the applicability of HRV-guided training for enhancing mortality predictors in patients with CAD. Predefined exercise-based CR programmes enhance PNS tone and CRF in patients with CAD, which may explain why HRV-guided

training is not superior to predefined training for improving these mortality predictors. Nonetheless, we cannot confirm that the results are not related to the intervention characteristics.

9) To test the effect of HRV-guided training on mortality predictors in females with CAD. It should be noted that most of the patients recruited to perform our experimental study, as well as in the studies included in our systematic review (study 4), were males. Therefore, our findings about the effect of HRV-guided training on mortality predictors in patients with CAD should be limited to male patients, and we cannot claim that the effect is the same in females.
10) To study individual changes in mortality predictors in response to HRV-guided training compared with predefined training. Our findings showed that individual changes in weekly averaged RMSSD seem to be less heterogenous after an HRV-guided training programme than after a predefined training programme. Nonetheless, statistical comparisons were not performed due to the low sample size. Future studies should be performed to compare the percentage of patients who enhances mortality predictors after both HRV-guided training and predefined training.

CHAPTER 7

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CHAPTER 8

APPENDICES

APPENDIX 1

STUDY 1

Heart rate-based indices to detect parasympathetic hyperactivity in functionally overreached athletes. A meta-analysis

Note. This study was published

Manresa-Rocamora A, Flatt AA, Casanova-Lizón A, Ballester-Ferrer JA, Sarabia JM, Vera-Garcia FJ, Moya-Ramón M. Heart rate-based indices to detect parasympathetic hyperactivity in functionally overreached athletes. A meta-analysis. *Scand J Med Sci Sports*. 2021 Jun;31(6):1164-1182. https://doi.org/10.1111/sms.13932

Chapter 8. Appendices

8.1. Appendix 1

8.1.1. Study 1. Heart rate-based indices to detect parasympathetic hyperactivity in functionally overreached athletes. A meta-analysis

Abstract

Investigations into the sensitivity of heart rate-(HR) derived indices for tracking parasympathetic nervous system (PNS) changes in functionally overreached (F-OR) endurance-trained athletes have produced equivocal findings. Lack of clarity may be a result of methodological inconsistencies. Therefore, the aims of this systematic review and meta-analysis were (a) to determine the sensitivity of resting and post-exercise vagal-related HR variability (HRV) and HR recovery (HRR) indices to detect PNS modulation in F-OR and non-overreached (non-OR) athletes, and (b) to investigate the influence of methodological factors on the sensitivity of HR-based indices to detect PNS hyperactivity in F-OR athletes. We searched CENTRAL, Scopus, PubMed, Embase and Web of Science up to May 2020 for the following terms: male and female endurance-trained athletes, controlled and uncontrolled studies that carried out an overload training period, and PNS modulation measured in resting and post-exercise, pre- and post-overload training period. A random-effects model of standardized mean difference (SMD) was estimated for each outcome measure based on the training-induced fatigue status (F-OR vs non-OR athletes) and the influence of methodological issues to detect PNS hyperactivity in F-OR was assessed by subgroup analyses. Pooled analysis showed that resting vagal-related HRV indices did not detect PNS hyperactivity in F-OR athletes (SMD_+ = −0.01; 95% confidence interval [CI] = −0.51, 0.50), and no statistical difference (p = .600) was found with non-OR athletes (SMD_+ = 0.15; 95% CI = −0.14, 0.45). However, subgroup analysis based on HRV parameter showed a moderate statistical increase in weekly averaged HRV in F-OR athletes (SMD_+ = 0.81; 95% CI = 0.35, 1.26), while isolated HRV values did not reach statistical significance (SMD_+ = −0.45; 95% CI = −0.96, 0.06). We observed a moderate and statistically significant increase in HRR indices among F-OR athletes (SMD_+ = 0.65; 95% CI = 0.44, 0.87), no changes for non-OR athletes (SMD_+ = 0.10; 95% CI = −0.15, 0.34), and statistically significant differences between F-OR and non-OR athletes (p < .001). Insufficient data prevented meta-analysis for post-exercise vagal-related HRV indices. Our findings show that when methodological factors are considered, HR-based indices are sensitive to increased PNS modulation in F-OR.

Keywords

Autonomic nervous system; endurance sports; heart rate recovery; heart rate variability; methodological issues; performance; training load; training-induced fatigue status

INTRODUCTION

Overload training is a common periodization strategy used by endurance athletes to stimulate physiological adaptations and enhance physical performance.[1] A state of functional overreaching (F-OR) commonly follows an overload, characterized by short-term decrements in performance capacity with or without alteration in physiological or psychological parameters.[2,3] Subsequent to a sufficient recovery period (i.e., tapering), F-OR athletes experience an increase in performance capacity above pre-overload values (i.e., supercompensation). However, if overload training persists, athletes may experience non-functional overreaching (N-FOR), characterized by prolonged stagnation or decrements in performance capacity, despite tapering. The time required for restoration of performance capacity has been used to distinguish F-OR (from several days to several weeks) and N-FOR (from several weeks to months).[3] Though maximal performance capacity assessments represent a gold standard for status assessment, these are fatiguing, time-consuming, and may be contraindicated for athletes at risk of developing N-FOR. Therefore, monitoring practical and sensitive markers of overload training-induced fatigue status may help identify athletes who are adapting unfavourably, while guiding individualized tapering strategies to avoid N-FOR.

Previous studies have suggested that changes in autonomous nervous system (ANS) modulation are associated with overreaching symptoms.[4-6] Since the ANS regulates heart rate (HR),[7] several HR-based indices such as resting, submaximal, or maximal HR have been proposed as practical, non-invasive tools to measure changes in ANS activity and infer training-induced fatigue status.[6,8] Though physiological mechanisms of altered HR regulation are not fully understood, it has been proposed that sinus node remodelling, attenuated sympathetic outflow, or reduced beta-adrenergic receptor sensitivity may occur in response to chronic exercise-induced sympathetic excitation.[4,9] For example, multiple investigations have reported a decrease in HR during submaximal and maximal exercise, as well as a decrease in resting HR in F-OR athletes,[8-11] supporting the hypothesis of increased parasympathetic nervous system (PNS) modulation in F-OR athletes. Other HR-based indices used to indirectly measure ANS activity and infer training-induced fatigue status are resting and post-exercise HR variability (HRV),[12] and post-exercise HR recovery (HRR).[13] Heart rate variability is defined as the oscillation between consecutive R-R intervals, influenced by continuous modulation of the ANS branches.[14] There is evidence that shows the validity of parasympathetic-mediated HRV indices (i.e., vagal-related HRV indices) to reflect PNS modulation, while the interpretation of sympathetic- and parasympathetic-mediated HRV indices are more controversial.[6,15] Heart rate recovery is defined as the rate at which HR decreases after exercise,[16] and it occurs due to PNS reactivation and sympathetic nervous system withdrawal.[17] The fast component of HRR (first minute) is mainly parasympathetic-mediated.[18] As such, both HRV and HRR indices show potential for providing information about PNS

modulation. However, complex methodological processes are necessary to properly measure HRV and HRR indices. Moreover, several confounding factors (i.e., lability in daily values, assessment position, exercise requirement, overload training period length, or training variable manipulated to increase training load throughout overload period) could affect the sensitivity of HR-based indices for detecting changes in PNS modulation in F-OR athletes [19-21] and therefore, obscure interpretations. The correct diagnosis of training-induced fatigue status is also necessary for drawing conclusions about the sensitivity of HR-based indices since the overload training period might induce different training-induced fatigue states such as acute fatigue (AF, athletes who maintain or increase performance capacity despite high levels of perceived-fatigue), F-OR and N-FOR.[3]

Numerous studies have analyzed changes in HRV and/or HRR after an overload training period in endurance trained-athletes [22,23] in an effort to identify practical tools that are sensitive to changes in PNS modulation and infer training-induced fatigue status. However, previous studies have been performed with relatively small samples that limit the precision and scope of their findings. Additionally, despite including studies of athletes that showed F-OR symptoms (decreased performance capacity, high levels of perceived fatigue, and decrease in HR during exercise), some studies reported no changes in resting vagal-related HRV indices [24] or HRR indices,[25] while other studies concluded that HR-based indices detected increased PNS modulation in F-OR athletes.[9,26] These controversial findings could be due to methodological inconsistencies when vagal-related HRV or HRR indices are assessed, and valuable information would be obtained from a comprehensive systematic review and meta-analysis. Bellenger, Fuller, Thomson, Davison, Robertson, Buckley [27] and Bellinger [28] carried out a meta-analysis and a narrative review, respectively. These authors highlighted the possible influence of some key methodological factors (i.e., weekly averaged HRV values, intensity of exercise test) on the sensitivity of these HR-based indices to detect PNS hyperactivity in F-OR athletes. However, the influence of these methodological issues was not investigated due to the low number of included studies.

In this systematic review and meta-analysis, we aimed to investigate the sensitivity of resting and post-exercise vagal-related HRV indices, and HRR indices to identify changes in PNS modulation in F-OR endurance-trained athletes and non-overreached (non-OR) athletes. A secondary aim was to determine the influence of potential moderator variables on the sensitivity of HR-based measures to identify F-OR athletes. Based on previous findings, we hypothesize that resting and post-exercise vagal-related HRV and HRR indices are sensitive to changes in PNS modulation in F-OR athletes. However, the sensitivity of HR-based indices is likely influenced by methodological issues.

METHODS

We conducted and reported a systematic review of the literature and a meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[29] The systematic review and meta-analysis protocol were prospectively registered in the PROSPERO database (CRD42020169189).

Data search and sources

Potential studies were identified via a comprehensive strategy. We carried out a systematic review in the Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 5), Scopus, PubMed, Embase and Web of Science (all databases were searched) databases from inception to May 2020 using free-text terms based on the PIO (participants, intervention and outcomes) strategy. We did not apply language restrictions during this phase. The electronic search of individual database was adapted as necessary (the full search strategy in each database is depicted in Supplementary file 1). We also searched the OpenGrey (System for Information on Grey Literature in Europe) database. Moreover, we manually checked the reference list of previous reviews and full-text articles to assess for eligibility. Authors of selected studies were contacted via e-mail in an attempt to identify unpublished or ongoing studies that fulfil our selection criteria. Finally, we screened the publication list of key journals in the field to find studies that had yet to be indexed in the electronic databases.

Study selection

We established the eligibility criteria according to the PICOS (participants, intervention, comparison, outcomes, and study design) guideline. Males and females who were recreational, well-trained, or high-level endurance-trained athletes (participants) were included. Studies that performed an endurance overload training period, or combined endurance and strength training were included. Restrictions were not imposed regarding the minimal length of the overload period to analyze the influence of overload training period length (intervention). Controlled trials included a group that maintained the previous training load (comparison). Each selected study had to report vagal-related HRV indices in resting and/or post-exercise conditions, and/or HRR indices. We selected the root-mean-square difference of successive normal R-R intervals (RMSSD) in the time domain, high frequency (HF) in the frequency domain, and the standard deviation of instantaneous beat-to-beat R-R interval variability (SD_1) from the nonlinear measures as vagal-related HRV indices according to previous recommendations.[6,15] The recovery of HR and raw HR at a given time of recovery, as well as the negative reciprocal of slope of regression line between natural logarithm of heart rate from first 30 s after exercise (T30), the smallest time constant using negative reciprocal of slope of regression line between natural logarithm of heart rate from first 30 seconds after exercise (T30 min) and mono-exponential function were also included as HRR indices. Additionally, we only included studies that reported a valid

measurement of athletic performance (maximal oxygen uptake was not considered a valid measurement of performance) [3,30] tested before and after the overload training period. Finally, we included randomized, non-randomized, controlled and uncontrolled trial study designs in English or Spanish. We limited the inclusion of studies with more than one article based on the same sample population of the original publication.

Two authors (AC and AB) assessed all identified titles/abstracts for possible inclusion. The same authors reviewed the full texts of the remaining studies against the inclusion criteria. We settled disagreements by consensus. In cases where consensus was not achieved, a third author (AM) assessed the study to obtain agreement.

Data extraction, coding study characteristics, and potential moderator variables

Two authors (AC and AB) coded the characteristics of the included studies using a standardized data extraction form. We settled disagreements by consensus. In cases where consensus was not achieved a third author (AM) assessed the study to obtain agreement.

The following information was extracted from included studies: (a) study characteristics (publication year, country, study design, and journal); (b) baseline participant characteristics (sample size, male percentage, age, maximal oxygen uptake, height, weight, HR rest, and HR peak); (c) athletic characteristics (sport, training experience, and athletic level [low or high]); (d) overload training period characteristics (type of exercise [endurance or combined endurance and strength training], increased training variable [intensity, volume, or both], training load at overload period, and overload training length); (e) performance assessment (test, parameter assessed, and athletic performance change); (f) other indicators of fatigue status in athletes who were diagnosed as F-OR; (g) overload training-induced fatigue status (AF or F-OR) based on the allocation/diagnosis carried out by the authors after overload training (studies where fatigue status diagnosis was performed) or changes in performance capacity and other indicators of fatigue status after the overload training period (studies where fatigue status diagnosis was not performed); (h) resting and post-exercise HRV assessment characteristics (sampling rate, equipment, data processing, method used, and power spectral density method [if applicable]); (i) resting HRV assessment characteristics (time of day, assessment position, breathing control, breathing rate [if applicable], stabilization period, recording length of the analyzed information, HRV value used [isolated or averaged], and number of averaged values [if applicable]); (j) exercise testing characteristics (type of exercise test, exercise requirement [maximal test until volitional exhaustion or submaximal test], exercise length [if applicable], and exercise mode); (k) recovery characteristics (type [active or passive], length, intensity [if applicable], position, breathing control, and breathing rate [if applicable]); and (l) mean and standard deviation (*SD*) of vagal-related HRV indices and HRR indices before and after the overload training period. For

articles that did not report outcome data (i.e., mean and *SD*), authors were contacted via e-mail to obtain this information. If a response was not received, the article was excluded from the quantitative synthesis.

Based on previous evidence, the following was considered as potential moderator variables of vagal-related HRV and/or HRR changes after overload training period: (a) resting vagal-related HRV index (RMSSD, HF, and SD_1); (b) HRV assessment position (standing or other) [31]; (c) HRV values (isolated or averaged) [32]; (d) overload training period length (≤ 14 days or > 14 days) [8]; (e) training variable increased throughout overload period (volume, intensity, or both) [28]; (f) exercise testing requirement (maximal or submaximal) [21]; (g) athletic level (low [recreational and well-trained] or high) [33] based on reporting statements, athlete characteristics, training experience and/or athletic performance; and (h) sex of the sample (males, females, or both).[34]

Computation of effect size and statistical analyses

The standardized mean difference (SMD) with a 95% CI was used as the ES index to assess changes in vagal-related HRV and HRR indices after overload training. We transformed the data into its absolute logarithmic value before calculating the SMD for the absolute HF and RMSSD values according to previous recommendations.[35] The SMD was calculated by subtracting the post-overload training mean value from the pre-overload training mean value divided by the SD at pre-overload training, corrected by a factor for small samples.[36,37]

Separate analyses were performed for each SMD index based on the training-induced fatigue status (F-OR vs non-OR) according to the outcome measure to avoid statistical dependence (resting vagal-related HRV indices, post-exercise vagal-related HRV indices, and HRR indices). Based on potential moderator variables described above, we selected RMSSD and SD_1 as preferential indices to calculate the pooled ES of resting and post-exercise HRV among studies reporting several HRV indices. Previous studies have demonstrated that during longitudinal follow-up, these markers provide the same HRV variations regardless of the breathing pattern.[38] Moreover, we selected the standing position and averaged HRV values as preferential according to previous recommendations. The standing position is less sensitive than other positions (i.e., supine position) to parasympathetic saturation [31] and averaged values reduces the natural day-to-day variations of HRV indices.[32,39] We also selected the results obtained during slow-wave sleep (SWS) as preferential in studies that performed nocturnal assessments. Previous studies have reported that SWS shows high standardization of environmental factors and respiratory influences on HRV.[40] Additionally, we selected as preferential measures those obtained after maximal tests since previous studies have reported lower reliability of HRR after submaximal exercise.[41,42] Regarding the method used to report the HRR, we selected HRR1 min as the preferential index in studies reporting several indices. The recovery of HR throughout the first minute of exercise is

due to reactivation of the parasympathetic branch of the ANS, while recovery of HR indices beyond 1 min is influenced by both ANS branches.[17,18,43] Finally, we averaged the findings reported in studies that obtained HR-based indices in several conditions (i.e., period length, submaximal test at different intensities, maximal tests with varying exercise duration).

A random effects model was applied for each meta-analysis in which the weighting factor was the inverse variance, defined as the sum of the within-study and the between-studies variance [$W = 1/(Vi + \tau^2)$]).[44] We used a conservative value of 0.7, previously proposed by Rosenthal,[45] to calculate the variance of each study when the studies did not report the correlations between pre- and post-overload training measures. The analysis comprised calculating the mean ES with its 95% CI, a heterogeneity statistical test, chi-square, and the I^2 index to evaluate the degree of homogeneity of the ESs around the average effect.[46,47] We classified the magnitude of the SMD as trivial (< 0.2), small (0.2–0.6), moderate (0.6–1.2), large (1.2–2.0) or very large (> 2.0).[48] We considered a statistically significant effect when $p \leq .050$. Heterogeneity was classified as low, moderate, or high at 25%, 50%, and 75%, respectively.[49] Tests for subgroup comparisons between F-OR and non-OR athletes were also performed based on these heterogeneity criteria. Additionally, within F-OR athletes, the relationship between the ESs and the moderator variables were assessed using subgroup analyses to identify which variables were related to the sensitivity of HR-based indices. All analyses were conducted using weighted least squares and assuming mixed-effects models.[50] The aforementioned heterogeneity criteria were also applied to conduct subgroup analysis. We carried out heterogeneity analyses within F-OR athletes whether at least two studies were included in two or more categories of the moderator variable. In other cases, the influence of the potential moderator variable was qualitatively discussed. We did not carry out statistical tests for subgroup difference when multiple comparisons were reported from the same athletes (i.e., supine and standing position) within the moderator variable (i.e., assessment position). We maintained the preferential criteria in the remaining variables to perform heterogeneity analyses.

RESULTS

Study selection

Figure 1 illustrates the systematic review process. In brief, from a total of 1558 studies after removing duplicates, 34 were eligible for full-text analysis, of which we excluded 19 studies from qualitative synthesis as follow: they did not carry out pre- or post-overload training assessment of performance (N = 4), they were focused on training adaptation (N = 4), datasets were previously reported (N = 2), language (N = 1), they used an invalid measure of exercise performance (N = 5), they did not include endurance-trained athletes (N = 1), and they did not perform an overload training period (N = 2). From the 15 studies included for qualitative

synthesis, we included 12 studies for meta-analysis and excluded 3 because they reported HF values as normalized units (N = 1) and they did not report sufficient information to calculate the ES (N = 2). Although we attempted to locate unpublished studies, all selected studies had been published in peer-reviewed journals.

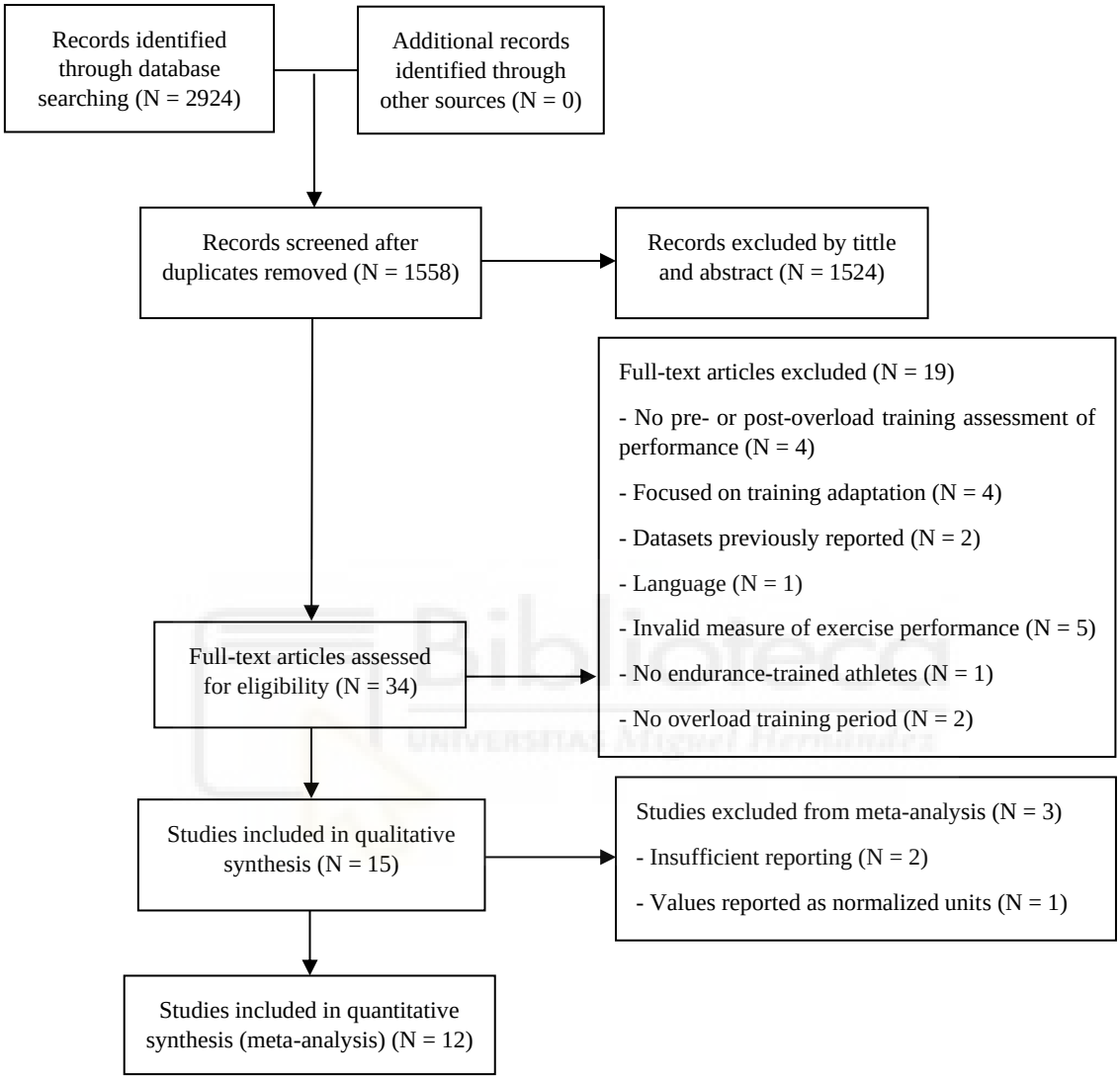

Figure 1. Flow chart of the systematic review process

Study characteristics

Study and participant characteristics are summarized in Table 1. The 15 included studies are from 6 countries and were published between 2000 and 2018. Three studies (20%) were randomized controlled trials, and 12 (80%) were single-group design studies. In total, there were 227 athletes (196 athletes allocated in the overload training group and 31 in the CG) with a mean ± *SD* age of 30.5 ± 5.8 years, of which, 197 were males and 30 were females. Ten studies (67%) included exclusively male athletes and 5 (33%) used a mixed sample. Study sample size varied from 7 to 31 athletes. Eight studies (53%) recruited athletes from several disciplines, six (40%) recruited

athletes from a specific discipline, and one (7%) did not report this information. Fourteen studies (93%) recruited low-level athletes and one (7%) included high-level athletes.

The overload training period and performance assessment characteristics are reported in Table 2. Fourteen studies (93%) carried out an overload training period exclusively based on endurance training and one (7%) combined endurance and strength training. Eight studies (53%) manipulated volume and intensity of training to increase training load, four (27%) increased exclusively volume, and three (20%) did not report this information. The overload training length ranged from 6 to 21 days. Seven studies (47%) performed an overload training period shorter than or equal to 14 days and eight (53%) carried out an intervention longer than 14 days. A description of the overload training period can be found in Table 2. Five studies (33%) carried out a maximal test to measure athletic performance, five (33%) performed a maximal incremental test until volitional exhaustion, one (7%) carried out a maximal constant test until volitional exhaustion, and four (27%) combined different maximal tests. Changes in athletic performance and other indicators of training-induced fatigue status, as well as the diagnosis of fatigue status can also be found in Table 2. Out of 193 athletes who completed the overload training period, 34 (18%) were diagnosed as AF and 159 (82%) were considered as F-OR. For subsequent analyses, AF athletes and those allocated in the CG were considered non-OR athletes (N = 65).

Table 1. Study and participant characteristics

		Study characteristics	Participant characteristics		Athletic characteristics
Study (author, year)	**Training group**	**Country; study design; journal**	**Sample size; men percentage; age; VO_2 max**	**Height; weight; HR rest; HR peak**	**Sport; training experience; athletic level statement (level)**
Aubry 2015 [26]	OTG	France; randomised controlled trial; Plos One	21; 100%; 34.4 ± 5.8 years; 4446.6 ± 463.2 ml·min^{-1}	179.0 ± 6.1 cm; 73.0 ± 8.0 kg; NR; 182.0 ± 8.0 bpm	Triathlon; 13.4 ± 8.3 years; well-trained (L)
	CG		10; 100%; 37.0 ± 6.0 years; 4300.0 ± 359.0 ml·min^{-1}	183.0 ± 6.0 cm;75.0 ± 7.0 kg; NR; 185.0 ± 5 bpm	
Baumert 2006 [51]	OTG	Australia; one-group design; Biomedizinische Technik	10; 50%; 24.8 [24.7 – 26.4] years (F), 26.6 [26.5 – 28.8] years (M); 51.1 [48.9 – 52.2] ml·kg^{-1}·min^{-1} (F), 65.9 [61.4 – 74.6] ml·kg^{-1}·min^{-1} (M)	163.0 [162.0 – 168.0] cm (W), 181.0 [181.0 – 182.0] cm (M); 54.8 [50.4 – 61.8] kg (W), 72.0 [69.0 – 86.8] kg (M); NR; NR	Track and field or triathlon; at least 2 years in competition; experienced athletes (L)
Bellenger 2016 [52]	OTG	Australia; one-group design; International Journal of Sports Physiology and Performance	15; 100%; 35.1 ± 7.0 years; NR	NR ;76.5 ± 8.6 kg; NR; 188.0 ± 8.0 bpm	Running and triathlon; NR; recruited from local clubs (L)
Bellenger 2017 [25]	OTG	Australia; one-group design; European Journal of Applied Physiology	12; 100%; 33.8 ± 10.2 years; NR	NR ;76.7 ± 12.4 kg; NR; 180.7 ± 10.5 bpm	Cycling and triathlon; NR; Recruited from a metropolitan area (L);
Bosquet 2003 [53]	OTG	France; one-group design; The Journal of Sports Medicine and Physical Fitness	9; 100%; 27.0 ± 5.0 years; NR	172.0 ± 5.0 cm; 64.4 ± 6.8 kg; 56.1 ± 11.5 bpm; 182.0 ± 11.0 bpm	Running and triathlon; 6.9 ± 2.3 years; moderately to well-trained (L)
Bourdillon 2018 [54]	OTG	Switzerland; one-group design; Journal of Science and Medicine in Sport	15; 53.3%; 25.0 ± 5.0 years; NR	175.0 ± 8.0 cm; 64.0 ± 11.0 kg; NR; NR	Running and cycling; NR; based on inclusion criteria (at least 4 hours per week) (L)
Coates 2018 [55]	OTG	Canada; randomised controlled trial; European Journal of Sport Science	15; 53.3%; 37.7 ± 8.0 years; 54.5 ± 7.0 ml·kg^{-1}·min^{-1}	173.3 ± 7.8 cm; 71.6 ± 11.3 kg; 60.0 [55.0 – 65.0] bpm; NR	Cycling and triathlon; NR; recruited from local clubs (L)
	CG		13; 61.5%; 35.8 ± 10.5 years; 54.8 ± 8.8 ml·kg^{-1}·min^{-1}	175.6 ± 8.6 cm; 72.5 ± 10.1 kg; 60.0 [56.0 – 63.0] bpm; NR	
Dupuy 2013 [12]	OTG	Canada; one-group design; Applied Physiology, Nutrition and Metabolism	11; 100%; 29.5 ± 9.3 years; 58.9 ± 4.3 ml·kg^{-1}·min^{-1}	177.0 ± 6.2 cm; 71.6 ± 7.5 kg; 53.8 ± 5.4 bpm; 186.0 ± 9.0 bpm	NR; NR; provincial level (L)

Table 1. Continued

		Study characteristics	Participant characteristics		Athletic characteristics
Study (author, year)	**Training group**	**Country; study design; journal**	**Sample size; men percentage; age; VO_2 max**	**Height; weight; HR rest; HR peak**	**Sport; training experience; athletic level statement (level)**
Garet 2004 [56]	OTG	France; one-group design; Medicine and Science in Sports and Exercise	7; 57.1%; 16.6 ± 0.5 years; NR	169.3 ± 5.9 cm; 59.3 ± 6.5 kg; 55.7 ± 3.3 bpm; 186.0 ± 6.0 bpm	Swimming; 6.4 ± 0.9 years; regional level (L)
Hammes 2016 [57]	OTG	Germany; one-group design; International Journal of Sports Physiology and Performance	23; 100%; 28.8 ± 7.6 years; 59.0 ± 7.0 $ml \cdot kg^{-1} \cdot min^{-1}$	180.0 ± 6.0 cm; 73.7 ± 7.7 kg; NR; 188.0 ± 8.0 bpm	Cycling and triathlon; NR; national level (L)
Hedelin 2000 [24]	OTG	Sweden; one-group design; Medicine and Science in Sports and Exercise	9; 66.7%; 20.1 ± 1.9 years; 4990 ± 970 $ml \cdot min^{-1}$	NR; 79.6 ± 10.9 kg; NR; NR	Canoeing; 6 to 14 years; international level (H)
Hug 2014 [23]	OTG	Switzerland; one-group design; International Journal of Sports Medicine	9; 100%; 34.6 ± 5.7 years; 59.5 ± 2.9 $ml \cdot kg^{-1} \cdot min^{-1}$	180.0 ± 9.0 cm; 69.0 ± 6.3 kg; 52.7 ± 9.0 bpm; 182.0 ± 13.0 bpm	Running; at least 5 years; well-trained (L)
Le Meur 2013 [9]	OTG	France; randomised controlled trial; Medicine and Science in Sports and Exercise	16; 100%; 30.0 ± 5.0 years; 62.0 ± 5.0 $ml \cdot kg^{-1} \cdot min^{-1}$	NR; NR; NR; NR	Triathlon; at least 2 years in competition; trained (L)
	CG		8; 100%; 32.0 ± 8.0 years; 62.0 ± 3.0 $ml \cdot kg^{-1} \cdot min^{-1}$		
Thomson 2016 [13]	OTG	Australia; one-group design; Journal of Science and Medicine in Sport	11; 100%; 32.5 ± 10.1 years; 59.2 ± 5.9 $ml \cdot kg^{-1} \cdot min^{-1}$	NR; 77.5 ± 9.7 kg; NR; 178.2 ± 9.4 bpm	Cycling and triathlon; NR; well-trained (L)
Woods 2018 [58]	OTG	Australia; one-group design; Plos One	13; 100%; 35.0 ± 8.0 years; 61.1 ± 6.2 $ml \cdot kg^{-1} \cdot min^{-1}$	185.0 ± 7.0 cm; 80.5 ± 7.3 kg; NR; 180.6 ± 8.6 bpm	Cycling; more than 4 years; recruited from local clubs (L)

bpm, beats per minute; *CG*, control group; *F*, females; *H*, high-level; *HR*, heart rate; *L*, low-level; *M*, males; *NR*, no reported; *OTG*, overload training group; VO_2 oxygen uptake
Values are depicted by mean ± standard deviation or median [intercuartil range]

Table 2. Overload characteristics, performance assessment and other indicators of overload-induced fatigue

	Overload training characteristics		**Performance assessment**				
Study (author)	**Type of exercise; increased variable; length**	**Overload period description**	**Test**	**Parameter assessed**	**MC**	**Other indicators of fatigue status in overreached athletes**	**Fatigue status diagnosis (n)**
Aubry [26]	Endurance; volume; 21 days	The duration of each training session was increased by 30%	Maximal incremental test	MAP	6.09 W −9.20 W	Increase of perceived fatigue; decreased HR peak, and plasma epinephrine and norepinephrine peak	AF[b] (11) F-OR[b] (10)
Baumert [51]	Endurance; volume and intensity; 6 days	Volume and intensity were individually increased	Maximal incremental test	MAP	−22.00 W	Changes in POMS questionnaire subscales (vigor and fatigue); elevated HR during the training camp	F-OR[b] (10)
Bellenger [52]	Endurance; volume and intensity; 14 days	Running exercise for 66 min per day, 36% performed above 88% of HR peak	5 km time trial	Time to complete 5 km	21.80 s	Decreased HR peak and energy levels; increased fatigue, muscle soreness and DALDA worse-than-normal score	F-OR[c] (15)
Bellenger[25]	Endurance; volume and intensity; 14 days	Cycling exercise for 124 min per day, 34% performed above 88% of HR peak	5 min maximal test 60 min maximal test	Work done Work done	−6.42 kJ −80.54 kJ	Decreased HR peak, energy levels and mood state; increased fatigue, muscle soreness, DALDA worse-than-normal score and maximal rate of HR increase assessed at 200 W	F-OR[c] (12)
Bosquet [53]	Endurance; volume; 21 days	Training volume was increased weekly from baseline by 33%, 66% and 100%	Maximal incremental test Maximal constant test at 85% of MAS	MAS Time to exhaustion	−0.37 km·h^{-1} −6.40 min	Decreased peak blood lactate concentration and HR max; increased fatigue and score of a standardised questionnaire to detect overtraining	F-OR[b] (9)
Bourdillon [54]	Endurance; volume and intensity; 21 days	Training load was increased by at least 40%	3 km time trial Maximal constant test at 80% HR max	Time to complete 3 km Distance	−35.66 s 200.00 m 14.88 s 90.00 m	Increased scores of POMS questionnaire and 14-item questionnaire for physical fatigue (POMS score also increased in athletes diagnosed as acute fatigue status)	AF[b] (7) F-OR[b] (8)
Coates [55]	Endurance; volume and intensity; 21 days	Three supplementary cycling sessions per week (one HIIT session)	Maximal incremental test	MAP	−8.54 W	Decreased performance (derived formula to individually diagnose OR), POMS questionnaire score and HR max	F-OR[b] (15)
Dupuy [12]	Endurance; volume; 14 days	Volume was increased by 100%	Maximal incremental test Maximal constant test at 85% MAS	MAS Time to exhaustion	−0.20 km·h^{-1} −7.70 min	Decreased HR max; changes in POMS questionnaire subscales (vigor, depression and energy) RESTQ-sport questionnaire subscales	F-OR[b] (11)

Table 2. Continued

Study (author)	Overload training characteristics: Type of exercise; increased variable; length	Overload training characteristics: Overload period description	Performance assessment: Test	Performance assessment: Parameter assessed	Performance assessment: MC	Other indicators of fatigue status in overreached athletes	Fatigue status diagnosis (n)
Garet [56]	Endurance; NR; 21 days	Six 1.5 hours of training per week	400 m time trial	Time to complete 400 m	2.50 s	No changes in HR max, perceived exertion and median nocturnal HR	AF[c] (7)
Hammes [57]	Endurance; volume and intensity; 6 days	Morning. HIIT session (all-out) or 1 hour of cycling at HR to 95% AT. Afternoon. 3 hours of cycling at HR to 80% AT	Maximal incremental test	Peak PO	−11.00 W	Increased of the Acute Recovery and Stress questionnaire subscales (muscular and overall stress); decreased HR peak	F-OR[b] (23)
			40 km time trial	Mean PO	−11.00 W		
				Time to complete 40 km	68.00 s		
Hedelin [24]	Combined endurance and strength training; NR; 6 days	Training load was increased by ≈50%. 65% low or moderate endurance training, 25% high intensity/anaerobic training and 10% strength training	Maximal incremental test	Time to exhaustion	−1.10 min	Decreased HR max, maximal blood lactate concentration and resting blood parameters (red blood cells, erythrocyte volume fraction and hemoglobin)	F-OR[c] (9)
Hug [23]	Endurance; volume and intensity; 21 days	Training load was increased by 23 ± 10% (one 1-hour high intensity session per week and the duration was prolonged by 30 min)	Maximal constant test at 95% oxygen uptake peak	Time to exhaustion	11.00 s	No changes in HR peak and lactate concentration peak	AF[c] (9)
Le Meur [9]	Endurance; volume; 21 days	Training load was increased by 40%	Maximal incremental test	Total distance covered	[a]Decrease in performance, high levels of perceived fatigue and decreased HR at low intensity, AT, high intensity and exertion		F-OR[b] (13)
Thomson [13]	Endurance; volume and intensity; 14 days	Training load increased by 300%. Volume increased from 32 to 124 min per day and time spent above high intensity from 22% to 34%	5 min maximal test	Work done	−2.30 kJ	Decreased HR at the end of exercise	F-OR[c] (11)
Woods [58]	Endurance; NR; 21 days	Training load was increased by 20% for one week and 40 – 50% for two weeks	15 s sprint	Peak PO	−90.20 W	Increased scores of Multicomponent Training Distress Scale questionnaire and RESTQ-sport questionnaire; decreased HR peak and rating of perceived exertion	F-OR[c] (13)
			4 km time trial	Mean PO	−4.30 W		

AF, acute fatigue; *AT*, anaerobic threshold; *DALDA questionnaire*, Daily Analysis of Life Demands for Athletes questionnaire; *F-OR*, functional overreaching; *HIIT*, high-intensity interval training; *HR*, heart rate; *MAP*, maximal aerobic power, *MAS*, maximal aerobic speed; *MC*, mean change; *n*, number of diagnosed athletes; *NR*, no reported; *POMS questionnaire*, Profile of Mood States questionnaire; *PO*, power output; *RESTQ-sport questionnaire*, Recovery Stress Questionnaire for Athletes questionnaire

[a]Insufficient data reported to calculate mean change

[b]Based on the allocation or diagnosis performed by the authors after overload training

[c]Based on changes of athletic performance and other fatigue status indicators after overload training

Resting vagal-related HRV indices

Assessment characteristics

The HRV assessment characteristics are summarized in Table S1 (see Supplementary file 2). Out of 15 studies included in the qualitative synthesis, 12 (80%) measured resting vagal-related HRV indices, of which, four (33%) reported RMSSD [23,25,52,58] and two (17%) reported HF [24,53], while five (42%) reported RMSSD and HF [9,51,54-56] and one (8%) reported RMSSD, HF, and SD_1.[12] Out of eight studies which reported HF, four (50%) determined power spectral density by FFT,[12,51,53,54] three (38%) used other methods (auto-regressive, wavelet decomposition, or Goertz algorithms) [9,24,56] and one (12%) did not report this information.[55] Ten studies (83%) recorded the R-R interval with a HR monitor [9,12,23-25,52-54,56,58] and two (17%) used an electrocardiogram.[51,55] Authors of 10 studies (83%) explicitly stated that data processing to identify and remove artifacts and ectopic beats was performed before carrying out HRV analyses, of which, six studies (60%) performed data processing by interpolation algorithms,[12,24,51,53,54,56] three (30%) by filtering,[9,25,52] and one (10%) did not report this information.[55]

Three studies (25%) performed nocturnal assessments while athletes slept to obtain HRV indices,[12,53,56] five (42%) carried out laboratory-based measures [23,24,51,55,58] and four (33%) performed daily morning waking assessments,[9,25,52,54] using a 7-day averaged HRV value (henceforth, weekly averaged HRV value). The recording length of nocturnal measures varied from 240 to 360 min. One study analyzed the fully retained HRV recording and the first 10-min stationary segment from the first SWS.[12] Out of nine studies that performed laboratory-based or daily morning waking assessments, three (33%) carried out assessments in the supine position,[51,55,58] one (11%) in the standing position,[25] three (33%) performed measures in supine and standing positions,[9,52,54] and two (22%) used other positions.[23,24] Four studies (44%) allowed the athletes to breathe spontaneously throughout HRV assessment,[9,23,54,55] one (11%) controlled the breathing rate [24] and four (44%) did not explicitly report this information.[25,51,52,58] The recording length of laboratory-based and daily waking measures ranged from 5 to 30 min and from 2 to 6 min, respectively. Four studies (33%) reported their findings based on averaged HRV values,[25,52,54,56] seven (58%) used isolated HRV values [12,23,24,51,53,55,58] and one (8%) reported averaged and isolated HRV values.[9]

Changes in resting vagal-related HRV

Pooled analyses based on the training-induced fatigue status revealed no statistically significant changes in resting vagal-related HRV for F-OR (p = .990) and non-OR athletes (p = .310). The overall SMD reached a trivial effect for F-OR (SMD_+ = −0.01; 95% CI = −0.51, 0.50; Figure 2) and non-OR athletes (SMD_+ = 0.15; 95% CI = −0.14, 0.45; Figure 2). The heterogeneity was statistically significant, and the inconsistency was high for vagal-related HRV changes for F-OR athletes (p < .001; I^2 = 83%), while no heterogeneity was found in non-OR athletes (p = .740;

I^2 = 0%). The test for subgroup comparisons showed a statistically non-significant difference with no heterogeneity in resting vagal-related HRV changes between F-OR and non-OR athletes (p = .600; I^2 = 0%).

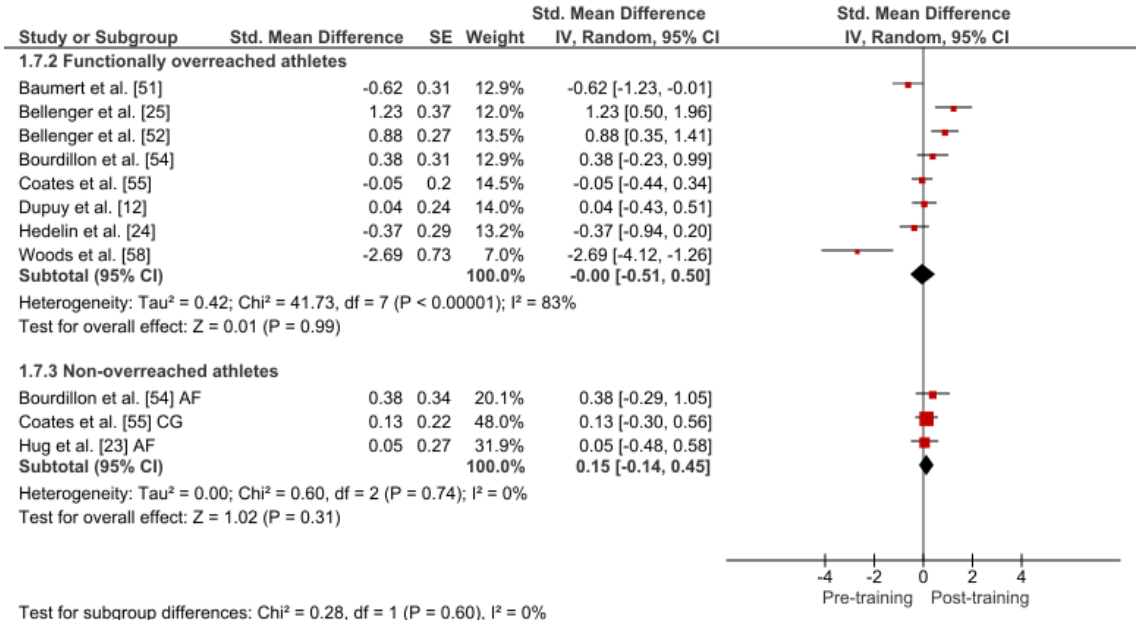

Figure 2. Forest plot of the standardized mean difference for resting vagal-related heart rate variability. *AF*, acute fatigue; *CG*, control group; *CI*, confidence interval; *IV*, inverse variance; *SE*, standard error

Influence of moderator variables on resting vagal-related HRV sensitivity in F-OR athletes

The results of analyzing the influence of moderator variables on resting vagal-related HRV changes in F-OR athletes can be found in Table 3. The subgroup analysis showed a significant between-group difference, with high heterogeneity for the HRV value (p < .001; I^2 = 92%). The overall SMD showed a statistically significant increase for averaged vagal-related HRV changes (p < .001), and the magnitude of the increase was moderate (SMD_+ = 0.81; 95% CI = 0.35, 1.26). The heterogeneity did not reach statistical significance, and the inconsistency was low (p = .190; I^2 = 39%). The pooled SMD showed a non-statistically significant decrease for isolated vagal-related HRV changes (p = .080), and the magnitude of the decrease was small (SMD_+ = −0.45; 95% CI = −0.96, 0.06). The heterogeneity was statistically significant, and the inconsistency was high (p = .004; I^2 = 74%). The subgroup analyses did not reach a significant between-group difference, and no low heterogeneity was found for the sex of the sample (p = .700; I^2 = 0%) and overload training period length (p = .250; I^2 = 26%). Testing for subgroup differences was not applicable for the vagal-related HRV index and assessment position. Pooled analysis based on the vagal-related HRV index showed no statistically significant change for RMSSD (p = .880) and HF (p = .360). The magnitude of the change was trivial for RMSSD (SMD_+ = 0.04; 95% CI = −0.53, 0.61) and HF (SMD_+ = −0.11; 95% CI = −0.33, 0.12). The heterogeneity was statistically significant, and the inconsistency was high for RMSSD (p < .001; I^2 = 85%), while the heterogeneity did not reach statistical significance, and no heterogeneity was found for HF (p = .390; I^2 = 3%).

Table 3. Influence of moderator variables on the sensitivity of vagal-related HRV indices in functionally overreached athletes

Moderator variable	Category	*k*	SMD (95% CI)	*Chi²*	*p*	I^2	Test for subgroup differences		
							Chi²	*p*	I^2
Vagal-related HRV index	RMSSD	7	0.04 (−0.53, 0.61)	38.90	< .001	85%	Not applicable[a]		
	HF	5	−0.11 (−0.33, 0.12)	4.11	.390	3%			
Assessment position	Standing	3	0.81 (0.35, 1.26)	3.27	.190	39%	Not applicable[a]		
	Other	6	−0.30 (−0.75, 0.16)	19.64	.001	75%			
HRV value	Isolated	5	−0.45 (−0.96, 0.06)	15.23	.004	74%	13.01	<.001	92%
	Averaged	3	0.81 (0.35, 1.26)	3.27	.190	39%			
Overload training period length	≤ 14 days	5	0.22 (−0.42, 0.86)	25.37	< .001	84%	1.35	.250	26%
	> 14 days	3	−0.53 (−1.61, 0.56)	15.00	< .001	87%			
Sex of the sample	Males	4	0.06 (−0.98, 1.10)	28.35	< .001	89%	0.15	.700	0%
	Both	4	−0.16 (−0.54, 0.22)	6.04	.110	50%			

Chi², chi-square statistic; *CI*, confidence interval around SMD; *HF*, high frequency; *HRV*, heart rate variability; I^2, heterogeneity index; *k*, number of studies; *p*, probability level associated to the *Chi²* statistic; *RMSSD*, the root-mean-square difference of successive normal R-R intervals; *SMD*, standardized mean difference

[a]test for subgroup differences was not carried out when the same athletes were included in two or more categories within the moderator variable

Post-exercise HRR and vagal-related HRV indices

Assessment characteristics

The post-exercise assessment characteristics are summarized in Table S2 (see Supplementary file 3). Out of 15 studies included in the qualitative synthesis, eight (53%) reported HRR indices.[12,13,23,25,26,55,57,59] All studies (100%) used HRR 1 min to analyze the HRR and three (38%) also reported other methods.[12,13,23] Additionally, two studies (13%) also reported post-exercise vagal-related HRV indices.[12,23]

Six studies (75%) performed a maximal requirement test to measure the post-exercise PNS reactivation,[12,13,23,26,55,59] one (13%) performed a submaximal test and [57] one (13%) combined maximal and submaximal tests.[25] Three studies (37%) performed running-based exercise tests [9,12,23] and five (63%) were cycling-based.[13,25,26,55,57] All studies performed a passive recovery after exercise, mostly with the athletes in a seated position (six studies [75%]).[12,23,25,26,55,57] The recovery length ranged from 1 to 10 min. Both studies that measured HRV captured the last five min of the recovery period (10 min) to calculate vagal-related HRV indices. One study allowed participants to breathe spontaneously [23] and another controlled the breathing rate (12 breaths per min).[12]

Changes in HRR

Pooled analyses based on the training-induced fatigue status showed a statistically significant increase in HRR for F-OR athletes ($p < .001$) and a statistically non-significant change for non-OR athletes ($p = .430$). The overall SMD reached a moderate effect for F-OR athletes ($SMD_+ = 0.65$; 95% CI = 0.44, 0.87; Figure 3) and a trivial effect for non-OR athletes

(SMD_+ = 0.10; 95% CI = −0.15, 0.34; Figure 3). The heterogeneity was not statistically significant, and no inconsistency was found for HRR changes in F-OR (p = .620; I^2 = 0%) and non-OR athletes (p = .730; I^2 = 0%). The test for subgroup comparisons showed a statistically significant difference with high heterogeneity between F-OR and non-OR athletes in HRR changes (p < .001; I^2 = 91%).

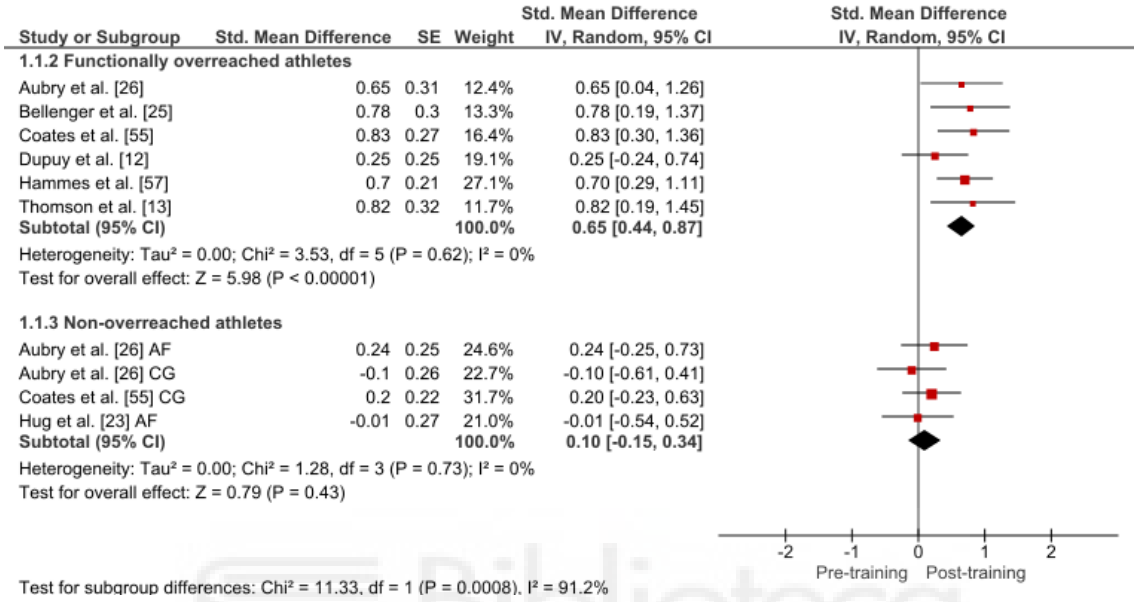

Figure 3. Forest plot of the standardised mean difference for heart rate recovery. *AF*, acute fatigue; *CG*, control group; *CI*, confidence interval; *IV*, inverse variance; *SE*, standard error

Influence of moderator variables on HRR sensitivity in F-OR athletes

The results of analyzing the influence of moderator variables on HRR changes in F-OR athletes can be found in Table 4. The subgroup analysis showed non-significant between-group differences, with no heterogeneity for the overload training period length (p = .570; I^2 = 0%), and with moderate heterogeneity for the training variable increased throughout the overload period (p = .130; I^2 = 57%). The overall SMD showed a statistically significant increase regardless of whether volume (p = .040) or volume and intensity (p < .001) were manipulated. The magnitude of the change was small when volume was increased (SMD_+ = 0.41; 95% CI = 0.02, 0.79) and moderate when volume and intensity were manipulated (SMD_+ = 0.77; 95% CI = 0.51, 1.03). The heterogeneity did not reach statistical significance, and no heterogeneity was found for volume (p = .320; I^2 = 1%), and for volume and intensity (p = .980; I^2 = 0%). Test for subgroup differences was not applicable for the exercise requirement. Pooled analysis based on the exercise requirement revealed a statistically non-significant change of HRR after submaximal tests (p = .310) and statistically significant increase after maximal tests (p < .001). The overall SMD reached a small effect for submaximal tests (SMD_+ = 0.36; 95% CI = −0.33, 1.04), and a moderate effect for maximal tests (SMD_+ = 0.64; 95% CI = 0.39, 0.89). The heterogeneity was statistically significant, and the inconsistency was high for submaximal tests (p = .020; I^2 = 80%), while the

heterogeneity did not reach statistical significance, and no inconsistency was found for maximal tests (p = .480; I^2 = 0%).

Table 4. Influence of moderator variables on the sensitivity of HRR indices in functionally overreached athletes

Moderator variable	Category	*k*	SMD (95% CI)	*Chi²*	*p*	I^2	Test for subgroup differences		
							Chi²	*p*	I^2
Exercise requirement	Submaximal	2	0.36 (−0.33, 1.04)	5.05	.020	80%	Not applicable[a]		
	Maximal	5	0.64 (0.39, 0.89)	3.46	.480	0%			
Training variable increased	Volume	2	0.41 (0.02, 0.79)	1.01	.320	1%	2.32	.130	57%
	Volume and intensity	4	0.77 (0.51, 1.03)	0.19	.980	0%			
Overload training period length	≤ 14 days	4	0.61 (0.36, 0.87)	3.01	.390	0%	0.33	.570	0%
	> 14 days	2	0.75 (0.35, 1.15)	0.19	.660	0%			

Chi², chi-square statistic; *CI*, confidence interval around SMD; I^2, heterogeneity index; *k*, number of studies; *p*, probability level associated to the *Chi²* statistic; *SMD*, standardized mean difference
[a]test for subgroup differences was not carried out when the same athletes were included in two or more categories within the moderator variable

Changes in post-exercise vagal-related HRV

There were insufficient data to perform pooled analysis based on training-induced fatigue status for post-exercise vagal-related HRV indices. Therefore, the sensitivity of this HR-based index will be qualitatively discussed in the next section.

DISCUSSION

This systematic review and meta-analysis investigated the sensitivity of resting and post-exercise vagal-related HRV and HRR indices to distinguish between F-OR and non-OR endurance-trained athletes, and to determine the influence of potential moderator variables on the sensitivity of these HR-based indices to identify F-OR athletes. Our pooled analysis based on training-induced fatigue status showed that resting vagal-related HRV indices are insensitive to increased PNS modulation in F-OR athletes without considering the influence of moderator variables. Our subgroup analysis based on the HRV values within F-OR athletes indicated that weekly averaged HRV values showed a moderate increase (0.81; 95% CI = 0.35, 1.26) with low inconsistency (p = .190; I^2 = 39%), while isolated HRV values showed a small decrease (−0.45; 95% CI = −0.96, 0.06) with high heterogeneity (p = .004; I^2 = 74%). Plews, Laursen, Le Meur, Hausswirth, Kilding, Buchheit [60] determined that at least three valid measurements should be averaged to obtain a valid HRV value due to the high day-to-day lability of HRV assessments. However, the number of averaged HRV values was not investigated in our review since all included studies used a 7-day averaged HRV value. Additionally, the influence of the remaining moderator variables did not reach statistical significance. Regarding HRR, our findings indicate that F-OR athletes showed a moderate HRR increase (0.65; 95% CI = 0.44, 0.87), while non-OR athletes showed no HRR increase (0.10; 95% CI = −0.15, 0.34). Although we did not find heterogeneity between the results

of the studies included, it should be noted that most used HRR 1 min, tested in the seated position after maximal exercise. These findings support our hypotheses that an increase in PNS modulation among F-OR athletes can be detected by using resting vagal-related HRV and HRR indices and that their sensitivity is influenced by methodological factors. Meta-analyses to determine the sensitivity of post-exercise vagal-related HRV indices were not performed due to insufficient data.

Resting vagal-related HRV indices

Our pooled analysis based on the training-induced fatigue status showed a statistically non-significant change in vagal-related HRV indices for F-OR and non-OR athletes, preventing distinction between both overload training-induced fatigue states. Although different methodological aspects were considered, Bellenger, Fuller, Thomson, Davison, Robertson, Buckley [27] also found a non-significant change in pooled resting vagal-related HRV indices in F-OR athletes (0.13; 95% CI = −0.03, 0.29). Authors of this meta-analysis carried out a subgroup analysis based on the vagal-related HRV index used to explain the heterogeneity found among the results of the included studies in their analysis. They found a small increase in RMSSD (0.26; 95% CI = 0.05, 0.47) with no heterogeneity (p = .640; I^2 = 0%), and a trivial change in HF (0.04; 95% CI = −0.25, 0.33) with moderate heterogeneity (p = .010; I^2 = 64%) in studies leading to decreased performance capacity. It was concluded that RMSSD seems to be more sensitive than HF for detecting increased PNS modulation in F-OR athletes, and it was hypothesized that the lower sensitivity of HF could be due to a marked sensitivity of this HR-based index to respiratory rates. While the higher sensitivity of HF to respiratory rates has been previously reported [61] and findings support the use of RMSSD as the preferred resting vagal-related HRV index,[6,15] it should be considered that Bellenger, Fuller, Thomson, Davison, Robertson, Buckley [27] acknowledged that their findings may be biased by their inclusion of multiple comparisons from the same studies (i.e., assessment position, recording length). Additionally, this analysis did not allow them to investigate the influence of assessment position on the sensitivity of vagal-related HRV indices to identify changes in PNS modulation. However, previous studies have highlighted the influence of this methodological issue on the vagal-related HRV sensitivity.[31] These concerns limit the scope of their conclusions and create uncertainty regarding the sensitivity of vagal-related HRV indices to detect changes in PNS activity. Additionally, the influence of another important methodological issue, such as the use of averaged or isolated HRV values,[28] was not investigated. Thus, our study is the first systematic review and meta-analysis to investigate the influence of potential moderator variables on the sensitivity of vagal-related HRV indices to identify changes in ANS modulation in F-OR athletes. Methodological issues must be considered when vagal-related HRV indices are used to detect PNS hyperactivity in F-OR, since our pooled analysis based on the training-induced fatigue status showed inconclusive results.

Our subgroup analyses performed within F-OR athletes showed that vagal-related HRV indices are only sensitive to increased PNS modulation when daily HRV values were averaged weekly, while findings obtained from isolated HRV values were inconclusive. It should be noted that all studies that met inclusion criteria for our meta-analysis based their findings on averaged HRV values using RMSSD assessed in the standing position as the vagal-related HRV index,[25,52,54] limiting our subgroup analysis based on the assessment position. Previous studies have suggested that the controversial findings within HRV literature may be due to the large day-to-day variation in HRV measures.[62] In this regard, there is evidence showing that weekly averaged HRV values provide superior methodological validity than isolated HRV values as a result of attenuated day-to-day HRV variations.[15,32] Bellenger, Fuller, Thomson, Davison, Robertson, Buckley [27] also hypothesized that the higher heterogeneity found in studies which used HF as the vagal-related HRV index could be due to the use of isolated HRV values. Interestingly, Le Meur, Pichon, Schaal, Schmitt, Louis, Gueneron, Vidal, Hausswirth [9] who were excluded from our meta-analysis because insufficient data were reported to calculate the ES, analyzed changes in PNS modulation in F-OR athletes using isolated and averaged HRV values. In line with our findings, they reported that increased PNS activity in F-OR athletes was only detected when weekly averaged HRV values were analysed. Plews, Laursen, Kilding, Buchheit [39] also found higher correlations between changes in performance and vagal-related HRV indices when averaged HRV values were used. Additionally, another study based on isolated HRV values, which did not fulfil our inclusion criteria, also reported symptoms of PNS hyperactivity without concomitant changes in vagal-related HRV indices in F-OR athletes.[63]

Regarding the resting vagal-related HRV index and assessment position used, Bourdillon, Yazdani, Nilchian, Mariano, Vesin, Millet [54] and Le Meur, Pichon, Schaal, Schmitt, Louis, Gueneron, Vidal, Hausswirth [9] reported weekly averaged RMSSD and HF values assessed in supine and standing positions. Bourdillon, Yazdani, Nilchian, Mariano, Vesin, Millet [54] reached the same conclusions regardless of the weekly averaged vagal-related HRV index and position used to perform the assessment. Although similar conclusions were drawn regardless of assessment position, it should be noted that a twofold increase in PNS activity was observed when assessments were performed in the standing position (see Supplementary file 2). Le Meur, Pichon, Schaal, Schmitt, Louis, Gueneron, Vidal, Hausswirth [9] reported inconclusive findings for weekly averaged HF values based on the assessment position, finding no changes in HF when HRV assessments were carried out in the supine position, while increased PNS modulation was reported in the standing position regardless of the vagal-related HRV index used. Bellenger, Karavirta, Thomson, Robertson, Davison, Buckley [52] reported weekly averaged RMSSD values in standing and supine positions. RMSSD increased in the standing position in F-OR athletes (0.88; 95% CI = 0.35, 1.41), while no RMSSD changes were found in the supine position (0.23; 95% CI = −0.18, 0.64). Thus, the authors concluded that weekly averaged RMSSD values obtained from the

standing position are more sensitive for detecting PNS hyperactivity in F-OR athletes than supine measures. Therefore, collective findings seem to support the use of weekly averaged RMSSD values assessed in the standing position to increase the sensitivity of resting vagal-related HRV to detect PNS hyperactivity in F-OR athletes.

HRR indices

Our findings showed that HRR is a sensitive index for detecting PNS hyperactivity in F-OR athletes (0.65; 95% CI = 0.44, 0.87), and inferring overload training-induced fatigue status in endurance-trained athletes. It should be noted that all studies included in our meta-analysis used HRR 1 min as the HRR index. In agreement with our results, Bellenger, Fuller, Thomson, Davison, Robertson, Buckley [27] reported a significant increase in HRR 1 min in studies leading to reduced performance capacity (0.46; 95% CI = 0.26, 0.66). Nevertheless, their results may be biased due to multiple comparisons from the same athletes to calculate changes in HRR, limiting the scope of their findings. We did not find heterogeneity between the results of studies included in our meta-analysis that estimated HRR changes in F-OR athletes, most of them (83%) tested this HR-based index after maximal exercise. Therefore, our findings should be restricted to the sensitivity of HRR 1 min after maximal tests, and the influence of methodological inconsistencies cannot be discarded as a threat against the sensitivity of HRR indices. Thus, valuable information could be obtained from subgroup analyses carried out to determine whether the sensitivity of HRR indices is affected by methodological issues.

Regarding the influence of the exercise requirement on the sensitivity of HRR to identify F-OR athletes, we found that HRR 1 min after maximal exercise showed a moderate statistical increase (0.64; 95% CI = 0.39, 0.89) with no inconsistency (I^2 = 0%), while HRR 1 min after submaximal exercise did not show a statistical change (0.36; 95% CI = −0.33, 1.04) and heterogeneity was high (I^2 = 80%). These findings suggest that HRR 1 min after submaximal exercise is not a sensitive marker of PNS hyperactivity in F-OR athletes. Maximal exercise to volitional exhaustion in athletes suspected of F-OR may increase the probability of progression into a state of N-FOR, limiting the diagnostic utility of HRR 1 min to infer training-induced fatigue status. Nevertheless, only two of the studies included in our meta-analysis tested HRR 1 min after submaximal exercise, and their findings are equivocal. Hammes, Skorski, Schwindling, Ferrauti, Pfeiffer, Kellmann, Meyer [57] assessed HRR 1 min after a submaximal incremental test (3 exercise bouts: 6 min at 60% and 80% of maximal HR, and 3 min at 90% of maximal HR) and found a moderate significant increase (0.70; 95% CI = 0.29, 1.11). The magnitude of this HRR 1 min increase after submaximal exercise in F-OR athletes was similar to increases observed after maximal exercise in other studies included in our meta-analysis (see Supplementary file 3). Similarly, Le Meur, Buchheit, Aubry, Coutts, Hausswirth [59] who were excluded from our meta-analysis because insufficient data were reported to calculate the ES, measured HRR 1 min across

a large range of exercise intensities (60 – 100% of maximal aerobic speed). They reported an increase in HRR 1 min among F-OR athletes regardless of the exercise intensity. Interestingly, they found that the increase of HRR 1 min is higher after lower exercise intensities (60 – 65% of maximal aerobic speed). These findings support the diagnostic utility of HRR 1 min after submaximal exercise carried out above 60 – 65% of maximal capacity. Bellenger, Thomson, Robertson, Davison, Nelson, Karavirta, Buckley [25] tested HRR 1 min after submaximal and maximal exercise in F-OR athletes and found an increase of HRR 1 min after maximal exercise (0.78; 95% CI = 0.19, 1.37). However, they did not find an increase of HRR 1 min after submaximal exercise carried out at 160 W (−0.17; 95% CI = −0.63, 0.29) or 200 W (0.15; 95% CI = −0.31, 0.60) (see Supplementary file 3). These authors concluded that only HRR 1 min after maximal exercise allowed detection of PNS hyperactivity in F-OR athletes. However, submaximal exercise was prescribed in absolute intensity values, and we do not know the relative intensity in relation to the maximal capacity. Thus, we hypothesize that the lack of sensitivity of HRR 1 min after submaximal exercise to detect PNS hyperactivity in F-OR athletes reported by Bellenger, Thomson, Robertson, Davison, Nelson, Karavirta, Buckley [25] could be because the relative intensity used was below the minimal intensity required. Therefore, studies show that HRR 1 min after maximal exercise is suitable to detect changes in PNS modulation in F-OR athletes. Additionally, it seems that HRR 1 min after submaximal exercise performed above 60 – 65% of maximal capacity may also allow identification of training-induced fatigue status. However, very few studies have investigated the sensitivity of HRR 1 min after submaximal exercise. The discrepancies between previous studies warrant future research to establish whether HRR 1 min after submaximal exercise is a sensitive marker of PNS changes in F-OR, and to confirm the minimal exercise intensity required to identify these changes.

Our subgroup analysis based on the increased training variable throughout the overload training period showed higher increases in HRR 1 min in studies that manipulated volume and intensity to boost training load (0.77; 95% CI = 0.51, 1.03) than in studies that only increased volume (0.41; 95% CI = 0.02, 0.79). This finding suggests that PNS hyperactivity in F-OR could be higher when intensity is also manipulated to increase training load. Thus, HRR indices may also distinguish between different levels of PNS activity increases within F-OR athletes. On the other hand, the overload training period length did not influence the sensitivity of HRR to infer changes in training-induced fatigue status. It should be noted that most of the studies included in our meta-analysis (75%) tested HRR 1 min in the seated position and therefore, subgroup analysis based on the assessment position was not performed. Thomson, Bellenger, Howe, Karavirta, Buckley [13] tested HRR 1 min in the supine position and observed an increase of HRR 1 min similar to increases reported in the seated position (see Supplementary file 3). Therefore, it seems that both seated and supine positions may be suitable to detect increased post-exercise PNS modulation in F-OR athletes.

Post-exercise vagal-related HRV indices

Dupuy, Bherer, Audiffren, Bosquet [12] and Hug, Heyer, Naef, Buchheit, Wehrlin, Millet [23] analyzed the sensitivity of post-exercise vagal-related HRV indices to infer training-induced fatigue status in endurance-trained athletes after overload training. However, athletes from Hug's study did not show symptoms of F-OR and were considered AF athletes (see Table 2). Therefore, meta-analyses to calculate PNS hyperactivity in F-OR athletes and analyze the sensitivity of this HR-based index to infer training-induced fatigue status were not carried out.

Within the studies included in our systematic review, Dupuy, Bherer, Audiffren, Bosquet [12] found an increase of post-exercise RMSSD after overload training in F-OR athletes (0.59; 95% CI = 0.04, 1.15), while Hug, Heyer, Naef, Buchheit, Wehrlin, Millet [23] reported no significant changes in post-exercise RMSSD in non-OR athletes (0.16; 95% CI = −0.37, 0.70). Regarding the vagal-related HRV index used to infer changes in PNS modulation, Dupuy, Bherer, Audiffren, Bosquet [12] reached the same conclusions regardless of the vagal-related HRV index used (RMSSD or HF) (see Supplementary file 3). It should be noted that the breathing rate was controlled throughout the recovery period when data acquisition was performed, which may increase the validity of HF to detect changes in PNS modulation.[64] Additionally, both studies assessed post-exercise vagal-related HRV indices in a seated position after maximal exercise only, warranting future research to determine the sensitivity of this index to detect PNS hyperactivity after submaximal exercise. Therefore, it seems that post-exercise vagal-related HRV indices after maximal exercise are also sensitive to increased PNS modulation in F-OR athletes. However, the low number of studies that investigated the sensitivity of this HR-based index to infer training-induced fatigue status warrants future study to increase our knowledge about this topic.

Strengths and limitations

This systematic review with meta-analysis is the first to analyze the sensitivity of resting and post-exercise vagal-related HRV indices and HRR indices to detect PNS hyperactivity with an exclusive focus on endurance-trained athletes. A strength of this investigation was that we assessed the influence of important methodological factors on the sensitivity of these HR-based indices for inferring training-induced fatigue status. Additionally, we also included changes in PNS modulation among non-OR athletes. Finally, overload training-induced fatigue status diagnosis was based on changes in performance capacity and other indicators of fatigue status. Nevertheless, there are also some limitations that should be noted. Risk of bias and publication bias assessments were not carried out since we considered that the controversial findings within the literature could be related to methodological issues, and the inclusion of these analyses would not give us relevant information about the validity of our findings. The influence of athletic level and type of exercise were not investigated since only one study included high-level athletes and combined endurance and strength training.[24] Our findings are therefore limited to recreationally-

and well-trained endurance athletes performing an overload endurance training period. Some analyses of moderator variables were carried out with a low number of studies, which limit the current findings. The influence of continuous moderator variables (i.e., cardiorespiratory fitness or participant age) was not investigated due to aggregated information at the trial level, which may produce spurious associations between continuous variables and treatment effects.[65] The influence of participant characteristics on the sensitivity of HR-based indices to detect parasympathetic hyperactivity requires future study. Additionally, despite symptoms of F-OR reported at the group level, some studies included in our systematic review and meta-analysis did not indicate how many athletes could be considered F-OR. In addition, previous studies have reported that PNS hyperactivity in endurance-trained athletes may also be indicative of a positive response to training.[27,66-68] Therefore, increased PNS modulation found in our meta-analysis in F-OR endurance-trained athletes should be contextualized and complemented with other subjective indicators of training-induced fatigue status to identify athletes who are not responding properly to overload training. Finally, we note that cardiac-autonomic responses to overload training are non-uniform. In some cases, parasympathetic activity is attenuated,[32,69-72] or more variable on a day-to-day basis [73,74] in fatigued-states. Thus, failure to detect reduced HR or increased HRV responses would not necessarily reflect an inability of these measures to detect meaningful responses.

PERSPECTIVE

Resting and post-exercise vagal-related HRV and HRR indices seem to be sensitive to changes in PNS modulation in F-OR athletes. Therefore, these HR-based indices could be used to identify athletes who are not properly responding to overload training before evolving into a status of N-FOR. The sensitivity of these HR-based indices seems to be influenced by methodological issues. For instance, weekly averaged RMSSD values measured in the standing position should be used to increase the sensitivity of resting vagal-related HRV indices to PNS hyperactivity in F-OR athletes. HRR 1 min tested in the seated position after maximal exercise is also a sensitive marker to detect PNS hyperactivity in F-OR. Though studies are limited, it seems that HRR 1 min after submaximal exercise performed above a minimal intensity (i.e., 60 – 65% of maximal aerobic speed) may also allow identification of training-induced fatigue status in endurance-trained athletes, increasing the diagnostic utility of HRR 1 min to identify changes in PNS modulation. Similarly, it seems that vagal-related HRV indices (RMSSD and HF) tested in seated position after maximal exercise also identify increases in PNS activity in F-OR, while their sensitivity after submaximal exercise has not been previously investigated. Finally, our findings support the hypothesis of PNS hyperactivity in F-OR athletes.

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8.1.2. Supplementary material study 1

Supplementary file 1. Electronic database search

Cochrane

#1. (endurance NEAR/3 training OR endurance NEAR/3 exercise*): ti,ab,kw

#2. (aerobic NEAR/3 training OR aerobic NEAR/3 exercise*): ti,ab,kw

#3. (strenuous NEAR/3 training OR strenuous NEAR/3 exercise*): ti,ab,kw

#4. (inten* NEAR/2 training OR inten*NEAR/2 exercise*): ti,ab,kw

#5. (control* NEAR/2 training OR control* NEAR/2 exercise*): ti,ab,kw

#6. (run* NEAR/2 training OR run* NEAR/2 exercise*): ti,ab,kw

#7. (physical NEAR/3 training OR physical NEAR/3 exercise*): ti,ab,kw

#8. (overload NEAR/3 training OR overload NEAR/3 exercise*): ti,ab,kw

#9. (interval* NEAR/2 training OR interval* NEAR/2 exercise*): ti,ab,kw

#10. hiit OR hit: ti,ab,kw

#11. overreaching: ti,ab,kw

#12. overtraining: ti,ab,kw

#13. training NEAR/2 status: ti,ab,kw

#14. “phase train*” OR “heavy train*” OR “light train*”:ti,ab,kw

#15. “intensive period”: ti,ab,kw

#16. “exercise train*”: ti,ab,kw

#17. “distance train*”: ti,ab,kw

#18. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

#19. “heart rate variability”: ti,ab,kw

#20. “heart rate recovery”: ti,ab,kw

#21. hrv OR hrr: ti,ab,kw

#22. “heart rate regulation”: ti,ab,kw

#23. “autonomic nervous system” OR “sympathetic nervous system” OR “parasympathetic nervous system”: ti,ab,kw

#24. (parasympathetic NEAR/2 indice* OR parasympathetic NEAR/2 indicator OR parasympathetic NEAR/2 modulation OR parasympathetic NEAR/2 function OR parasympathetic NEAR/2 activity OR parasympathetic NEAR/2 tone OR parasympathetic NEAR/2 adaptation OR parasympathetic NEAR/2 control): ti,ab,kw

#25. (vagal NEAR/2 indice* OR vagal NEAR/2 indicator OR vagal NEAR/2 modulation OR vagal NEAR/2 function OR vagal NEAR/2 activity OR vagal NEAR/2 tone OR vagal NEAR/2 adaptation OR vagal NEAR/2 control): ti,ab,kw

#26. (autonomic NEAR/2 control OR autonomic NEAR/2 balance OR autonomic NEAR/2 modulation OR autonomic NEAR/2 function OR autonomic NEAR/2 activity OR autonomic NEAR/2 tone OR autonomic NEAR/2 adaptation OR autonomic NEAR/2 regulation OR autonomic NEAR/2 drive): ti,ab,kw

#27. #19 OR #20 OR #21 OR #22 #23 OR #24 OR #25 OR #26

#28. runn*: ti,ab,kw

#29. swimm*: ti,ab,kw

#30. cycli*: ti,ab,kw

#31. triathl*: ti,ab,kw

#32. athlete*: ti,ab,kw

#33. rower*: ti,ab,kw

#34. cross-countr*: ti,ab,kw

#35. canoeist*: ti,ab,kw

#36. kayak*: ti,ab,kw

#37. skier*: ti,ab,kw

#38. “distance athlete*”: ti,ab,kw

#39. “endurance-train*”: ti,ab,kw

#40. “subjects train*”: ti,ab,kw

#41. #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40

#42. #18 AND #27 AND #41

Scopus

#1. (endurance PRE/3 training OR endurance PRE/3 exercise*): ti,ab,kw

#2. (aerobic PRE/3 training OR aerobic PRE/3 exercise*): ti,ab,kw

#3. (strenuous PRE/3 training OR strenuous PRE/3 exercise*): ti,ab,kw

#4. (inten* PRE/2 training OR inten* PRE/2 exercise*): ti,ab,kw

#5. (control* PRE/2 training OR control* PRE/2 exercise*): ti,ab,kw

#6. (run* PRE/2 training OR run* PRE/2 exercise*): ti,ab,kw

#7. (physical PRE/3 training OR physical PRE/3 exercise*): ti,ab,kw

#8. (overload PRE/3 training OR overload PRE/3 exercise*): ti,ab,kw

#9. (interval* PRE/2 training OR interval* PRE/2 exercise*): ti,ab,kw

#10. hiit OR hit: ti,ab,kw

#11. overreaching: ti,ab,kw

#12. overtraining: ti,ab,kw

#13. training PRE/2 status: ti,ab,kw

#14. “phase train*” OR “heavy train*” OR “light train*”: ti,ab,kw

#15. “intensive period”: ti,ab,kw

#16. “exercise train*”: ti,ab,kw

#17. “distance train*”: ti,ab,kw

#18. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

#19. “heart rate variability”: ti,ab,kw

#20. “heart rate recovery”: ti,ab,kw

#21. hrv OR hrr: ti,ab,kw

#22. “heart rate regulation”: ti,ab,kw

#23. (“autonomic nervous system” OR “sympathetic nervous system” OR “parasympathetic nervous system”): ti,ab,kw

#24. (“parasympathetic indice*” OR “parasympathetic indicator” OR “parasympathetic modulation” OR “parasympathetic function” OR “parasympathetic activity” OR “parasympathetic tone” OR “parasympathetic adaptation” OR “parasympathetic control”): ti,ab,kw

#25. ("vagal indice*" OR "vagal indicator" OR "vagal modulation" OR "vagal function" OR "vagal activity" OR "vagal tone" OR "vagal adaptation" OR "vagal control"): ti,ab,kw

#26. ("autonomic control" OR "autonomic balance" OR "autonomic modulation" OR "autonomic function" OR "autonomic activity" OR "autonomic tone" OR "autonomic adaptation" OR "autonomic regulation" OR "autonomic drive"): ti,ab,kw

#27. #19 OR #20 OR #21 OR #22 #23 OR #24 OR #25 OR #26

#28. runn*: ti,ab,kw

#29. swimm*: ti,ab,kw

#30. cycli*: ti,ab,kw

#31. triathl*: ti,ab,kw

#32. athlete*: ti,ab,kw

#33. rower*: ti,ab,kw

#34. cross-countr*: ti,ab,kw

#35. canoeist*: ti,ab,kw

#36. kayak*: ti,ab,kw

#37. skier*: ti,ab,kw

#38. "distance athlete*": ti,ab,kw

#39. "endurance-train*": ti,ab,kw

#40. "subjects train*": ti,ab,kw

#41. #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40

#42. #18 AND #27 AND #41

PubMed

#1. "endurance training" OR "endurance exercise*":ti,ab

#2. "aerobic training" OR "aerobic exercise*":ti,ab

#3. "strenuous training" OR "strenuous exercise*":ti,ab

#4. "intensive training" OR "intensive exercise": ti,ab

#5. "control* training" OR "control* exercise": ti,ab

#6. "run* training" OR "run* exercise": ti,ab

#7. "physical training" OR "physical exercise*":ti,ab

#8. "overload training" OR "overload exercise": ti,ab

#9. "interval* training" OR "interval* exercise": ti,ab

#10. hiit OR hit: ti,ab

#11. overreaching: ti,ab

#12. overtraining: ti,ab

#13. "training status": ti,ab

#14. "phase train*" OR "heavy train*" OR "light train*": ti,ab

#15. "intensive period": ti,ab

#16. "exercise train*": ti,ab

#17. "distance train*": ti,ab

#18. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

#19. “heart rate variability”: ti,ab

#20. “heart rate recovery”: ti,ab

#21. hrv OR hrr: ti,ab

#22. “heart rate regulation”: ti,ab

#23. “autonomic nervous system” OR “sympathetic nervous system” OR “parasympathetic nervous system”: ti,ab

#24. “parasympathetic indice” OR “*parasympathetic indicator” OR “*parasympathetic modulation” OR “*parasympathetic function” OR “*parasympathetic activity” OR “*parasympathetic tone” OR “*parasympathetic adaptation*” OR “parasympathetic control”: ti,ab

#25. “vagal indice” OR “*vagal indicator” OR “*vagal modulation” OR “*vagal function” OR “*vagal activity” OR “*vagal tone” OR “*vagal adaptation*” OR “vagal control”: ti,ab

#26. “autonomic control” OR “autonomic balance” OR “autonomic modulation” OR “autonomic function” OR “autonomic activity” OR “autonomic tone” OR “autonomic adaptation*” OR “*autonomic regulation” OR “autonomic drive”: ti,ab

#27. #19 OR #20 OR #21 OR #22 #23 OR #24 OR #25 OR #26

#28. runn*: ti,ab

#29. swimm*: ti,ab

#30. cycli*: ti,ab

#31. triathl*: ti,ab

#32. athlete*: ti,ab

#33. rower*: ti,ab

#34. cross-countr*: ti,ab

#35. canoeist*: ti,ab

#36. kayak*: ti,ab

#37. skier*: ti,ab

#38. “distance athlete*”: ti,ab

#39. “endurance athlete*”: ti,ab

#40. “subjects train*”: ti,ab

#41. #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40

#42. #18 AND #27 AND #41

Embase

#1. (endurance NEXT/3 training OR endurance NEXT/3 exercise*): ti,ab,kw

#2. (aerobic NEXT/3 training OR aerobic NEXT/3 exercise*): ti,ab,kw

#3. (strenuous NEXT/3 training OR strenuous NEXT/3 exercise*): ti,ab,kw

#4. (inten* NEXT/2 training OR inten* NEXT/2 exercise*): ti,ab,kw

#5. (control* NEXT/2 training OR control* NEXT/2 exercise*): ti,ab,kw

#6. (run* NEXT/2 training OR run* NEXT/2 exercise*): ti,ab,kw

#7. (physical NEXT/3 training OR physical NEXT/3 exercise*): ti,ab,kw

#8. (overload NEXT/3 training OR overload NEXT/3 exercise*): ti,ab,kw

#9. (interval* NEXT/2 training OR interval* NEXT/2 exercise*): ti,ab,kw

#10. hiit OR hit: ti,ab,kw

#11. overreaching: ti,ab,kw

#12. overtraining: ti,ab,kw

#13. (training NEXT/2 status): ti,ab,kw

#14. “phase train*” OR “heavy train*” OR “light train*”: ti,ab,kw

#15. “intens* period”: ti,ab,kw

#16. “exercise train*”: ti,ab,kw

#17. “distance train*”: ti,ab,kw

#18. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

#19. “heart rate variability”: ti,ab,kw

#20. “heart rate recovery”: ti,ab,kw

#21. hrv OR hrr: ti,ab,kw

#22. “heart rate regulation”: ti,ab,kw

#23. “autonomic nervous system” OR “sympathetic nervous system” OR “parasympathetic nervous system”: ti,ab,kw

#24. (“parasympathetic indice*” OR “parasympathetic indicator” OR “parasympathetic modulation” OR “parasympathetic function” OR “parasympathetic activity” OR “parasympathetic tone” OR “parasympathetic adaptation” OR “parasympathetic control”): ti,ab,kw

#25. (“vagal indice*” OR “vagal indicator” OR “vagal modulation” OR “vagal function” OR “vagal activity” OR “vagal tone” OR “vagal adaptation” OR “vagal control”): ti,ab,kw

#26. (“autonomic control” OR “autonomic balance” OR “autonomic modulation” OR “autonomic function” OR “autonomic activity” OR “autonomic tone” OR “autonomic adaptation” OR “autonomic regulation” OR “autonomic drive”): ti,ab,kw

#27. #19 OR #20 OR #21 OR #22 #23 OR #24 OR #25 OR #26

#28. runn*: ti,ab,kw

#29. swimm*: ti,ab,kw

#30. cycli*: ti,ab,kw

#31. triathl*: ti,ab,kw

#32. athlete*: ti,ab,kw

#33. rower*: ti,ab,kw

#34. cross-countr*: ti,ab,kw

#35. canoeist*: ti,ab,kw

#36. kayak*: ti,ab,kw

#37. skier*: ti,ab,kw

#38. “distance athlete*”: ti,ab,kw

#39. “endurance-train*”: ti,ab,kw

#40. “subjects train*: ti,ab,kw

#41. #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40

#42. #18 AND #27 AND #41

Web of Science (All databases were searched)

#1. (endurance NEAR/3 training OR endurance NEAR/3 exercise*): tp

#2. (aerobic NEAR/3 training OR aerobic NEAR/3 exercise*): tp

#3. (“strenuous training” OR “strenuous exercise*”): tp

#4. (“inten* training” OR “inten* exercise*”): tp

#5. (“control* training” OR “control* exercise*”): tp

#6. (“run* training” OR “run* exercise*”): tp

#7. (“physical training” OR “physical exercise*"): tp

#8. (“overload training” OR “overload exercise*”): tp

#9. (“interval* training” OR “interval* exercise*”): tp

#10. hiit OR hit: tp

#11. overreaching: tp

#12. overtraining: tp

#13. training NEAR/2 status: tp

#14. “phase train*” OR “heavy train*” OR “light train*”: tp

#15. “intens* period”: tp

#16. “exercise train*”: tp

#17. “distance train*”: tp

#18. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17

#19. “heart rate variability”: tp

#20. “heart rate recovery”: tp

#21. hrv OR hrr: tp

#22. “heart rate regulation”: tp

#23. “autonomic nervous system” OR “sympathetic nervous system” OR “parasympathetic nervous system”: tp

#24. (“parasympathetic indice*” OR “parasympathetic indicator” OR “parasympathetic modulation” OR “parasympathetic function” OR “parasympathetic activity” OR “parasympathetic tone” OR “parasympathetic adaptation” OR “parasympathetic control”): tp

#25. (“vagal indice*” OR “vagal indicator” OR “vagal modulation” OR “vagal function” OR “vagal activity” OR “vagal tone” OR “vagal adaptation” OR “vagal control”): tp

#26. (“autonomic control” OR “autonomic balance” OR “autonomic modulation” OR “autonomic function” OR “autonomic activity” OR “autonomic tone” OR “autonomic adaptation” OR “autonomic regulation” OR “autonomic drive”): tp

#27. #19 OR #20 OR #21 OR #22 #23 OR #24 OR #25 OR #26

#28. Runn*: tp

#29. Swimm*: tp

#30. Cycli*: tp

#31. Triathl*: tp

#32. Athlete*: tp

#33. Rower*: tp

#34. Cross-countr*: tp

#35. Canoeist*: tp

#36. Kayak*: tp

#37. Skier*: tp

#38. “distance athlete*”: tp

#39. “endurance-train*”: tp

#40. “subjects train*”: tp

#41. #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40

#42. #18 AND #27 AND #41

Supplementary file 2; Table S1. Resting HRV assessment characteristics and outcome measures

Study (author)	Sampling rate; equipment; data processing; method used; power spectral density method	Resting HRV assessment characteristics: Time of day; recording posture; breathing; breathing rate	Resting HRV assessment characteristics: Stabilization period; recording length; HRV valued used; number of averaged days	Outcome measure details: Parameter assessed	Outcome measure details: Training group (n); SMD (95% CI)
Baumert [51]	1600 Hz; ECG; yes; interpolation algorithms; FFT	At time of laboratory test; supine; NR; NR	NR; 30 min; isolated; NA	RMSSD	F-OR (10); −0.62 (−1.23, −0.01)[b]
				HF	F-OR (10); −0.33 (−0.86, 0.20)
Bellenger [52]	1000 Hz; HR monitor; yes; automatic and manual filtering; NA	Daily morning waking; supine and standing; NR; NR	Yes; 2 min (supine), 2 min (standing); averaged; 7 days	RMSSD standing	F-OR (15); 0.88 (0.35, 1.41)[b]
				RMSSD supine	F-OR (15); 0.23 (−0.18, 0.64)
Bellenger [25]	1000 Hz; HR monitor; yes; automatic and manual filtering; NA	Daily morning waking; standing; NR; NR	Yes; 2 min; averaged; 7 days	RMSSD	F-OR (12); 1.23 (0.50, 1.96)
Bosquet [53]	1000 Hz; HR monitor; yes; interpolation algorithms; FFT	Sleeping; laying; NA; NA	NR; 300 min; isolated; NA	HF	Data were reported as normalised units[a]
Bourdillon [54]	1000 Hz; HR monitor; yes; interpolation algorithms; FFT	Daily morning waking; supine and standing; spontaneous; NA	No; 3 min (daily), 6 min (every third day); averaged; depending on the training period (baseline period, 14 days; overload period, last 7 days)	RMSSD standing	AF (7); 0.38 (−0.29, 1.05)[b]
				RMSSD supine	AF (7); 0.14 (−0.48, 0.76)
				HF standing	AF (7); 0.23 (−0.40, 0.86)
				HF supine	AF (7); 0.13 (−0.49, 0.75)
				RMSSD standing	F-OR (8); 0.38 (−0.23, 0.99)[b]
				RMSSD supine	F-OR (8); 0.17 (−0.40, 0.74)
				HF standing	F-OR (8); 0.39 (−0.22, 1.00)
				HF supine	F-OR (8); 0.12 (−0.45, 0.69)
Coates [55]	NR; ECG; yes; NR; NR	At time of laboratory test; supine; spontaneous; NA	Yes; 5 min; isolated; NA	RMSSD	F-OR (15); −0.05 (−0.44, 0.34)[b]
				HF	F-OR (15); −0.08 (−0.47, 0.31)
				RMSSD	CG (13); 0.13 (−0.30, 0.56)[b]
				HF	CG (13); 0.11 (−0.33, 0.54)

Table S1. Continued

Study (author)	Sampling rate; equipment; data processing; method used; power spectral density method	Resting HRV assessment characteristics: Time of day; recording posture; breathing; breathing rate	Resting HRV assessment characteristics: Stabilization period; recording length; HRV valued used; number of averaged days	Outcome measure details: Parameter assessed	Outcome measure details: Training group (n); SMD (95% CI)
Dupuy [12]	1000 Hz; HR monitor; yes; interpolation algorithms; FFT	Sleeping; laying; NA; NA	Yes; 240 min (full period), 10 min (SWS); isolated; NA	RMSSD (full period)	F-OR (11); 0.16 (−0.32, 0.64)
				RMSSD (SWS)	F-OR (11); 0.04 (−0.43, 0.51)[b]
				HF (full period)	F-OR (11); 0.35 (−0.15, 0.86)
				HF (SWS)	F-OR (11); −0.08 (−0.55, 0.39)
				SD_1 (full period)	F-OR (11); 0.16 (−0.32, 0.64)
				SD_1 (SWS)	F-OR (11); −0.14 (−0.61, 0.33)
Garet [56]	1000 Hz; HR monitor; yes; interpolation algorithms; wavelet decomposition	Sleeping; laying; NA; NA	No; 360 min; averaged; 2 days	RMSSD HF	Insufficient reporting[a]
Hedelin [24]	NR; HR monitor; yes; interpolation algorithms; auto-regressive	At time of laboratory test; laying; controlled; 12 breath per min	NR; NR; isolated; NA	HF	F-OR (9); −0.37 (−0.94, 0.20)
Hug [23]	1000 Hz; HR monitor; NR; NR; NA	At time of laboratory test; seated; spontaneous; NA	Yes; 8 min; isolated; NA	RMSSD	AF (9); 0.05 (−0.48, 0.58)
Le Meur [9]	1000 Hz; HR monitor; yes; NR; Goertz algorithms	Daily morning waking; supine and standing; spontaneous; NA	Yes; 4 min (supine), 4 min (standing); averaged and isolated (day value test); 7 days	RMSSD HF	Insufficient reporting[a]
Woods [58]	NR; HR monitor; NR; NR; NA	At time of laboratory test; supine; NR; NR	Yes; 5 min; isolated; NA	RMSSD	F-OR (11); −2.69 (−4.12, −1.26)

AF, acute fatigue; *CG*, control group; *CI*, confidence interval; *ECG*, electrocardiogram; *FFT*, Fast-Fourier transform; *F-OR*, functional overreaching; *HF*, high frequency; *HR*, heart rate, *HRV*, heart rate variability; *n*, number of athletes included in the analysis; *NA*, no applicable; *NR*, no reported; *RMSSD*, the root-mean-square difference of successive normal R-R intervals; SD_1, the standard deviation of instantaneous beat-to-beat R-R interval variability; *SMD*, standardized mean difference; *SWS*, slow-wave sleep

[a]Excluded from meta-analysis

[b]Preferential outcome

Supplementary file 2; Table S2. Post-exercise assessment characteristics and outcome measures

		Testing characteristics	Recovery characteristics	HRV assessment characteristics	Outcome measure details	
Study (author)	**Variable**	**Type; intensity; length; mode**	**Type; intensity; length; position**	**Length; breathing; breathing rate**	**Parameter assessed**	**Group (n); SMD (95% CI)**
Aubry [26]	HRR	Maximal incremental test; NA; volitional exhaustion; cycling	Passive; NA; 1 min; seated		HRR 1 min	AF (11); 0.24 (−0.25, 0.73)
						F-OR (10); 0.65 (0.04, 1.26)
						CG (10); −0.10 (−0.61, 0.41)
Bellenger [25]	HRR	Submaximal test; 160 W; 5 min; cycling	Passive; NA; 1 min; seated		HRR 1 min	F-OR (12); −0.17 (−0.63, 0.29)
		Submaximal test; 200 W; 5 min; cycling				F-OR (12); 0.15 (−0.31, 0.60)
		Maximal test; NA; 5 min; cycling				F-OR (12); 1.00 (0.35, 1.65)[b,c]
		Maximal test; NA; 60 min; cycling				F-OR (12); 0.56 (0.04, 1.08)[b,c]
Coates [55]	HRR	Maximal incremental test; NA; volitional exhaustion; cycling	Passive; NA; 1 min; seated		HRR 1 min	F-OR (15); 0.83 (0.30, 1.36)
						CG (13); 0.20 (−0.23, 0.63)
Dupuy [12]	HRR Post-exercise HRV	Maximal incremental test; NA; volitional exhaustion; running	Passive; NA; 10 min; seated	5 min; controlled; 12 breaths per min	HRR 1 min	F-OR (11); 0.07 (−0.40, 0.54)[b,c]
					T30	F-OR (11); −0.45 (−0.97, 0.08)
					HRRT	F-OR (11); −0.45 (−0.98, 0.07)
					RMSSD	F-OR (11); 0.53 (−0.01, 1.07)[b]
					HF	F-OR (11); 0.68 (0.10, 1.27)
		Maximal constant test; 85% peak treadmill speed; volitional exhaustion; running			HRR 1 min	F-OR (11); 0.42 (−0.10, 0.93)[b,c]
					T30	F-OR (11); −0.45 (−0.97, 0.07)
					HRRT	F-OR (11); −0.18 (−0.66, 0.30)
					RMSSD	F-OR (11); 0.66 (0.08, 1.24)[b]
					HF	F-OR (11); 0.47 (−0.06, 1.00)

Table S2. Continued

Study (author)	Variable	Testing characteristics Type; intensity; length; mode	Recovery characteristics Type; intensity; length; position	HRV assessment characteristics Length; breathing; breathing rate	Outcome measure details Parameter assessed	 Group (n); SMD (95% CI)
Hammes [57]	HRR	Submaximal test (3 stages); 60%, 80% and 90% HR max; 6, 6 and 3 min; cycling	Passive; NA; 1.5 min; seated		HRR 1 min	F-OR (20); 0.70 (0.29, 1.11)
Hug [23]	HRR Post-exercise HRV	Maximal constant test (3 stages); 60%, 80% and 95% maximal oxygen uptake; 10, 8 and volitional exhaustion; running	Passive; NA; 10 min; seated	5 min; spontaneous; NA	HRR 1 min	AF (9); −0.01 (−0.54, 0.52)[b]
					HRR 10 min	AF (9); −0.03 (−0.56, 0.50)
					T30	AF (9); −0.19 (−0.73, 0.35)
					HRRT	AF (9); −0.02 (−0.54, 0.51)
					HR 1 min	AF (9); 0.00 (−0.53, 0.52)
					HR 10 min	AF (9); 0.00 (−0.53, 0.53)
					RMSSD	AF (9); 0.16 (−0.37, 0.70)
Le Meur [9]	HRR	Maximal incremental test; NA; volitional exhaustion; running	Passive; NA; 1 min; NR		HRR 1 min	Insufficient reporting[a]
Thomson [13]	HRR	Maximal test; NA; 5 min; cycling	Passive; NA; 1 min; supine		HRR 1 min	F-OR (11); 0.82 (0.19, 1.45)[b]
					T30	F-OR (11); −0.47 (−0.99, 0.06)
					T30 min	F-OR (11); −0.74 (−1.34, −0.14)
					HR 1 min	F-OR (11); −0.90 (−1.55, −0.24)

AF, acute fatigue; *CG*, control group; *CI*, confidence interval; *F-OR*, functional overreaching; *HF*, high frequency; *HR*, heart rate; *HR 1 min*, heart rate 1 min after exercise heart rate; *HR 10 min*, heart rate 10 min after exercise heart rate; *HRR, heart rate recovery; HRR 1 min*, number of heart beats recovered within 1 min after exercise; *HRR 10 min*, number of heart beats recovered within 10 min after exercise; *HRRT*, time constant of heart rate recovery; *HRV*, heart rate variability; *n*, number of athletes included in the analysis; *NA*, no applicable; *NR*, no reported; *RMSSD*, the root-mean-square difference of successive normal R-R intervals; *SMD*, standardized mean difference; *T30*, negative reciprocal of slope of regression line between natural logarithm of heart rate from first 30 s after exercise; *T30 min*, smallest time constant using negative reciprocal of slope of regression line between natural logarithm of heart rate from first 30 s after exercise

[a]Excluded from meta-analysis

[b]Preferential outcome

[c]Results were pooled before carrying out analyses

APPENDIX 2

STUDY 2

Exercise-based cardiac rehabilitation and parasympathetic function in patients with coronary artery disease: a systematic review and meta-analysis

Note. This study was published

Manresa-Rocamora A, Ribeiro F, Sarabia JM, Íbias J, Oliveira NL, Vera-García FJ, Moya-Ramón M. Exercise-based cardiac rehabilitation and parasympathetic function in patients with coronary artery disease: a systematic review and meta-analysis. *Clin Auton Res*. 2021 Apr;31(2):187-203. https://doi.org/10.1007/s10286-020-00687-0

8.2. Appendix 2

8.2.1. Study 2. Exercise-based cardiac rehabilitation and parasympathetic function in patients with coronary artery disease: a systematic review and meta-analysis

Abstract

Purpose The effects of exercise-based cardiac rehabilitation (CR) on parasympathetic modulation are controversial. This systematic review and meta-analysis aims to (a) determine the effect of exercise-based CR on heart-rate-derived indices associated with cardiac parasympathetic modulation in resting and post-exercise conditions in coronary artery disease (CAD) patients and (b) identify the possible moderator variables of the effect of exercise-based CR on parasympathetic modulation.

Methods We searched CENTRAL and Web of Science up to November 2018 for the following terms: adult CAD patients, controlled exercise-based CR interventions and parasympathetic modulation measured in resting (vagal-related heart rate variability [HRV] indices of the root mean square of the differences in successive RR interval [RMSSD] and high frequency [HF]) and post-exercise (heart rate recovery [HRR]) pre- and post-intervention. We estimated a random effect model of standardised mean difference (SMD) and mean difference (MD) for vagal-related HRV indices and HRR, respectively. We assessed the influence of categorical and continuous variables.

Results The overall effect size showed significant differences in RMSSD (SMD_+ = 0.30; 95% confidence interval [CI] = 0.12–0.49) and HRR (MD_+ = 5.35; 95% CI = 4.08–6.61 bpm) in favour of the exercise-based CR group. The overall effect size showed no differences in HF between groups (SMD_+ = 0.14; 95% CI, -0.12–0.40). Heterogeneity analyses reached statistical significance, with high heterogeneity for HF ($p < 0.001$; I^2 = 70.0%) and HRR ($p < 0.001$; I^2 = 85.0%). Analysis of the moderator variables showed that the effect on HRR is greater in young patients ($p = 0.008$) and patients treated with percutaneous intervention ($p = 0.020$).

Conclusions Exercise-based CR improves the post-exercise parasympathetic function, with greater effects in younger CAD patients and in those who were revascularised with percutaneous intervention. The effects on resting parasympathetic function are more controversial due to methodological inconsistencies in measuring HRV, with the use of RMSSD recommended instead of HF because its results show higher consistency. Future studies involving women, focusing on methodological issues, and performing other training methods are needed to increase our knowledge about this topic.

Keywords

Acute myocardial infarction; aerobic training; autonomic nervous system; coronary heart disease; resistance training

INTRODUCTION

The autonomic control of cardiovascular function, assessed by heart rate variability (HRV) [1, 2] or heart rate recovery (HRR) [3, 4], is severely altered in patients with coronary artery disease (CAD) after acute myocardial infarction (AMI) or surgical intervention. Reduced HRV or HRR are strong predictors of mortality risk, sudden cardiac death or cardiac arrhythmias [5–10]. Exercise-based cardiac rehabilitation programmes (CR) improve cardiovascular mortality rates [11], cardiorespiratory fitness (CRF) and quality of life in CAD patients [12]. Although the mechanisms that underlie these beneficial effects remain speculative, the improvement of autonomic dysfunction following exercise-based CR might involve a possible triggering of these effects [13]. Heart rate variability is the oscillation in the interval between heartbeats; it depends on the continuous modulation of the autonomous nervous system (ANS) branches [14]: the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS). Within HRV indices, the root-mean-square difference in successive normal R-R interval (RMSSD; time domain method) and high frequency (HF; frequency domain method) are considered to be vagal-related HRV indices [15]. Heart rate recovery is defined as the difference in the heart rate (HR) between the peak of exercise and one or more minutes after exercise cessation [16]. The recovery of HR after exercise occurs due to SNS deactivation and PNS reactivation [17]. However, the first minute of recovery is predominantly determined by PNS reactivation [16, 18-20]. Although vagal-related HRV indices and HRR are parasympathetically mediated, previous studies reported that these indices might represent independent aspects—but complementary information—with regard to PNS function [21].

However, studies that investigated the exercise-based CR-induced effect on PNS modulation often provide contradictory findings. For instance, Butz and Kober [22] and Currie et al. [23] revealed no changes in HRV and HRR after a 3- and 12-week exercise-based CR programme, respectively. Nascimento et al. [24] only found an HRR increase after exercise-based CR in patients with low functional capacity and parasympathetic activity, while Mendes et al. [25] observed an improvement in HRV following an inpatient exercise-based CR programme. Previous inconclusive findings could be due to participant characteristics (e.g. age, sex, physical fitness and/or surgical intervention) [26] and differences in the structure of the exercise-based CR programmes (e.g. wait time, exercise mode and dosage) [27]. Besides, Billman et al. [28] and Catai et al. [29] highlighted the necessity of improving HRV measurement methodologies to reach conclusive findings.

A previous meta-analysis carried out by Nolan et al. in 2008 [30] showed that exercise-based CR increases HRV, based upon a composite of time- and frequency-domain vagal-related indices (0.36; 95% confidence interval [CI] = 0.18–0.55). However, this meta-analysis did not investigate the exercise-based CR-induced effect on post-exercise PNS modulation. Notably, the authors included CAD and chronic heart failure patients without performing a subgroup analysis based on the clinical condition, and better reported and controlled trials have since been published. Therefore, in this

systematic review and meta-analysis, we aim to determine the effect of exercise-based CR, compared with usual care and psychosocial and/or educational interventions, on the resting and post-exercise parasympathetic function in CAD patients and to identify the possible moderator variables of the exercise-based CR-induced effect.

METHOD

We conducted and reported a systematic review of the literature and a meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [31]. We registered prospectively the systematic review and meta-analysis protocol in the PROSPERO database (CRD42019122419).

Data search and sources

We identified potential studies via a comprehensive strategy. We performed a systematic review in the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 11) and Web of Science (all databases) databases. We also searched conference proceedings on the Web of Science Core Collection. The search strategy involved crosschecking the selected keywords based on Medical Subjects Headings (MeSH) and free text; it was based on a previous meta-analysis [11]. We selected studies published prior to November 2018 and did not apply language restrictions during this phase (the full search strategy is presented in Online Resource 1). In addition, we hand-reviewed all full-text articles assessed for eligibility, and we contacted the authors to identify possible additional published and unpublished studies.

Study selection

We established the eligibility criteria according to the PICOS (participants, intervention, comparisons, outcomes and study design) guideline. We included male and female adult patients (≥ 18 years) if they suffered an AMI, had a diagnosis of angina pectoris, underwent revascularisation (percutaneous transluminal coronary angioplasty [PTCA] or coronary artery bypass grafting [CABG]) or had a CAD diagnosis via angiography (participants). We delineated exercise-based CR as a supervised outpatient or a home-based intervention, including aerobic training, resistance training or combined aerobic and resistance training, either alone or in addition to psychosocial and/or educational interventions. We did not impose restrictions regarding the minimal length of exercise-based CR to analyse the minimal duration of the treatment to produce changes on ANS activity (intervention). The comparison group could include usual care and psychosocial and/or educational interventions but not a structured exercise training programme (comparison). Each selected study had to report HRV, HRR or both. For HRV, we selected only those studies that reported vagal-related HRV indices in the frequency domain (HF) or in the time domain (RMSSD); both recommended as preferential PNS measures [15]. We included studies that reported HF if power was derived from an autoregressive model (AR) or fast-Fourier transformation (FFT). Previous studies stated that both methods produce very similar estimates

of HF power [32]. We included studies that measured PNS in absolute values, logarithmically transformed values or normalised units of HF. For HRR, the relevant studies measured this variable during the first minute after maximal exercise (outcomes). Finally, we included randomised and non-randomised controlled trials (study design) in English, Spanish, French or Italian. We limited the inclusion of studies with more than one article based on the same sample to only one.

Two authors (A.M. and J.M.S.) assessed all identified titles/abstracts for possible inclusion. When there was not a consensus, the article was included in the next stage for a review of the full text. The same authors reviewed the full texts of the remaining studies against the inclusion criteria. Subsequently, we settled disagreements by consensus.

Data extraction and coding moderator variables

Two authors (A.M. and J.M.S.) independently extracted study characteristics using a standardised data extraction form. Disagreements were resolved by consensus. We classified all possible moderator characteristics as extrinsic, participant, treatment or methodological variables to measure HRV. To analyse the heterogeneity among the results of the primary studies, we calculated the mean value between the two groups in each continuous variable as a potential moderator variable for quantitative synthesis.

We coded the extrinsic and participant variables as follows: (a) year of publication; (b) country where the study was performed; (c) sample size; (d) age of the sample (years); (e) men (%); (f) AMI (%); (g) type of revascularisation surgery (PTCA, CABG or mixed); (h) left ventricular ejection fraction (%); (i) CRF ($ml \cdot kg^{-1} \cdot min^{-1}$); and (j) patients who used beta-adrenergic blocking agents (%).

We coded the following treatment variables: (a) exercise mode (aerobic, resistance or combined aerobic and resistance training); (b) aerobic training method (high-intensity interval training [HIIT] or moderate continuous training [MCT]); (c) intensity (%); (d) training frequency (days per week); (e) treatment length (weeks); (f) number of exercise sessions; (g) setting (supervised hospital/centre- or home-based); (h) implementation of extra physical activities (yes or no); and (i) wait time to start exercise-based CR after procedure or event (< 3 months or ≥ 3 months).

The methodological conditions used to measure HRV were coded as follows: (a) equipment (electrocardiogram or HR monitor); (b) method used to calculate the power spectral density (AR or FFT); (c) units (normalised, logarithmically transformed, or absolute values); (d) setting (24-h ambulatory monitoring or lab-based); (e) assessment position; (f) breathing rate (spontaneous or controlled); and (g) wash-out treatment before assessments.

Assessment of risk of bias

Using the Cochrane Collaboration's core risk of bias items, two reviewers (A.M. and J.M.S.) independently assessed the systematic risk of bias of each study included in the quantitative synthesis [33]. We resolved disagreements between these authors by consensus. We used this tool to assess the

following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias). We classified studies as high, unclear or low risk of bias from each item based on the descriptive judgements proposed in the Cochrane Handbook [33].

Computation of effect sizes and statistical analyses

We used the standardised mean difference (SMD) as the effect size (ES) index to assess the change in vagal-related HRV indices and the mean difference (MD) as the ES for HRR. We transformed the data into its absolute logarithmic value before calculating the SMD for the absolute HF and RMSSD values [34]. We calculated the SMD by subtracting the mean change in the exercise-based CR group from the mean change in the control group divided by the pooled standard deviation (*SD*) at baseline. We then corrected the data by a factor $c(df_{E,C})$ for small samples [35]. We classified the magnitude of the SMD as trivial (< 0.20), small (0.21–0.60), moderate (0.61–1.20), large (1.21–2.00) or very large (> 2.01) [36]. We defined the MD as the difference between the average change between the two groups. Positive values of SMD or MD indicated a favourable outcome to the treatment.

We performed separate analyses for each SMD or MD index according to the outcome measure to avoid statistical dependence. We applied a random-effects model for each meta-analysis, in which the mean ES was weighted by its inverse variance; the sum of the within-study variance was an estimate for the variance among studies. We used a conservative value of 0.7, previously proposed by Rosenthal [37], to calculate the variance of each study when the studies did not report the correlations between pre- and post-treatment measures. The analysis included calculating the mean ES with its 95% CI, a heterogeneity statistical test, chi-square and the I^2 index to evaluate the degree of homogeneity of the ESs around the average effect [38, 39]. We considered a statistically significant effect when $p \leq 0.050$. We classified heterogeneity as low, moderate or high at 25.0%, 50.0% and 75.0%, respectively. We considered I^2 index values greater than 50.0% to indicate substantial heterogeneity [40]. We analysed the relationship between the ESs and the categorical and continuous moderator variables using analysis of variance (ANOVA) or subgroup analysis for categorical variables and simple meta-regressions with Q_B and Z statistics for continuous variables if we observed the existence of heterogeneity between the ESs. We conducted all analyses using weighted least squares and assuming mixed-effects models [41]. We also applied the above-mentioned criteria regarding heterogeneity analyses to conduct subgroup analysis.

We analysed publication bias using a funnel plot [42] and Egger's regression intercept [43]. In case of suspected bias, we implemented a trim-and-fill method for imputing missing ESs [44]. We utilised Review Manager (RevMan) 5.3, Comprehensive Meta-analysis 3.3 and macros for SPSS elaborated by David B. Wilson for statistical analyses.

Sensitivity analysis

Regarding the decisions we made when obtaining our results, we examined the robustness of the meta-analytic findings related to the design and analysis decisions using sensitivity analyses [45]. We analysed the impact of including or excluding non-randomised controlled trials. In addition, we used the outlier-labelling rule [46] to check the effect of outliers in our results. We also tested the influence of using an unknown correlation for pre- and post-intervention values using analyses carried out using different supposed correlations (e.g., 0.5, 0.6, 0.8 and 0.9).

RESULTS

Study selection

Figure 1 illustrates the systematic review process. In brief, from a total of 3541 studies, 45 were eligible for full-text analysis, of which we excluded 20 studies from qualitative synthesis (please see the reasons in Figure 1) [22, 25, 47–64]. From the 25 studies included for qualitative synthesis, we included 21 for meta-analysis. We excluded four because they showed a median and interquartile range without a normal data distribution (n = 2) [65, 66] or there was insufficient data to calculate the ES (n = 2) [67, 68]. The studies included in the quantitative synthesis also allowed us to define 26 independent comparisons between exercise-based CR and control groups as follows: HF (n = 12) [69–80], RMSSD (n = 5) [73, 75–78] and HRR (n = 9) [81–89]. Although we attempted to locate unpublished studies, all the selected studies had been published in peer-reviewed journals.

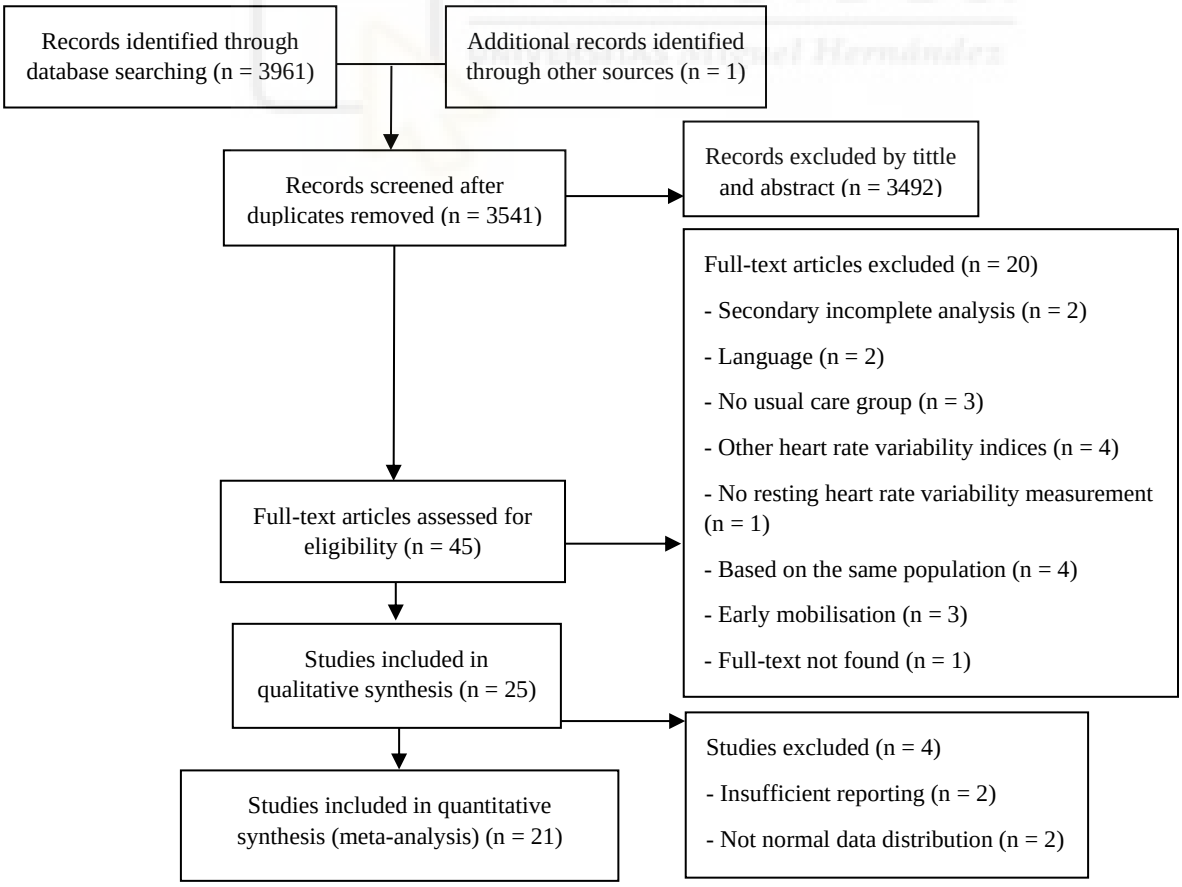

Figure 1. Flow chart of the study selection procedure

Study characteristics

The characteristics of the studies are summarised in Table 1. The 25 included studies are from 11 countries. Seventeen studies (68%) were randomised and eight (32%) were non-randomised controlled trials. In total, there were 1,346 patients (697 patients in the exercise-based CR group and 649 in the control group) with a mean age of 59.45 ± 5.85 years. Trial sample sizes varied from 18 to 268 patients (mean ± *SD* = 53.84 ± 50.76 patients). Seven studies (28%) included exclusively male patients and one (4%) included only females, while 15 studies (60%) used a mixed sex sample and two (8%) did not report this information. Fourteen trials (56%) included post-AMI patients and three (12%) recruited exclusively post-revascularisation patients (CABG or PTCA). Fifteen trials (60%) reported CRF, which varied from 13.4 to 31.7 $ml \cdot kg^{-1} \cdot min^{-1}$ (mean ± *SD* = 21.28 ± 5.95 $ml \cdot kg^{-1} \cdot min^{-1}$). The percentage of patients taking beta-adrenergic blocking agents ranged from 0 to 100% (mean ± *SD* = 64.18 ± 34.58%), as reported by 21 trials (84%).

The treatment characteristics are reported in Table 2. Twenty-two studies (88%) compared aerobic training with control, and three (12%) compared combined aerobic and resistance training with control. Regarding the resistance training performed on the studies that combined both training methods, Chen et al. [81] performed between 12 and 15 repetitions at 40–60% of one-repetition maximum (1RM), Medeiros et al. [86] carried out 15 repetitions at 50% of 1RM and Kalka et al. [85] included 8–10 resistance exercises and performed from 12 to 15 repetitions based on the rating of perceived exertion. Twenty-three trials (92%) applied MCT and two (8%) applied HIIT as the aerobic training method (please see aerobic intensity in Table 2). The mean weekly training frequency was three sessions per week, during an average of 12 weeks, in a supervised hospital/centre-based setting (88% of the studies). Nineteen trials (76%) started exercise-based CR within 3 months after the procedure or event, while six of them (24%) started after 3 months. The authors of three studies (12%) explicitly reported that they performed the assessments during drug wash-out [67, 70, 86].

Out of 15 trials that measured the effect of exercise-based CR on HRV, 10 (67%) reported HF and five (33%) reported HF and RMSSD (Table 1). Thirteen studies (87%) recorded the RR interval with an electrocardiogram [67–75, 77–80] and two (13%) recorded their data with an HR monitor [65, 76]. Eight trials (53%) determined power spectral density by FFT [68, 69, 71, 76–80], five (33%) by AR [67, 70, 72–74] and two (14%) did not report that information [65, 75]. Four trials (27%) assessed HRV by 24-h ambulatory monitoring [67, 68, 75, 78] and 11 (73%) by lab-based measures [65, 69-74, 76, 77, 79, 80], mainly in a supine position (82%) [65, 69, 71–74, 76, 77, 80]. Out of the 11 studies that performed lab-based measures, seven trials (64%) allowed the patients to breathe spontaneously [69, 70, 72–74, 77, 80], three (27%) controlled the breathing rate [65, 71, 76] and one (9%) did not report that information [79].

Table 1. Outcome measures, subject and extrinsic characteristics

Study (author, year)	Outcome measure	Country	*N* CR / C	Age (years ± *SD*)	Men (%)	AMI (%)	LVEF (% ± *SD*)	CRF ($ml \cdot kg^{-1} \cdot min^{-1}$)	Beta-adrenergic blocking (%)	Revascularization procedure
Chen et al. [81], 2014[b]	HRR	Taiwan	21	69.7 ± 4.5	76.0	71.0	54.1 ± 7.6	14.0 ± 2.5	71.0	Both
			15	69.0 ± 4.6	80.0	67.0	50.7 ± 7.1	14.7 ± 2.5	60.0	
Duru et al. [69], 2000	HF nu	Switzerland	12	56.0 ± 5.0	100	100	32.0 ± 7.0	19.3 ± 3.0	NR	Both
			13	55.0 ± 7.0			33.0 ± 6.0	NR		
Fujimoto et al. [68], 1999[a]	HF ab	Japan	20	59.0 ± 11.0	100	100	59.2 ± 7.2	18.1 ± 3.0	0.0	PTCA
			20				54.3 ± 10.5	19.0 ± 4.0		
Giallauria et al. [83], 2011	HRR	Italy	37	61.0 ± 7.0	75.0	100	42.4 ± 9.9	16.4 ± 1.5	86.0	PTCA
			38	60.0 ± 8.0	84.0		44.1 ± 8.3	16.7 ± 2.2	84.0	
Giallauria et al. [82], 2006[b]	HRR	Italy	104	68.0 ± 3.0	77.9	100	44.6 ± 2.7	14.7 ± 1.3	76.9	NR
			164	68.3 ± 3.0	82.9		44.5 ± 2.7	14.4 ± 0.2	75.0	
Kalka et al. [85], 2016[b]	HRR	Poland	89	60.4 ± 9.3	100	67.8	57.0 ± 7.0	NR	94.4	PTCA
			35	61.4 ± 8.8		54.3	55.0 ± 7.2		94.3	
La Rovere et al. [70], 1992	HF nu	Italy	18	47.0 ± 6.0	100	100	NR	NR	NR	NR
			10	54.0 ± 10.0						
Lai et al. [71], 201[b]	HF nu	Taiwan	16	64.2 ± 5.9	0.0	100	> 50%	NR	31.3	Both
			16	66.7 ± 5.3						
Lucini et al. [72], 2002[b]	HF nu	Italy	29	63.0 ± 10.6	82.8	31.0	50.0 ± 16.2	18.1 ± 4.9	62.1	Both
			11	53.0 ± 7.9	72.7	36.4	51.0 ± 13.3	18.0 ± 3.3	54.5	
Malfatto et al. [73], 1998[b]	HF nu RMSSD ab	Italy	20	53.0 ± 2.0	NR	100	56.0 ± 3.0	NR	100	NR
			14	53.0 ± 3.0						
Martinez et al. [74], 2011	HF nu	Brazil	14	56.0 ± 7.5	NR	100	53.0 ± 7.5	20.6 ± 3.7	100	PTCA
			14	50.0 ± 7.5			55.0 ± 7.5	20.4 ± 6.0	92.9	
Mazzuero et al. [67], 1992[a]	HF ab	Italy	22	50.0 ± 8.0	NR	100	49.0 ± 11.0	NR	NR	NR
			16							
Medeiros et al. [86], 2018[b]	HRR	Brazil	16	52.1 ± 6.5	100	100	43.1 ± 2.8	26.6 ± 3.0	100	PTCA
			11	50.4 ± 8.8			44.6 ± 5.2	30.2 ± 4.0		

Table 1. Continued

Study (author, year)	Outcome measure	Country	*N* CR / C	Age (years ± *SD*)	Men (%)	AMI (%)	LVEF (% ± *SD*)	CRF ($ml \cdot kg^{-1} \cdot min^{-1}$)	Beta-adrenergic blocking (%)	Revascularization procedure
Munk et al. [75], 2010	HF ln RMSSD ln	Norway	20 12	57.7 ± 10.4 59.7 ± 8.5	85.0 83.3	0.0	63.0 ± 7.0 64.0 ± 6.0	NR	40.0 61.1	PTCA
Noites et al. [66], 2017[a]	HRR	Portugal	16 16	62.5 ± 4.6 59.5 ± 7.3	81.3 75.0	100	56.0 ± 8.1 52.0 ± 3.9	26.0 ± 9.6 28.8 ± 7.3	100	PTCA
Oliveira et al. [76], 2014	HF ln RMSSD ab	Portugal	47 45	54.8 ± 10.6 58.6 ± 10.7	85.1 82.2	100	52.8 ± 9.5 54.5 ± 7.4	27.6 ± 7.3 26.9 ± 5.6	91.5 100	PTCA
Ribeiro et al. [84], 2012	HRR	Portugal	20 18	54.3 ± 10.8 57.0 ± 7.6	90.0 72.2	100	55.1 ±7.7 55.5 ± 6.8	30.8 ± 7.8 32.6 ± 5.8	90.0 88.9	PTCA
Sandercock et al. [77], 2007[b]	HF ln RMSSD ab	England	38 23	65.6 ± 11.6 64.9 ± 9.0	55.2 60.9	44.7 8.7	NR	NR	63.2 65.2	Both
Stâhle et al. [78], 1999	HF ln RMSSD ln	Sweden	27 33	71.0 ± 4.0 72.0 ± 5.0	75.9 77.8	37.9 22.2	NR	NR	86.2 88.9	Both
Takeyama et al. [79], 2000	HF ab	Japan	13 15	58.8 ± 6.3 61.7 ± 8.7	100 86.7	76.9 66.7	62.5 ± 12.7 61.6 ± 11.1	13.1 ± 1.7 13.7 ± 2.5	0.0	CABG
Tamburus et al. [65], 2015[a]	HF nu	Brazil	12 12	56.2 ± 7.4 60.4 ± 6.1	100	33.3 20.0	NR	NR	58.3 50.0	Both
Tsai et al. [80], 2006	HF ln	Taiwan	34 33	57.1 ± 8.9 56.8 ± 9.9	85.3 75.8	5.9 15.2	62.4 ± 11.1 61.3 ± 10.0	18.3 ± 5.3 17.9 ± 4.5	76.5 66.7	PTCA
Tsai et al. [87], 2005	HRR	Taiwan	15 15	61.2 ± 9.5 63.2 ± 14.6	NR	0.0	NR	NR	0.0	CABG
Wu et al. [88], 2006	HRR	Taiwan	18 18	62.8 ± 6.9 62.2 ± 9.6	100	0.0	50.6 ± 2.1 50.7 ± 2.4	15.7 ± 3.9 16.0 ± 4.2	27.8 22.2	CABG
Zheng et al. [89], 2008	HRR	China	27 30	NR	NR	100	> 45	12.6 ± 1.5 11.7 ± 1.9	NR	PTCA

ab, absolute units; *AMI*, acute myocardial infarction; *CABG*, coronary artery bypass grafting; *C*, control group; *CR*, exercise-based cardiac rehabilitation group; *CRF*, cardiorespiratory fitness; *HF*, high frequency; *HRR*, heart rate recovery; *ln*, natural logarithm; *LVEF*, left ventricular ejection fraction; *N*, number of patients included; *NR*, not reported; *nu*, normalised units; *PTCA*, percutaneous transluminal coronary angioplasty; *RMSSD*, the root-mean-square difference in successive normal R-R interval; *SD*, standard deviation

[a]Study excluded from the meta-analysis but included for the qualitative synthesis

[b]Non-randomised controlled trial

Table 2. Treatment characteristics

Study (author)	Exercise mode	Aerobic training method / intensity	Frequency (days a week) / treatment length (weeks)	Number of exercise sessions	Application mode	Wait time
Chen et al. [81][b]	CT	MCT / 60–80% HRreserve	3 / 12	36	Supervised	L
Duru et al. [69]	AT	MCT / 70% HRreserve	4 / 8	32	Supervised	S
Fujimoto et al. [68][a]	AT	MCT / 80% AnT	7 / 2	14	Supervised	S
Giallauria et al. [83]	AT	MCT / 60–70% VO_2 peak	3 / 24	72	Supervised	S
Giallauria et al. [82][b]	AT	MCT / 60% VO_2 peak	3 / 12	36	Supervised	S
Kalka et al. [85][b]	CT	MCT / 40–70% PO peak	5 / 24	120	Supervised	L
La Rovere et al. [70]	AT	MCT / 75–95% AnT	NR / 4	NR	Supervised	S
Lai et al. [71][b]	AT	MCT / 13–15 RPE	3 / 8	24	Home-based	L
Lucini et al. [72][b]	AT	MCT / 70–85% HRm	3 / 12	36	Supervised	S
Malfatto et al. [73][b]	AT	MCT / 80% HRm	5 / 8	40	Supervised	S
Martinez et al. [74]	AT	MCT / 100% AnT (HR)	3 / 24	72	Supervised	S
Mazzuero et al. [67]	AT	MCT / NR	3 / 24	72	Supervised	S
Medeiros et al. [86][b]	CT	MCT / 60–75% HRt	2 / 12	24	Supervised	S
Munk et al. [75]	AT	HIIT / 3 × 4 min > 85% HRm (recovery NR)	3 / 24	72	NR	S
Noites et al. [66][a]	AT	MCT / 60–70% HRp	3 / 8	24	Home-based	L
Oliveira et al. [76]	AT	MCT / 70–85% HRm	3 / 8	24	Supervised	S
Ribeiro et al. [84]	AT	MCT / 65–75% HRm	3 / 8	24	Supervised	S
Sandercock et al. [77][b]	AT	MCT / 70% HRm*	1 / 8	8	Supervised	L
Stâhle et al. [78]	AT	HIIT / 4 × 4 min 90–95% HRp (recovery 3 min 50–70% HRp)	3 / 12	36	Supervised	S
Takeyama et al. [79]	AT	MCT /AnT	7 / 2	14	Supervised	S
Tamburus et al. [65][a]	AT	MCT / 80–110% AnT (PO)	3 / 16	48	Supervised	L
Tsai et al. [80]	AT	MCT / 60–85% HRreserve	3 / 8	24	Supervised	S
Tsai et al. [87]	AT	MCT / 60–85% HRp	3 / 12	36	Supervised	S
Wu et al. [88]	AT	MCT / 60–85% HRp	3 / 12	36	Supervised	S
Zheng et al. [89]	AT	MCT / AnT (VO_2)	3 / 24	72	Supervised	S

AT, aerobic training; *AnT*, anaerobic threshold; *CT*, combined aerobic and resistance training; *HIIT*, high-intensity interval training; *HR*, heart rate; *HRm*, maximal heart rate; *HRp*, heart rate peak; *HRreserve*, heart rate reserve; *HRt*, heart rate target; *L*, wait time longer than or equal to 3 months; *MCT*, moderate continuous training; *NR*, not reported; *PO*, power output; *RPE*, rating of perceived exertion; *S*, wait time less than 3 months; *VO_2*, oxygen uptake; *VO_2 peak*, peak oxygen uptake

*Shuttle-walking test

[a]Study excluded from the meta-analysis but included for the qualitative synthesis

[b]Non-randomised controlled trial

Risk of bias assessment

The risk of bias assessment is detailed in Online Resource 2. We judged random sequence generation and allocation concealment (selection bias) as unclear and high risk, respectively. Only two randomised controlled trials [76, 80] clearly reported details about the generation and concealment of the random allocation sequence. Only four trials blinded the outcome assessment [74, 76, 83, 88], and we judged the detection bias as high risk. However, the outcomes measured in this meta-analysis can be considered to be objective, a finding that reduces the risk of detection bias. Finally, we considered attrition and reporting bias to represent an unclear risk.

Outcomes

Resting HRV

Pooled analysis revealed no statistically significant differences (p = .290) in HF between groups, and the overall SMD reached a trivial effect (SMD_+ = 0.14; 95% CI = -0.12–0.40; Fig. 2). The heterogeneity was statistically significant (p < .001) for HF, and the inconsistency was moderate (70.0%). According to meta-regressions (Online Resource 3) and subgroup analyses (Online Resource 4), none of the analysed variables were statistically related to the ES magnitude (p > .050) for HF. The inconsistency was moderate for the type of intervention surgery (I^2 = 59.4%) and wait time to start exercise-based CR (I^2 = 48.9%).

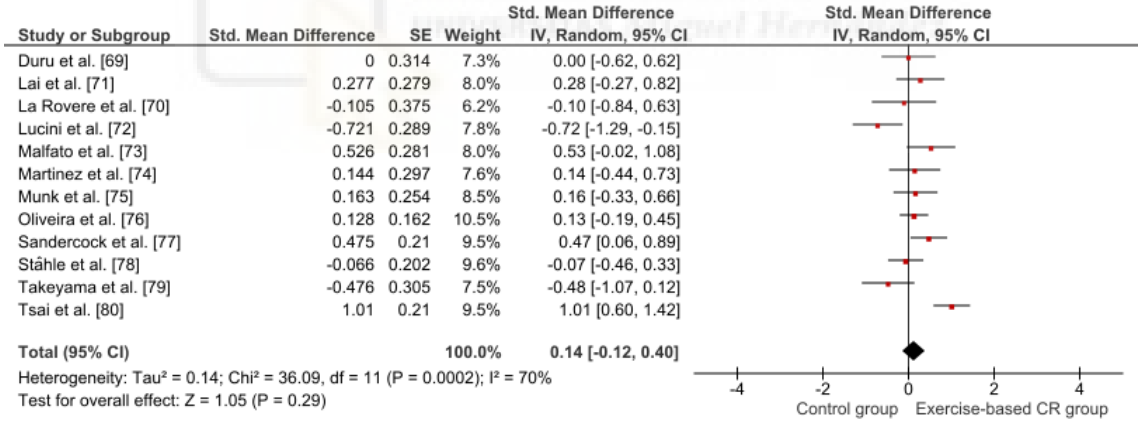

Figure 2. Forest plot of standardized mean difference indices for high frequency (HF)

The pooled analysis showed statistical differences (p = .001) in RMSSD between groups in favour of the exercise-based CR group, and the overall SMD reached a small effect (SMD_+= 0.30; 95% CI = 0.12–0.49; Fig. 3). The heterogeneity was not statistically significant (p = .430) for RMSSD; we did not identify inconsistency (0%).

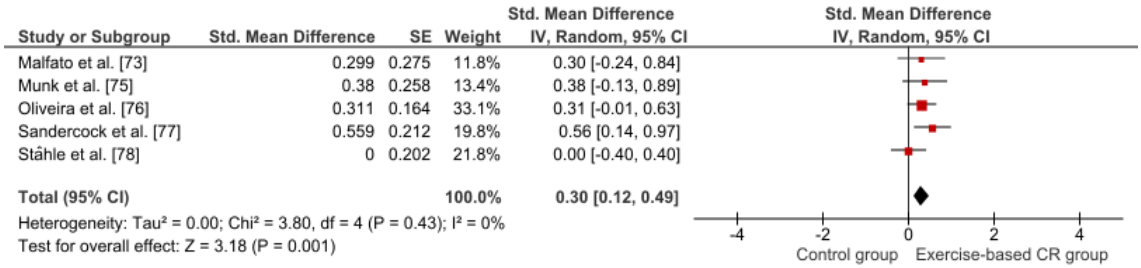

Figure 3. Forest plot of standardized mean difference indices for the root-mean-square difference of successive normal R-R intervals (RMSSD)

HRR

The pooled analysis revealed statistically significant differences ($p < .001$) in HRR between both groups, with higher values in the exercise-based CR group ($MD_+ = 5.35$; 95% CI = 4.08–6.61 bpm; Fig. 4). The heterogeneity was statistically significant ($p < .001$), and the inconsistency was high (85.0%). Therefore, we analysed moderator variables. The meta-regression findings revealed that the mean age of the patients was inversely related to the ES magnitude ($p = .008$; Online Resource 5). The subgroup analysis for HRR (Online Resource 6) showed significant between-group heterogeneity with high inconsistency for the type of intervention surgery procedure ($p = .020$; $I^2 = 75.6\%$). For wait time to start exercise-based CR, there was no significant between-group heterogeneity and moderate inconsistency ($p = .080$; $I^2 = 66.7\%$). There were greater differences for exercise-based CR patients who underwent PTCA surgery ($MD_+ = 7.04$; 95% CI = 4.40–9.68 bpm) compared with CABG patients ($MD_+ = 5.11$; 95% CI = 3.11–7.11 bpm) or both conditions ($MD_+ = 2.50$; 95% CI = 0.61–4.39 bpm). In addition, patients who started to receive exercise-based CR within the first 3 months after the event showed a higher effect ($MD_+ = 5.89$; 95% CI = 4.42–7.35 bpm) than those who had to wait at least 3 months ($MD_+ = 3.58$; 95% CI = 1.41–5.74 bpm).

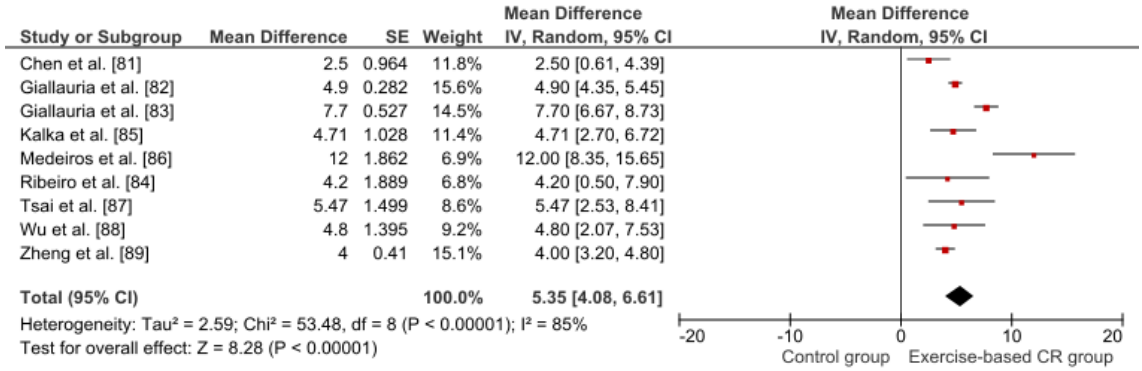

Figure 4. Forest plot of mean difference indices for heart rate recovery (HRR)

Sensitivity analysis

After removing the non-randomised controlled trials for HF [71–73, 77], RMSSD [73, 77] and HRR [81, 82, 85, 86], the results did not change. We did not identify outliers for HF and RMSSD, a finding that obviated the need to assess the overall effect after removing outliers. The analysis

was performed after removing an outlier (MD = 12.00) [86] for HRR (lower critical value: MD = 0.37; upper critical value: MD = 10.31). Notwithstanding a decrease in the overall ES (from MD_+ = 5.35; 95% CI = 4.08–6.61 bpm to MD_+ = 4.87; 95% CI = 3.71–6.04 bpm), the result was similar to that observed before removing the outlier. The results for HF, RMSSD and HRR did not change when using different supposed correlations between pre- and post-intervention values (0.5, 0.6, 0.8 and 0.9).

Publication bias

We did not find evidence of asymmetry in the funnel plots for HF, RMSSD and HRR, and the Egger tests were not statistically significant (HF, $t(11) = -0.922$, $p = .378$; RMSSD, $t(4) = 0.230$, $p = .833$; HRR, $t(8) = 0.469$, $p = .653$). Thus, publication bias can be discarded as a threat against the findings of the current meta-analysis on a reasonable basis. The funnel plots for HF, RMSSD and HRR are presented in Online Resources 7–9, respectively.

DISCUSSION

This systematic review with a meta-analysis assessed the effect of exercise-based CR on resting and post-exercise measures of the parasympathetic function in patients with CAD. Our main results indicate that exercise-based CR improves both post-exercise HRR (5.35; 95% CI = 4.08–6.61 bpm) and RMSSD (0.30; 95% CI = 0.12–0.49), a resting measure of parasympathetic function. Besides, the exercise-based CR-induced effect on the post-exercise parasympathetic function was inversely related to the participant age ($p = .008$), and patients treated with PTCA achieved a greater improvement after exercise-based CR ($p = .020$).

Resting HRV

Although HF and RMSSD are vagal-related HRV indices [13, 90], we found contradictory results according to the variable used to reflect the exercise-based CR-induced effect on the resting PNS function. Our findings showed an increase in RMSSD after exercise-based CR, without the influence of moderator variables, while we did not observe any significant changes and high heterogeneity in HF alterations.

Because of the high inconsistency (I^2 = 70.0%) observed, we carried out heterogeneity analyses to explain these controversial findings. These analyses included patient characteristics that have been previously reported as potential moderator variables of cardiac autonomic control. For instance, previous studies reported that ageing and low physical fitness are related to a decline in parasympathetic control of the heart [91–93]. Nevertheless, proper management of training variables (i.e., intensity, frequency and duration) in exercise training would allow the induction of positive autonomic adaptations in older patients [94]. There is also evidence that both cardiac autonomic modulation [95, 96] and the exercise-based CR-induced effect on PNS status [97, 98],

are influenced by sex. Although there are widely reported differences in autonomic control based on the patient and exercise-based CR programme characteristics, our findings showed no influence of these potential moderator variables on the HF changes. Similarly, previous meta-analyses did not identify an influence of participant and treatment characteristics on vagal-related HRV indices in cardiac patients [30] and older participants [99].

Another issue that might determine HRV changes after exercise-based CR is the patients' myocardial injury state. Two characteristics could be primarily related to injury state: the type of revascularisation surgery and wait time to start exercise-based CR after the procedure or event. Regarding the surgery type, the combined effect of surgical manipulation on the heart, anaesthesia and cardioplegia during a CABG surgery can produce a worse heart condition after surgery compared with the PTCA procedure [14]. In fact, previous studies have reported that CABG seems to lead to higher and more prolonged autonomic dysfunction compared with PTCA [100, 101]. Regarding wait time, it is well known that early repression of the inflammatory response is essential to reduce the affected myocardial area after AMI [102]. Besides, a shorter wait time before commencing exercise-based CR is related to greater improvements in cardiac function [103] and left ventricular remodelling [104]. Overall, this phenomenon highlights the importance of considering the wait time before starting exercise-based CR and the type of intervention surgery to correctly interpret the results of empirical studies. Santos-Hiss et al. [62] performed a 5-day phase I exercise-based CR programme based on low-intensity exercise following AMI; they reported an increase in HF values after this short exercise-based CR programme. Badrov et al. [105] reported no HF changes following a delayed (68 ± 11 days following hospital discharge) 6-month exercise-based CR programme based on aerobic and resistance training. Thus, delaying the start of exercise-based CR might limit the exercise-based CR-induced effect on this variable. Szmigielska et al. [106] investigated the effect of an 8-week exercise-based CR programme on HRV indices in men treated with PTCA or CABG. The authors reported that exercise-based CR seems to be more effective for improving HRV values in CABG than in PTCA patients, but they did not find a difference in HF changes between CABG and PTCA. Although our findings showed no influence of the wait time to start exercise-based CR and the type of intervention surgery on the effect of exercise-based CR on HF values, a very small number of the included studies involved exclusively CABG patients. Besides, the wait time to start exercise-based CR was dichotomised because most of the studies did not report the mean time to start exercise-based CR after the event. Notably, dichotomisation might create considerable loss of power and residual confounding [107]. Thus, we attempted to use the original scale of the remaining variables.

The methodological aspects related to the assessment of HRV should also be considered to explain, at least partially, our results. The status of the ANS is highly sensitive to environmental factors and respiratory influences [108]. In addition, previous studies have reported that HRV

indices show a natural day-to-day variation [109]. Thus, the use of the long-term daily HRV recordings values helps to reduce noise and might be more consistent with regard to reflecting PNS function compared with a single-day record [110, 111]. Buchheit [108] reported that time domain indices, specifically RMSSD, have a lower sensitivity towards breathing patterns and day-to-day variability than spectral indices. Similarly, previous studies reported that when frequency domain indices are used, it is necessary to normalise the breathing rate to control respiratory sinus arrhythmia [112, 113]. However, all the studies included in our meta-analysis reported HRV values based on a single data point. Besides, among studies that used HF as a vagal-related HRV index, only two specified that they collected data by controlling the breathing rate [71, 76]. Therefore, similar to our findings, methodological inconsistencies in measuring HRV might have a greater impact on the results of studies that use HF as vagal-related HRV index. The impact of these methodological inconsistencies on HF values has also been identified in previous meta-analyses performed with healthy people [26] and endurance-trained athletes [114]. Current evidence seems to support that RMSSD might be more suitable than HF to reflect resting PNS function, because RMSSD is less affected by respiratory influences and methodological limitations.

In conclusion, methodological issues, including the lack of breathing control and the use of a single data point to reflect the PNS status, might explain our inconclusive findings and the high heterogeneity in studies that used HF as a vagal-related index in the resting condition. Thus, we recommend using time domain indices, specifically RMSSD, to study the exercise-based CR-induced effect on the PNS status. Future studies that use frequency domain indices should also consider these methodological issues to confidently reflect the resting PNS function in CAD patients. Subsequently, researchers could investigate the influence of moderator variables on the exercise-based CR-induced effect to design exercise-based CR programmes focused on improving autonomic function.

HRR

To the best of our knowledge, this meta-analysis is the first to assess the exercise-based CR-induced effect on post-exercise PNS function in CAD patients. Nine studies reported an overall statistically relevant ES of 5.35 bpm (ranging from 2.50 to 12.00 bpm) in favour of the exercise-based CR group. Therefore, in accordance with studies carried out in other populations [115, 116], our findings showed that exercise training improves post-exercise PNS function in patients with CAD. In previous studies, delayed HRR is a strong predictor of mortality [5], and improvement of the post-exercise PNS modulation might exert a protective effect on the cardiovascular system [117]. This outcome could help to reduce the mortality risk in CAD patients [118].

In contrast to what happened with HF, analyses of moderator variables demonstrated a crucial influence of the age of the patients and the type of intervention surgery, as well as a possible influence of the CRF and the wait time to start exercise-based CR, on the exercise-based CR-induced effect on the post-exercise PNS function.

We found that ageing adversely affects the capacity to improve PNS function after exercise. This result supports the findings of a meta-analysis performed with healthy people, in which the authors reported that physiological ageing is correlated with a decreased trainability of the heart [26]. Although the CRF analysis did not reach statistical significance, our result showed a residual direct relationship between this variable and the exercise-based CR-induced effect on HRR (p = .066). Beckie et al. [119] carried out a 12-week exercise-based CR programme with 236 female CAD patients. Consistent with our findings, those authors reported that CRF and age are associated with the exercise-based CR-induced effect on HRR. Regarding the type of intervention surgery, our findings showed a higher exercise-based CR-induced effect in patients who underwent PTCA. This result is contrary to what would be expected based on the post-surgery evolution of the patient [101]. However, to the best of our knowledge, no previous studies have investigated whether the exercise-based CR-induced effect on HRR might differ based on the type of intervention surgery.

Our subgroup analysis based on the wait time to commence exercise-based CR showed a considerable heterogeneity between categories, with higher HRR improvement in patients who waited less than 3 months to start exercise-based CR. This result is consistent with previous studies that reported that a shorter time to start exercise-based CR might lead to better improvement after CR [102, 103]. Although the analysis did not reach statistical significance, as previously noted, the wait time to start exercise-based CR was dichotomised. This factor might reduce the power considerably.

Finally, the small number of studies that analysed the influence of the CRF, performed with patients who waited 3 or more months to start exercise-based CR or with CABG patients, warrants future research to understand the influence of these variables on the exercise-based CR-induced effect on the post-exercise PNS reactivation. Thus, ageing, type of intervention surgery, CRF and wait time to start exercise-based CR might underlie the heterogeneity we identified in the included studies.

Regarding exercise-based CR programme characteristics, the subgroup analysis according to the exercise mode revealed no ES differences between aerobic training and combined aerobic and resistance training. This finding indicates that the exercise mode does not influence the effect of exercise-based CR on the post-exercise PNS function. However, no studies analysed the effect of resistance training alone. On the other hand, we did not include an analysis on the aerobic training

method (HIIT versus MCT), because all the included studies applied MCT. Pattyn et al. [120] performed a meta-analysis to compare the effect of MCT and HIIT on peak oxygen uptake in cardiac patients (CAD and chronic heart failure patients). They also compared the effect of the two aerobic training methods on HRR as a secondary outcome. Their subgroup analysis based on underlying pathology revealed no differences (p = .760) between HIIT and MCT with regard to elevated post-exercise PNS function in CAD patients.

Several limitations to the previously mentioned analyses might explain why we did not identify an influence of any exercise variable on the exercise-based CR-induced effect on PNS modulation. Further, previous studies have reported that different forms and dosages of exercise (e.g. intensity, volume, training frequency) can elicit variable effects on the PNS function [27]. Aerobic training has received the most attention by researchers (88% of included studies), and it is already considered an important stimulus for increasing PNS tone [121]. Therefore, future studies should analyse the influence of other exercise modes (resistance training and combined aerobic and resistance training), as well as the effect of HIIT, and then analyse the influence of the different dosages of exercise on the exercise-based CR-induced effect on PNS function in CAD patients.

In conclusion, HRR seems to be a good method for measuring the exercise-based CR-induced effect on post-exercise PNS reactivation. However, variables like the age and CRF of patients, as well as the type of surgery that patients underwent and the time from the event until the beginning of exercise-based CR, should be considered—all of these variables might influence the results.

Strengths and limitations

This systematic review and meta-analysis is the first to analyse the effect of exercise-based CR on resting and post-exercise PNS function with an exclusive focus on CAD patients. In addition, our analyses were performed based on the characteristics of the patients and exercise-based CR programmes. However, there are some limitations. There was significant heterogeneity between study protocols and in the treatment effects. Our analyses exhibited moderate-to-high evidence of heterogeneity among studies, and therefore the results must be interpreted cautiously. In most of the randomised controlled trials, the generation and concealment of random allocation sequences was poorly reported, a factor that increased the selection bias risk in our results. Although we performed subgroup analyses, some groups had a relatively small number of studies. This fact limited the scope and power of these analyses. In addition, subgroup analysis based on the exercise mode or aerobic training method were limited because we did not include studies that performed resistance training in the meta-analysis—and only two studies used HIIT for aerobic training. Thus, we could not properly analyse the influence of these training variables on the effect of exercise-based CR on resting and post-exercise PNS function in CAD patients.

Conclusion

Our findings demonstrated that exercise-based CR improves the post-exercise parasympathetic function in CAD patients, with a greater enhancement in younger patients and patients treated with PTCA. However, deriving a definitive conclusion about the exercise-based CR-induced effect on resting parasympathetic function is difficult due to methodological inconsistencies in measuring HRV, mainly for studies that used HF. In this sense, our results showed a relevant increase of RMSSD; this finding suggests that exercise-based CR improves resting parasympathetic function. At the same time, the HF measure seems to be less consistent with regard to resting parasympathetic adaptations in CAD patients. We recommend the use of RMSSD instead of HF because its results show greater consistency—despite the methodological differences among studies. However, the conclusions of this meta-analysis should be limited to the effect of aerobic training, carried out by MCT, on the parasympathetic function in male patients with CAD. Future high-quality studies should involve women, focus on methodological aspects of HRV measures and perform resistance or high-intensity training exclusively to increase knowledge about the effect of exercise-based CR on resting parasympathetic modulation.

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8.2.2. Supplementary material study 2

Online Resource 1. Full search strategy

Cochrane CENTRAL

#1 MeSH descriptor: [Myocardial Ischemia] explode all trees

#2 (myocard* near isch*mi*):ti,ab,kw (Word variations have been searched)

#3 isch*mi* near heart:ti,ab,kw (Word variations have been searched)

#4 MeSH descriptor: [Coronary Artery Bypass] explode all trees

#5 myocard* near infarct*:ti,ab,kw (Word variations have been searched)

#6 heart near infarct*:ti,ab,kw (Word variations have been searched)

#7 angina:ti,ab,kw (Word variations have been searched)

#8 coronary near (disease* or bypass or thrombo* or angioplast*):ti,ab,kw (Word variations have been searched)

#9 MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees

#10 (percutaneous next coronary near/2 (interven* or revascular*)) (Word variations have been searched)

#11 MeSH descriptor: [Angioplasty] explode all trees

#12 angioplast* (Word variations have been searched)

#13 endoluminal next repair* (Word variations have been searched)

#14 MeSH descriptor: [Stents] explode all trees

#15 stent* (Word variations have been searched)

#16 pci or ptca (Word variations have been searched)

#17 CABG (Word variations have been searched)

#18 MeSH descriptor: [Atherectomy] explode all trees

#19 atherectom* (Word variations have been searched)

#20 acute next coronary next syndrom* (Word variations have been searched)

#21 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20

#22 MeSH descriptor: [Resistance training] explode all trees

#23 resist* near (train* or exercise*) (Word variations have been searched)

#24 stren* near (train* or exercise*) (Word variations have been searched)

#25 weight-bearing near stren* or program* (Word variations have been searched)

#26 weight-lifting near stren* or program* (Word variations have been searched)

#27(stren* near program*) (Word variations have been searched)

#28 MeSH descriptor: [Exercise] explode all trees

#29 physic* near (exercise* or activit*) (Word variations have been searched)

#30 aerob* near (train* or exercise*) (Word variations have been searched)

#31 (exercise* near train*) (Word variations have been searched)

#32 (exercise* near acute*) (Word variations have been searched)

#33 MeSH descriptor: [High-intensity interval training] explode all trees

#34 high-intensity near (interval* or train*) (Word variations have been searched)

#35 high-intensity near (intermittent* or exercise*) (Word variations have been searched)

#36 intermittent* near (train* or exercise*) (Word variations have been searched)

#37 interval* near (train* or exercise*) (Word variations have been searched)

#38 HIIT or HIT (Word variations have been searched)

#39 moderat* near (train* or contin* or exercise*) (Word variations have been searched)

#40 MeSH descriptor: [endurance, physical] explode all trees

#41 (enduranc* near physic*) (Word variations have been searched)

#42 enduranc* near (train* or exercise*) (Word variations have been searched)

#43 (combine*) near/5 (strength* or resistance* or endurance* or aerobic or exercise*) (Word variations have been searched)

#44 #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43

#45 MeSH descriptor: [Autonomic Nervous System] explode all trees

#46 (autonom* or vegetativ* near nervou*) (Word variations have been searched)

#47 MeSH descriptor: [Parasympathetic Nervous System] explode all trees

#48 (parasympathetic near nervous near system*) (Word variations have been searched)

#49 MeSH descriptor: [Sympathetic Nervous System] explode all trees

#50 (sympathetic near nervous near system*) (Word variations have been searched)

#51 sympathovagal balance (Word variations have been searched)

#52 (sympath* near hyperactivit*) (Word variations have been searched)

#53 (parasympath* near withdrawal*) (Word variations have been searched)

#54 (vagal near withdrawal*) (Word variations have been searched)

#55 (sympath* next nerv* near/2 (activit* or traffic*)) (Word variations have been searched)

#56 MeSH descriptor: [Heart Rate] explode all trees

#57 (heart near rate*) (Word variations have been searched)

#58 (pulse* near rate*) (Word variations have been searched)

#59 (cardiac* near chronotrop*) (Word variations have been searched)

#60 (hear rate near control*) (Word variations have been searched)

#61 (heart rate near/2 recover*) (Word variations have been searched)

#62 (heart rate near/2 rest*) (Word variations have been searched)

#63 (heart rate near variabil*) (Word variations have been searched)

#64 RMSD or SDNN or pNN50 (Word variations have been searched)

#65 “high frequency” or “low frequency” (Word variations have been searched)

#66 (cardiac* next autonomic* near/2 (function*)) (Word variations have been searched)

#67 (autonomic* near/2 (function*)) (Word variations have been searched)

#68 MeSH descriptor: [Baroreflex] explode all trees

#69 baroreflexes (Word variations have been searched)

#70 (baroreceptor near reflex*) (Word variations have been searched)

#71 barore* near (*function* or arterial*) (Word variations have been searched)

#72 barore* next (sensitivity* or response* or modulation*) (Word variations have been searched)

#73 MeSH descriptor: [Electrocardiography] explode all trees

#74 ECG or ECK (Word variations have been searched)

#75 Electrocardiogra* (Word variations have been searched)

#76 Microneurogra* (Word variations have been searched)

#77 MSNA (Word variations have been searched)

#78 (muscle* next metaboreflex*) (Word variations have been searched)

#79 #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78

#80 #21 AND #44 AND #79

Web of Science (SCI & CPCI-S)

1 TI(((myocard*) SAME (isch?emia or infarct* or revasculari?*)))

2 TI=(((coronary* or heart*) SAME (by?pass or disease*)))

3 TI=(((heart) SAME (infarct* or isch?emia or failure or attack)))

4 TI=((angina or cardiac* or PTCA or CABG))

5 TI=(PCI or percutaneous or angioplast* or "endoluminal repair*" or stent* or atherectom* or "acute coronary syndrom*")

6 #1 or #2 or #3 or #4 or #5

7 TS=(((Resist* or stren*) SAME (train* or exercise*)))

8 TS=(((weight-bearing or weight-lifting) SAME (stren* or program*)))

9 TS=((((exercise*) SAME (train* or activit* or aerob* or acute))))

10 TS=("High-intensity interval* train*" or "High-intensity intermittent* train*" or "High-intensity intermittent* exercise*" or "interval* train*" or "interval* exercise*")

11 TS=(HIIT or HIT)

12 TI=(moderat* NEAR/3 (train* or contin* or exercise*))

13 TI=(endurance* NEAR/3 (physic* or train* or exercise*))

14 TI= (combine* NEAR/3 (strength* or resistance* or endurance* or aerobic or exercise*))

15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

16 TS=((Autonomic Nervous System*) SAME (vegetativ* nervous system*))

17 TS=(((((((("Parasympathetic Nervous System*" or "Sympathetic Nervous System*" or "sympathovagal balance*" or "sympathy* withdrawal*" or "vagal withdrawal*" or "sympathy* nerv* activit*" or "sympathy* nerv* traffic*)))))))

18 TS=(("heart rate*" or "heart pulse*"))

19 TS=("cardiac chronotrop*")

20 TI=(heart rate* NEAR/3 (recover* or rest* or variabil*))

21 TI=(autonomic* NEAR/2 (function*))

22 TI=(barore* NEAR/3 (function* or arterial* or sensitivity* or response* or modulation*))

23 TS=(((Electrocardiogra* or ECG or ECK)))

24 TS=(((microneurogra* or MSNA or "muscle* metaboreflex*)))

25 TS=("heart rate* variabil*")

26 #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25

27 #6 AND #15 AND #26

28 Indexes=SCI-EXPANDED, CPCI-S Timespan=2009-2014

Online Resource 2. Risk of bias: review author´s judgements about each risk of bias item across all included studies

Risk of bias item	Low risk of bias n / N (%)	Unclear risk of bias n / N (%)	High risk of bias n / N (%)
Random sequence generation (selection bias)	3 / 21 (14)	10 / 21 (48)	8 /21 (38)
Allocation concealment (selection bias)	3 / 21 (14)	1 / 21 (5)	17 / 21 (81)
Blinding of outcome assessment (detection bias)	4 / 21 (19)	0 / 21 (0)	17 / 21 (81)
Incomplete outcome data (attrition bias)	5 / 21 (24)	14 / 21 (67)	2 / 21 (9)
Selective reporting (reporting bias)	7 / 21 (33)	11 / 21 (53)	3 / 21 (14)

Online Resource 3. Results of analysing the influence of continuous moderator variables on HF

			95% CI			
Moderator variable	***k***	***B***	**Lower**	**Upper**	***Z***	***p***
Publication year	12	0.020	−0.022	0.063	0.945	.345
Sample size	12	0.007	−0.005	0.019	1.097	.273
Mean age	12	−0.004	−0.051	0.042	−0.189	.850
AMI percentage	11	−0.002	−0.010	0.006	−0.475	.635
Beta-blocking percentage	8	−0.001	−0.017	0.016	−0.085	.932
LVEF	9	0.014	−0.025	0.053	0.694	.488
CRF	6	0.033	−0.108	0.174	0.464	.642
Treatment length	12	0.001	−0.041	0.043	0.034	.973
Training frequency	11	−0.110	−0.302	0.083	−1.113	.266
Number of sessions	11	−0.002	−0.016	0.013	−0.267	.789

95% CI, 95% confidence interval; *AMI*, acute myocardial infarction; *B*, regression coefficient; *CRF*, cardiorespiratory fitness; *HF*, high frequency; *k*, number of studies; *LVEF*, left ventricular ejection fraction; *p*, probability level associated to the *Z* statistic; *Z*, statistic for testing the significance of the moderator variable

Online Resource 4. Results of analysing the influence of categorical moderator variables on HF

				95% CI		Subgroup differences		
Moderator variable	**Category**	***k***	**SMD**	**Lower**	**Upper**	***Chi²***	***p***	***I²* (%)**
Sex	Men	2	−0.04	−0.52	0.43	0.81	.670	0.0
	Women	1	0.28	−0.27	0.82			
	Both	9	0.15	−0.17	0.47			
Type of intervention surgery	PTCA	4	0.37	−0.08	0.82	4.93	.090	59.4
	CABG	1	−0.48	−1.07	0.12			
	Both	5	0.01	−0.38	0.40			
Wait time	< 3 months	10	0.08	−0.22	0.39	1.96	.160	48.9
	≥ 3 months	2	0.40	0.07	0.73			
Aerobic training method	MCT	10	0.15	−0.16	0.47	0.34	.560	0.0
	HIIT	2	0.02	−0.29	0.33			

95% CI, 95% confidence interval; *CABG*, coronary artery bypass grafting; Chi^2, between-categories *Q* statistic for testing the significance of the moderator variable; *HF*, high frequency; *HIIT*, high-intensity interval training; I^2, heterogeneity index; *k*, number of studies; *MCT*, moderate continuous training; *p*, probability level associated to the Chi^2 statistic; *PTCA*, percutaneous transluminal coronary angioplasty; *SMD*, standardized mean difference

Online Resource 5. Results of analysing the influence of continuous moderator variables on HRR

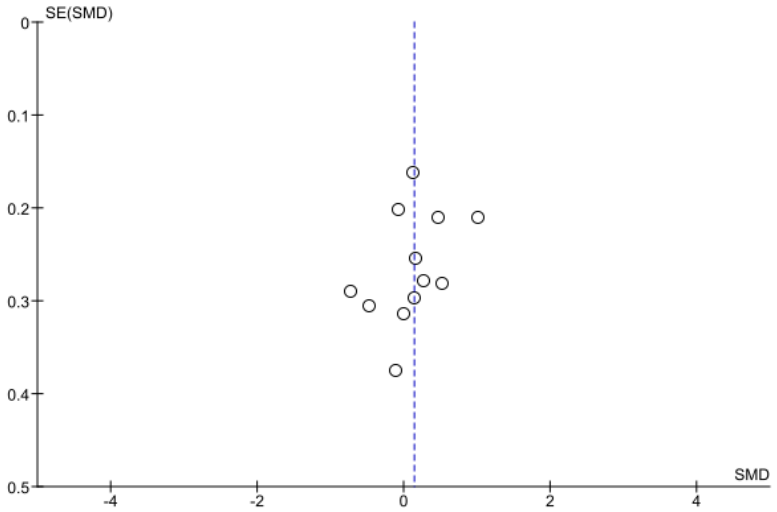
			95% CI			
Moderator variable	***k***	***B***	**Lower**	**Upper**	***Z***	***p***
Publication year	9	0.173	−0.149	0.494	1.053	.293
Sample size	9	−0.003	−0.024	0.017	−0.323	.747
Mean age	8	−0.327	−0.566	−0.087	−2.676	.008
AMI Percentage	9	0.012	−0.023	0.047	0.686	.493
Beta-blocking percentage	8	−0.028	−0.073	0.017	−1.213	.225
LVEF	9	−0.029	−0.117	0.059	−0.643	.520
CRF	7	0.210	−0.014	0.434	1.838	.066
Treatment length	9	0.021	−0.227	0.269	0.168	.866
Training frequency	9	−1.219	−3.036	0.598	−1.315	.189
Number of sessions	9	−0.008	−0.058	0.041	−0.328	.743

95% CI, 95% confidence interval; *AMI*, acute myocardial infarction; *B*, regression coefficient; *CRF*, cardiorespiratory fitness; *HRR*, heart rate recovery; *k*, number of studies; *LVEF*, left ventricular ejection fraction; *p*, probability level associated to the *Z* statistic; *Z*, statistic for testing the significance of the moderator variable

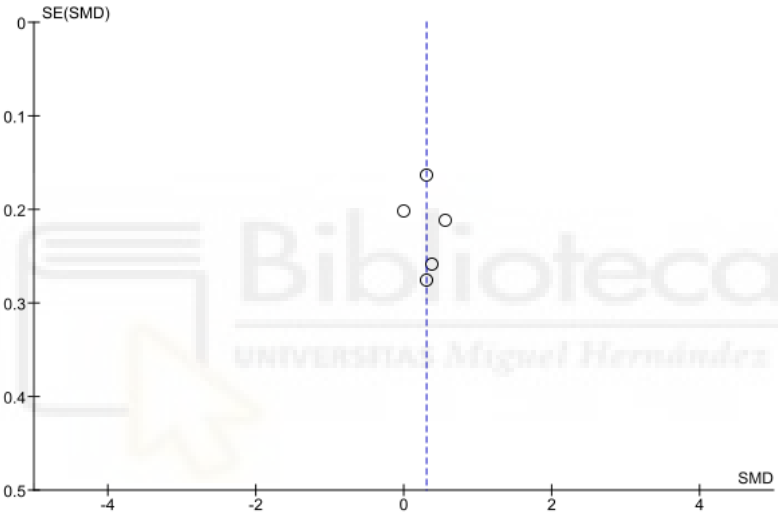
Online Resource 6. Results of analysing the influence of categorical moderator variables on HRR

				95% CI		Subgroup differences		
Moderator variable	**Category**	***k***	**MD**	**Lower**	**Upper**	***Chi²***	***p***	***I²* (%)**
Sex	Men	3	6.93	2.94	10.91	0.94	.330	0.0
	Both	5	4.81	3.28	6.35			
Type of intervention	PTCA	4	7.04	4.40	9.68	8.20	.020	75.6
surgery	CABG	2	5.11	3.11	7.11			
	Both	1	2.50	0.61	4.39			
Wait time	< 3 months	7	5.89	4.42	7.35	3.00	.080	66.7
	≥ 3 months	2	3.58	1.41	5.74			
Exercise mode	Aerobic	6	5.29	3.95	6.63	0.12	.730	0.0
	Combined	3	6.11	1.71	10.51			

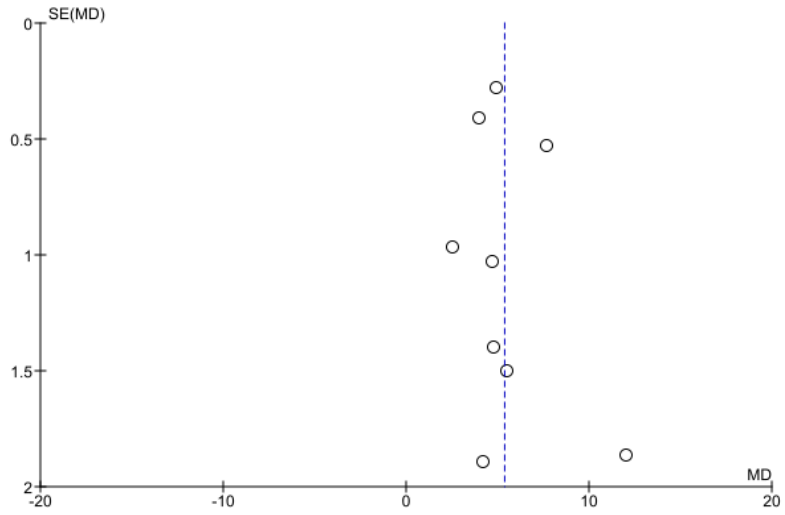
95% CI, 95% confidence interval; *CABG*, coronary artery bypass grafting; Chi^2, between-categories *Q* statistic for testing the significance of the moderator variable; *HRR*, heart rate recovery; I^2, heterogeneity index; *k*, number of studies; *MD*, mean difference; *p*, probability level associated to the Chi^2 statistic; *PTCA*, percutaneous transluminal coronary angioplasty



Online Resource 7. Funnel plot of standardized mean difference (SMD) indices for high frequency (HF)



Online Resource 8. Funnel plot of standardized mean difference (SMD) indices for the root-mean-square difference in successive normal R-R interval (RMSSD)



Online Resource 9. Funnel plot of mean difference (MD) indices for heart rate recovery (HRR)

APPENDIX 3

STUDY 3

Are the current cardiac rehabilitation programs optimized to improve cardiorespiratory fitness in patients? A meta-analysis

Note. This study was published

Manresa-Rocamora A, Sarabia JM, Sánchez-Meca J, Oliveira J, Vera-Garcia FJ, Moya-Ramón M. Are the current cardiac rehabilitation programs optimized to improve cardiorespiratory fitness in patients? A Meta-Analysis. *J Aging Phys Act*. 2020 Aug 14;29(2):327-342. https://doi.org/10.1123/japa.2019-0363

8.3. Appendix 3

8.3.1. Study 3. Are the current cardiac rehabilitation programs optimized to improve cardiorespiratory fitness in patients? A meta-analysis

Abstract

Previous meta-analyses have shown that high-intensity interval training (HIIT) is more suitable than moderate continuous training (MCT) for improving peak oxygen uptake (VO_2peak) in patients with coronary artery disease. However, none of these meta-analyses have tried to explain the heterogeneity of the empirical studies in optimizing cardiac rehabilitation programs. Therefore, our aims were (a) to estimate the effect of MCT and HIIT on VO_2peak, and (b) to find the potential moderator variables. A search was conducted in PubMed, Scopus, and ScienceDirect. Out of the 3110 references retrieved, 29 studies fulfilled the selection criteria to be included in our meta-analysis. The mean difference was used as the effect size index. Our results showed significant enhancements in VO_2peak after cardiac rehabilitation based on MCT and HIIT (mean difference = 3.23; 95% confidence interval [2.81, 3.65] $ml \cdot kg^{-1} \cdot min^{-1}$ and mean difference = 4.61; 95% confidence interval [4.02, 5.19] $ml \cdot kg^{-1} \cdot min^{-1}$, respectively), with greater increases after HIIT ($p < .001$). Heterogeneity analyses reached statistical significance with moderate heterogeneity for MCT ($p < .001$; $I^2 = 67.0\%$), whereas no heterogeneity was found for the effect of HIIT ($p = .220$; $I^2 = 22.0\%$). Subgroup analyses showed significant between-group heterogeneity of the MCT-induced effect based on the training mode ($p < .001$; $I^2 = 90.4\%$), the risk of a new event ($p = .010$; $I^2 = 77.4\%$), the type of cardiovascular event ($p = .009$; $I^2 = 84.8\%$), the wait time to start CR ($p = .010$; $I^2 = 76.6\%$), and participant allocation ($p = .002$; $I^2 = 89.9\%$). Meta-regressions revealed that the percentage of patients undergoing a revascularization procedure ($B = -0.022$; $p = .041$) and cardiorespiratory fitness at baseline ($B = -0.103$; $p = .025$) were inversely related to the MCT-induced effect on the VO_2peak.

Keywords

Acute myocardial infarction; aerobic training; angina pectoris; coronary artery bypass grafting; percutaneous coronary intervention

INTRODUCTION

According to the World Health Organization (2018), cardiovascular diseases continue to be the most prevalent cause of death worldwide. In 2015, more than 17 million people died from this cause, representing 31% of all deaths registered in the world. Of these deaths, 7.4 million were due to coronary artery disease (CAD). Exercise-based cardiac rehabilitation (CR) is an effective strategy for reducing total and cardiovascular mortality in patients with CAD (Anderson et al., 2016). Furthermore, cardiorespiratory fitness (CRF), which is measured directly as peak oxygen uptake (VO_2peak), has been deemed to be a strong predictor of mortality (Kodama et al., 2009). A traditional training methodology used in CR programs to increase VO_2peak is moderate continuous training (MCT). The MCT is characterized by long-term training periods (between 30 and 60 min) at 60–85% VO_2peak (Fletcher et al., 2001). More recently, high-intensity interval training (HIIT) emerged as an alternative to MCT to improve CRF. The main principle of HIIT is to perform brief periods of high-intensity exercise (e.g., >85% VO_2peak or above anaerobic threshold) interspersed by periods of low-intensity exercise (e.g., <60% VO_2peak or below aerobic threshold) or rest (Gayda, Ribeiro, Juneau, & Nigam, 2016). Previous meta-analyses have shown that HIIT is more effective than MCT for increasing VO_2peak in patients with CAD (Elliott, Rajopadhyaya, Bentley, Beltrame, & Aromataris, 2015; Gomes-Neto et al., 2017; Hannan et al., 2018; Liou, Ho, Fildes, & Ooi, 2016; Pattyn, Beulque, & Cornelissen, 2018; Pattyn, Coeckelberghs, Buys, Cornelissen, & Vanhees, 2014; Xie, Yan, Cai, & Li, 2017). However, the findings of these meta-analyses showed high heterogeneity. A cornerstone of the meta-analytic process is to analyze all the variables that could be related to the effect size (ES) magnitude to explain the heterogeneity of the results. None of these previous meta-analyses tried to analyse all these variables and, therefore, reach conclusive findings.

Despite the higher efficiency of HIIT in improving CRF, there is evidence that shows the relevance of managing training variables like frequency, intensity, time (duration), and type (modality) properly to increase the long-term effects of exercise training (Vanhees et al., 2012). As we can see, the training method used in CR is just a part of the training prescription, and the lack of control of the other training variables could explain part of the heterogeneity found in the results of the previous meta-analyses (Ballesta García, Rubio Arias, Ramos Campo, Martínez González-Moro, & Carrasco Poyatos, 2019; Conraads et al., 2015; Hannan et al., 2018). In addition, other potential moderator variables related to the pathology (i.e., type of cardiovascular event or revascularisation), sample characteristics (i.e., age, sex, or physical fitness), or study design (i.e., study quality) could modify the effect of MCT and HIIT on CRF.

Knowledge of the influence of all these variables when MCT and HIIT are performed in CR would allow CR programs to be designed and managed adequately, or at least limitations of the previous studies to be identified with a view to improving CR. Therefore, our aims were (a) to

estimate the effect of MCT and HIIT on VO_2peak, and (b) to analyze, if heterogeneity was found, the potential moderator variables of the impact of MCT and HIIT on VO_2peak.

METHOD

The systematic review and meta-analysis were reported following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (Liberati et al., 2009).

Study selection

Studies that enrolled adult patients (≥18 years), regardless of sex, who had experienced an acute myocardial infarction (AMI) or angina pectoris, who had undergone revascularization (percutaneous transluminal intervention or coronary artery bypass grafting), or who had experienced coronary heart disease documented by angiography were included. Exercise-based CR was delineated as a supervised outpatient intervention that included MCT or HIIT as aerobic training, either alone or in addition to psychosocial or educational interventions. Studies that applied CR, based on resistance training or combined resistance and aerobic training, as well as unsupervised interventions, were excluded. Randomized, nonrandomized, controlled, and uncontrolled trials were included. In the controlled studies, the control group (CG) could include usual care and psychosocial or educational interventions, but they did not include structured exercise training. Studies had to report direct measurements of VO_2peak, and they had to have been published between January 2000 and February 2020 to be included in this systematic review and meta-analysis.

Search procedure

The following databases were consulted to select the studies that fulfilled the selection criteria: *PubMed*, *Scopus*, and *ScienceDirect*. We combined the following keywords for the electronic searches: ("Coronary artery disease" OR "Coronary heart disease" OR "Myocardial infarction" OR "Angina pectoris" OR "Cardiac disease" OR "Cardiovascular disease") AND ("Aerobic interval training" OR "High-intensity interval training" OR "High-intensity exercise" OR "Exercise rehabilitation" OR "Anaerobic interval training" OR "Moderate continuous training"). We restricted the search of the keywords to titles and abstracts. We also reviewed the references of nine previously published meta-analyses (Ballesta García et al., 2019; Elliott et al., 2015; Gomes-Neto et al., 2017; Hannan et al., 2018; Kraal, Vromen, Spee, Kemps, & Peek, 2017; Liou et al., 2016; Pattyn et al., 2014, 2018; Xie et al., 2017).

Coding moderator variables

Study characteristics that could be related to the ESs were extracted, with the purpose of examining the heterogeneity between the results of the analysis units. Moderator variables were classified as treatment, subject, methodological, and extrinsic variables.

The treatment characteristics coded were: (a) the training mode (treadmill, cycle ergometer, or a combination of different exercises) and (b) the session duration (in minutes). In the analysis units of HIIT, the length of the training was calculated as *number of intervals* × *interval length*. As regards the training duration progression, the average weighted length was taken as the point of reference. In addition, in those interventions in which several training sessions were carried out over a day, the length of the training was calculated by adding them up; (c) the intensity percentage related to the maximum achieved. In those analysis units in which the intensity was prescribed as a range, we used the weighted average. When the intensity was not relative to the maximum, it was calculated using the maximum average values of the group; (d) the weekly training frequency (in days per week); (e) the treatment duration (in weeks); (f) the number of sessions; (g) the total time they were performing at target intensity during the intervention (in minutes); and (h) the wait time to start exercise-based CR (≤3, 4–12, or >12 weeks).

The subject characteristics coded for the samples of each analysis units were: (a) the number of patients; (b) the average age of the sample (in years); (c) the sex of the sample (male, female, or mixed); (d) the percentage of males; (e) the type of cardiovascular event; (f) the percentage of patients with AMI; (g) the percentage of patients that had undergone revascularization; (h) the type of revascularization surgery (percutaneous transluminal intervention, coronary artery bypass grafting, or mixed); and (i) the risk of a new event, that was established based on the VO_2peak and left ventricular ejection fraction (LVEF) (low: VO_2peak > 24.5 ml·kg^{-1}·min^{-1} and/or LVEF > 50%; moderate: VO_2peak = 17.5–24.5 ml·kg^{-1}·min^{-1} and/or LVEF 40–50%; high: VO_2peak < 17.5 ml·kg^{-1}·min^{-1} and/or LVEF < 40%) (Leon et al., 2005).

Finally, we also coded methodological and extrinsic variables, assessing the methodological quality of the study taking each item of the PEDro scale (Maher, Sherrington, Herbert, Moseley, & Elkins, 2003) as an independent categorical moderator variable. In addition, we analyzed the methodological quality score (on a scale from 0 to 10 points) as a continuous variable. We coded the publication year of the study as a continuous variable to analyse whether changes in the treatment and management of patients with CAD over the years could have influenced the CR-induced effect on the CRF.

Computation of effect sizes and statistical analysis

The literature search revealed the existence of studies that included a CG and studies without a CG. In order not to discard studies without a CG, we included all of them and, as a consequence, our analysis unit was the group, not the study. Thus, for each group (MCT, HIIT, and CG), the mean difference (MD) was used as the ES index. MD was defined as the difference between pre- and posttest means at VO_2peak. Although between-group ESs exhibit better internal validity than within-group ones, using one-group pre- and posttest ESs is recommended in the meta-analytic

area when there are many studies without CGs (Borenstein, Hedges, Higgins, & Rothstein, 2011; Hunter & Schmidt, 2004). A random-effects model was applied to carry out statistical analyses, according to which its inverse variance weighted each MD index. The overall ES obtained was represented using MD_+. A first analysis consisted of calculating the mean ES with its 95% confidence interval (CI), the heterogeneity test, χ^2, and the I^2 index (Higgins & Thompson, 2002; Huedo-Medina, Sánchez-Meca, Marín-Martínez, & Botella, 2006; Sánchez-Meca & Marín-Martínez, 2008). Statistical analyses were considered significant at $p \leq .05$. Heterogeneity was interpreted depending on I^2 magnitude as no heterogeneity (<25.0%), low (25.0–49.9%), moderate (50.0–74.9%), and large heterogeneity (>75.0%) (Higgins & Thompson, 2002; Huedo-Medina et al., 2006). We carried out subgroup analyses to compare the overall ES of the MCT, the HIIT, and the CG. If heterogeneity was found, the influence of moderator variables on training effects was evaluated separately for the MCT and HIIT groups. The relationships between the ESs and the categorical and continuous moderator variables were investigated using analysis of variances (or subgroup analysis) and meta-regressions with Q_B and Z statistics, respectively, and assuming mixed-effects models (Cooper & Hedges, 1993). The abovementioned criteria were also applied to perform subgroup analyses.

We carried out sensitivity analyses to investigate the robustness of our results. We assessed the impact of including or excluding outliers. To determine outliers, we used the outlier-labelling rule (Tukey, 1977). In addition, we also analyzed the effect of including/excluding nonrandomized trials to discover the impact of the study design on our findings.

Given that this meta-analysis did not include any unpublished paper, we carried out an analysis of publication bias using a funnel plot, the Egger test, and the trim-and-fill method for imputing missing ESs. We performed statistical analyses using Review Manager (version 5.3, Copenhagen, Denmark), Comprehensive Meta-analysis (version 3.3, Englewood, NJ), and macros for SPSS (Chicago, IL) elaborated by David B. Wilson.

RESULTS

Search procedure

The search strategy produced a total of 3110 references. Out of all the studies revised, 29 articles fulfilled the selection criteria to be included in this meta-analysis. Although we attempted to localize nonpublished works, all the selected works were studies that had been published in peer-reviewed journals. Out of all the studies selected, one of them included CG, MCT, and HIIT groups; nine included MCT and HIIT groups; 13 included CG and MCT groups; three included only MCT groups; and three included only HIIT groups (one of them with two different HIIT groups). A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of our literature search and selection is presented in Figure 1.

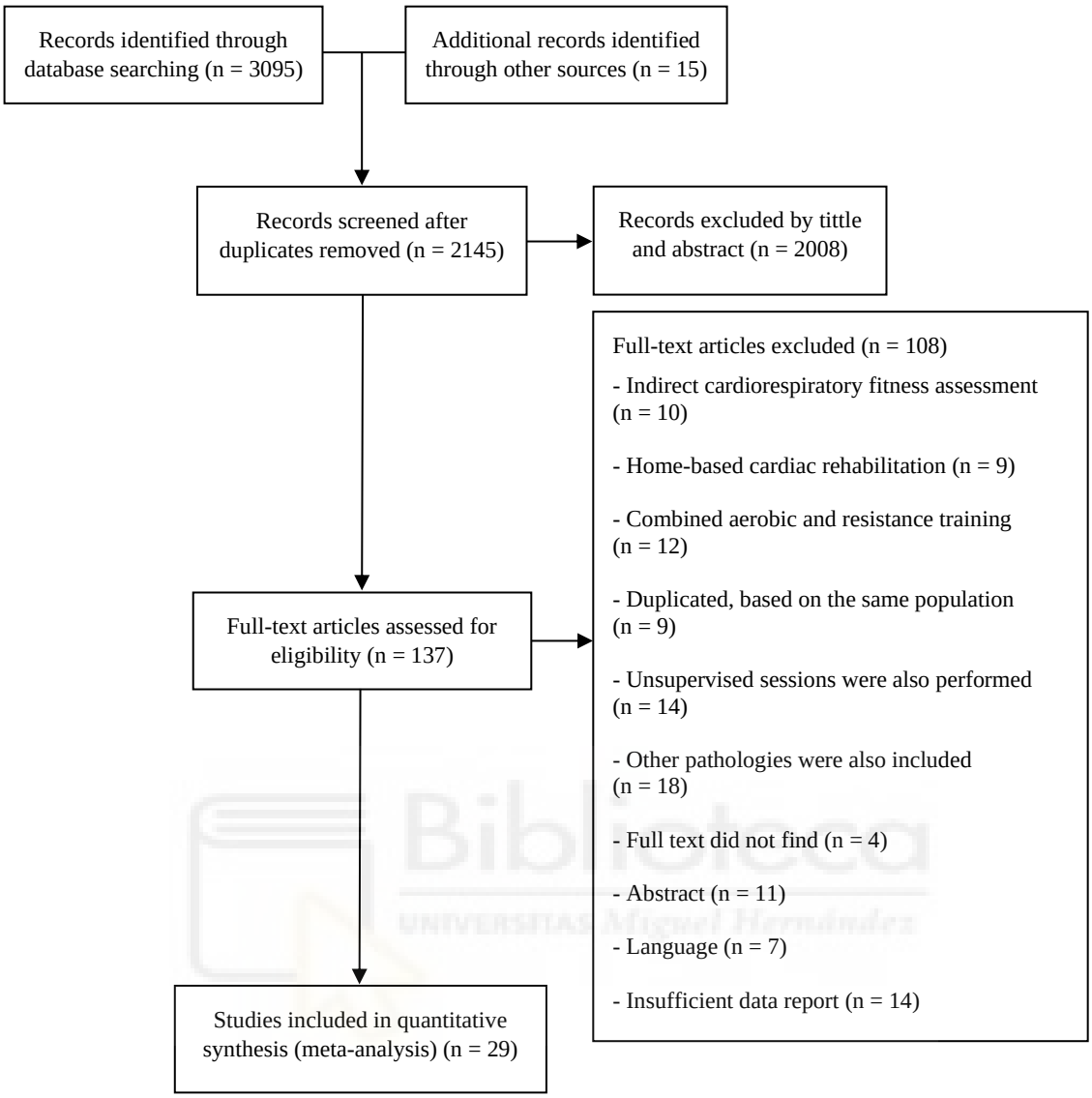


Figure 1. Systematic review and meta-analysis flowchart

Study characteristics and quality analysis

The total sample size of the meta-analysis was 1417 patients, of which 703 patients formed the 26 MCT groups (mean ± *SD* sample size = 27.1 ± 18.0 patients), 350 subjects formed the 14 HIIT groups (mean ± *SD* sample size = 25.0 ± 21.9 patients), and 364 patients formed the 14 CGs (mean ± *SD* sample size = 26.0 ± 12.8 patients). The average ± *SD* age of participants across groups was 58.7 ± 3.9 years for the MCT (min–max: 52–69 years), 58.1 ± 2.9 years for the HIIT (min–max: 53–63 years), and 58.8 ± 4.7 years for the CG (min–max: 52–68 years). Twenty-two MCT analysis units included patients of both sexes, three included only males, and one study did not report this. Thirteen HIIT analysis units included male and female patients, and one study included only males. In terms of the CG, 12 analysis units included patients of both sexes, and two included only males. The average ± *SD* CRF at baseline of participants across groups was 21.2 ± 5.3 $ml \cdot kg^{-1} \cdot min^{-1}$ for the MCT (min–max: 13.0–32.1 $ml \cdot kg^{-1} \cdot min^{-1}$), 25.6 ± 5.2 $ml \cdot kg^{-}$

$^{1}\cdot min^{-1}$ for the HIIT (min–max: 18.9–34.7 $ml\cdot kg^{-1}\cdot min^{-1}$), and 19.5 ± 5.4 $ml\cdot kg^{-1}\cdot min^{-1}$ for the CG (min–max: 13.7–32.6 $ml\cdot kg^{-1}\cdot min^{-1}$). The treatment length was between 2 and 26 weeks (mean = 11.7 weeks) for the MCT and between 5 and 16 weeks (mean = 11.3 weeks) for the HIIT. The training frequency varied between 2 and 14 weekly sessions (mean = 3.8 weeks) for the MCT and between 2 and 3 weekly sessions (mean = 2.6 weeks) for the HIIT, with a mean session length (without warm-up and cooldown) of 32.0 min for the MCT (min–max: 20–50 min) and 28.9 min for the HIIT (min–max: 20–42 min). The mode of exercise involved walking/jogging on a treadmill in nine studies, cycling in 15 studies, and a combination of exercises in four studies. One study did not report the training mode. The mean ± *SD* intensity was 63.9 ± 9.5% VO_2peak for MCT (min–max: 46.1–81.0 % VO_2peak) and 92.5 ± 8.2% VO_2peak for HIIT (min–max: 84.1–117.0% VO_2peak). Out of the 14 HIIT groups, nine of them used length intervals ≥3 min, two groups combined long and short intervals throughout the CR program, and three used short intervals. Only one group used a training intensity above the peak power output (PPO) achieved during the cardiopulmonary exercise test throughout the whole intervention.

The main characteristics of the samples and training are shown in Tables 1 and 2, respectively. The results of the methodological quality analysis using the PEDro scale appear in Table 3.

Table 1. Sample characteristics

Study	Group	Sample size	Male (%)	Age (years ± SD)	Time from the event (weeks)	AMI (%)	CRF at baseline ($ml \cdot kg^{-1} \cdot min^{-1}$)	Risk of a new event	Revascularization procedure	Undergoing an intervention (%)
Prado et al. (2016)	MCT	18	77.8	61.3 ± 9.3	NR	26.0	18.8	Moderate	Mixed	100
	HIIT	17	82.4	56.5 ± 11.1		17.0	19.9			100
Oliveira et al. (2014)	MCT	47	85.1	54.8 ± 10.6	4–12	100	27.6	Low	PCI	93.6
	CG	45	82.2	58.6 ± 10.7		100	26.9			86.7
Aamot et al. (2014)	HIIT	32	84.4	56.0 ± 9.0	NR	67.6	34.7	Low	CABG	26.5
Conraads et al. (2015)	MCT	89	89.9	59.9 ± 9.2	4–12	48.0	22.4	Moderate	Mixed	52.0
	HIIT	85	95.3	57.0 ± 8.8		67.0	23.5			33.0
Blumenthal et al. (2005)	MCT	48	64.6	62.0 ± 10.5	NR	50.0	19.1	Moderate	NR	NR
	CG	42	76.2	63.0 ± 9.0		60.0	20.2			
Cardozo, Oliveira, and Farinatti (2015)	MCT	24	66.7	62.0 ± 12.0	>12	62.0	21.8	Moderate	NR	NR
	HIIT	23	65.2	56.0 ± 12.0		43.0	20.6			
	CG	24	76.0	64.0 ± 12.0		62.0	21.9			
Choi, Han, Choi, Jung, and Joa (2018)	MCT	21	85.7	57.3 ± 12.6	≤3	100	28.0	Moderate	PCI	100
	HIIT	23	91.3	53.0 ± 6.84		100	31.9			100
Currie, Bailey, Jung, McKelvie, and MacDonald (2015)	MCT	10	90.0	66.0 ± 8.0	>12	66.7	19.8	Moderate	Mixed	100
	HIIT	9	100	63.0 ± 8.0		60.0	21.1			88.9
Eto et al. (2004)	MCT	18	94.4	58.4 ± 4.5	≤3	100	17.0	High	PCI	70.0
	CG	18	100	60.0 ± 7.9		100	16.2			67.0
Ghroubi et al. (2013)	MCT	16	NR	59.0 ± 5.9	4–12	100	20.4	Moderate	CABG	100
Giallauria, De Lorenzo, et al. (2006)	MCT	22	86.4	55.0 ± 2.0	≤3	100	16.3	High	PCI	90.0
	CG	22	90.9	54.0 ± 3.0		100	17.0			90.0
Giallauria, Lucci, et al. (2006)	MCT	20	80.0	68.6 ± 2.3	≤3	100	16.3	High	PCI	90.0
	CG	20	85.0	68.2 ± 2.6		100	15.7			95.0
Giallauria et al. (2011)	MCT	37	75.7	61.0 ± 7.0	≤3	100	16.4	High	PCI	55.0
	CG	38	84.0	60.0 ± 8.0		100	16.7			61.0
Giallauria et al. (2012)	MCT	24	95.8	54.0 ± 7.0	≤3	100	13.0	High	PCI	100
	CG	26	84.0	52.0 ± 10.0		100	14.0			100
Giallauria et al. (2013)	MCT	25	88.0	54.0 ± 7.0	≤3	100	14.0	High	PCI	100
	CG	21	86.0	54.0 ± 9.0		100	14.0			100

Table 1. Continued

Study	Group	Sample size	Male (%)	Age (years ± SD)	Time from the event (weeks)	AMI (%)	CRF at baseline ($ml \cdot kg^{-1} \cdot min^{-1}$)	Risk of a new event	Revascularization procedure	Undergoing an intervention (%)
Heber et al. (2020)	MCT	42	100	61.7 ± 9.8	4–12	62	22.9	Moderate	PCI	100
Helgerud et al. (2011)	HIIT	8	75.0	61.4 ± 3.7	NR	30.0	27.2	Low	Mixed	70.0
Jayo-Montoya et al. (2020)	HIIT-LV	21	85.7	58.9 ± 9.6	NR	100	23.2	Moderate	Mixed	100
	HIIT-HV	23	82.1	58.9 ± 8.0		100	23.2			100
Keteyian et al. (2014)	MCT	13	92.3	58.0 ± 9.0	NR	69.0	21.8	Moderate	Mixed	93.0
	HIIT	15	73.3	60.0 ± 7.0		53.0	22.4			93.0
Kim, Choi, and Lim (2015)	MCT	14	71.4	60.2 ± 13.6	≤3	100	27.1	Low	PCI	100
	HIIT	14	93.3	57.0 ± 11.6		100	29,2			100
Lee et al. (2009)	MCT	20	100	52.0 ± NR	>12	100	22.2	Moderate	PCI	100
	CG	19	100	52.0 ± NR		100	22.7			100
Madssen et al. (2014)	MCT	21	71.4	60.5 ± NR	NR	NR	29.8	Low	PCI	100
	HIIT	15	93.3	55.5 ± NR			31.2			100
Ribeiro et al. (2012)	MCT	20	90.0	54.3 ± 10.8	4–12	100	30.8	Low	PCI	85.0
	CG	18	72.2	57.0 ± 7.6		100	32.6			72.2
Rognmo, Hetland, Helgerud, Hoff, and Slørdahl (2004)	MCT	9	88.9	61.2 ± 7.3	>12	44.4	32.1	Low	Mixed	55.6
	HIIT	8	75.0	62.9 ± 11.2		50.0	31.8			37.5
Subiela, Torres, De Sanctis, and Hernández (2018)	MCT	17	100	53.9 ±8.0	4–12	100	21.2	Moderate	NR	NR
Takagi et al. (2016)	MCT	10	80.0	59.0 ± 10.0	≤3	100	18.1	Moderate	PCI	100
	CG	6	83.3	61.0 ± 9.0		100	18.6			100
Takeyama et al. (2000)	MCT	13	100	58.8 ± 6.3	NR	76.9	13.1	High	CABG	100
	CG	15	86.7	61.7 ± 8.7		66.7	13.7			100
Villelabeitia-Jaureguizar et al. (2019)	MCT	53	79.2	58.3 ± 9.5	4–12	NR	18.9	Moderate	Mixed	90.6
	HIIT	57	87.7	57.6 ± 9.8			19.5			91.1
Vona et al. (2009)	MCT	52	75.0	56.0± 6.0	≤3	100	22.0	Moderate	PCI	73
	CG	50	74.0	58.0 ± 7.0		100	22.3			76

AMI, acute myocardial infarction; *CABG*, coronary artery bypass grafting; *CG*, control group; *CRF*, cardiorespiratory fitness; *HIIT*, high-intensity interval training; *HV*, high volume; *LV*, low volume; *MCT*, moderate continuous training; *NR*, no reported; *PCI*, percutaneous coronary intervention; *SD*, standard deviation

Table 2. Training characteristics

Study	Group	Mode	Duration, frequency	MCT exercise program	MCT Intensity (%VO_2peak)	HIIT exercise program	HIIT Intensity (%VO_2peak)	
							W	R
Prado et al. (2016)	MCT HIIT	Treadmill	13 weeks 3×/week	5 min WU + 50 min (AT) + 5 min CD	NR	5 min WU + 3 × 7 × 3 min (RCP)/3 min (AT) + 5 min CD	NR	NR
Oliveira et al. (2014)	MCT	Mixed	8 weeks 3×/week	10 min WU + 30 min (70–85% HRm) + 10 min CD	65.1			
Aamot et al. (2014)	HIIT	Treadmill	12 weeks 2×/week			10 min (50–70% HRp) WU + 4 × 4 min (85–95% HRp)/4 min (70% HRp) + 3–5 min (70% HRp) CD	84.1	53.7
Conraads et al. (2015)	MCT HIIT	Bicycle	12 weeks 3×/week	5 min (60–70% HRp) WU + 37 min (70–75% HRp) + 5 min (60–70% HRp) CD	57.5	5 min (60–70% HRp) WU + 4 × 4 min (90–95% HRp)/3 min (50–70% HRp)	87.9	38.5
Blumenthal et al. (2005)	MCT	Treadmill	16 weeks 3×/week	10 min (50–70% HRr) WU + 35 min (70–85% HRr)	77.5			
Cardozo et al. (2015)	MCT HIIT	Treadmill	16 weeks 3×/week	5 min WU + 30 min (70–75% HRp) + 5 min CD	57.5	5 min WU + 7 × 2 min (90% HRp)/2 min (60% HRp) + 5 min CD	84.1	38.5
Choi et al. (2018)	MCT HIIT	NR	9 weeks 2×/week	5 min (40–50% HRm) WU + 28 min (60–70% HRm) + 5 min (40–50% HRm) CD	46.1	5 min (40–50% HRm) WU + 4 × 4 min (85–100% HRm)/3 min (50–60% HRm) + 5 min (40–50% HRm) CD	87.9	31
Currie et al. (2015)	MCT HIIT	Bicycle	13 weeks 2×/week	30 – 50 min (51–65% PPO)	57	10 × 1 min (85% PPO, month 1), (100% PPO, month 2), (108% PPO, month 3)/1 min (10% PPO)	100	10
Eto et al. (2004)	MCT	Bicycle	2 weeks 14×/week	30 min (AT)	75			
Ghroubi et al. (2013)	MCT	Bicycle	8 weeks 3×/week	10 min WU + 2 × 10 min (70% HRr)/5 min + 10 min CD	70			
Giallauria, De Lorenzo, et al. (2006)	MCT	Bicycle	13 weeks 3×/week	5 min WU + 30 min (60% VO_2peak) + 5 min CD	70			
Giallauria, Lucci, et al. (2006)	MCT	Bicycle	13 weeks 3×/week	5 min WU + 30 min (70% VO_2peak) + 5 min CD	60			
Giallauria et al. (2011)	MCT	Bicycle	26 weeks 3×/week	5 min WU + 30 min (60–70% VO_2peak) + 5 min CD	65			

Table 2. Continued

Study	Group	Mode	Duration, frequency	MCT exercise program	MCT Intensity (%VO_2peak)	HIIT exercise program	HIIT Intensity (%VO_2peak) W	HIIT Intensity (%VO_2peak) R
Giallauria et al. (2012)	MCT	Bicycle	26 weeks 3×/week	5 min WU + 30 min (60–70% VO_2peak) + 5 min CD	65			
Giallauria et al. (2013)	MCT	Bicycle	26 weeks 3×/week	5 min WU + 30 min (60–70% VO_2peak) + 5 min CD	65			
Heber et al. (2020)	MCT	Bicycle	6 weeks 4×/week	5 min (40% PPO) WU + 20 – 30 min (60% PPO) + 5 min (30% PPO) CD	60			
Helgerud et al. (2011)	HIIT	Treadmill	NR NR			5 min WU + 4 × 4 min (85–95% HRp)/3 min (60–70% HRp) + 5 min CD	84.1	46.1
Jayo-Montoya et al. (2020)	HIIT-LV HIIT-HV	Mixed	16 weeks 2×/week			Treadmill: 5 – 10 min (65–75% HRr) WU + 2 × 4 min (HIIT-LV); 2 – 4 × 4 min (HIIT-HV) (85–95% HRr)/3 min (65–75% HRr) + 4 min (65–75% HRr) CD Bicycle: 5 – 10 min WU + 4 – 8 × 30 s (HIIT-LV); 4 – 16 × 30 s (HIIT-HV) (85–95% HRr)/3 min (65–75% HRr) + 4 – 7 min (65–75% HRr) CD	90 90	70 70
Keteyian et al. (2014)	MCT HIIT	Treadmill	10 weeks 3×/week	5 min WU + 30 min (60–80% HRr) + 5 min CD	70	5 min WU + 4 × 4 min ((80–90% HRr)/3 min (60–70% HRr) + 5 min CD	85	65
Kim et al. (2015)	MCT HIIT	Treadmill	6 weeks 3×/week	10 min (50–70% HRr) WU + 25 min (70–85% HRr) + 10 min (50–70% HRr)	77.5	10 min (50–70% HRr) WU + 4 × 4 min (85–95% HRr)/3 min (50–70% HRr) + 10 min (50–70% HRr)	90	60
Lee et al. (2009)	MCT	Bicycle	13 weeks 3×/week	5 min WU + 20 min (55–70% VO_2peak) + 5 min CD	62.5			
Madssen et al. (2014)	MCT HIIT	Treadmill	12 weeks 3×/week	46 min (70% HRm)	53.7	10 min WU + 4 × 4 min (85–95% HRp)/3 min (70% HRp)	84.1	53.7
Ribeiro et al. (2012)	MCT	Mixed	8 weeks 3×/week	10 min WU + 35 min (65–75% HRm) + 10 min CD	53.7			
Rognmo et al. (2004)	MCT HIIT	Treadmill	10 weeks 3×/week	41 min (50–60% VO_2peak)	55	5 min (50–60% VO_2peak) WU + 4 × 4 min (80–90% VO_2peak)/3 min (50–60% VO_2peak) + 3 min (50–60% VO_2peak)	85	55

Table 2. Continued

Study	Group	Mode	Duration, frequency	MCT exercise program	MCT Intensity (%VO_2peak)	HIIT exercise program	HIIT Intensity (%VO_2peak)	
							W	R
Subiela et al. (2018)	MCT	Mixed	12 weeks 3×/week	20 – 30 min (60–80% VO_2peak)	77.5			
Takagi et al. (2016)	MCT	Bicycle	12 weeks 2×/week	30 min (AT minus 10 W)	47			
Takeyama et al. (2000)	MCT	Bicycle	12 weeks 2×/week	30 min (AT)	81			
Villelabeitia-Jaureguizar et al. (2019)	MCT HIIT	Bicycle	8 weeks 3×/week	12 – 5 min WU + 15 – 30 min (AT – AT + 10%) + 13 – 5 min CD	NR	12 – 5 min WU + 15 – 30 × 20 s (108–126% PPO)/40 s (22% PPO) + 13 – 5 min CD	117	22
Vona et al. (2009)	MCT	Bicycle	4 weeks 4×/week	10 min WU + 40 min (75% HRp) + 10 min CD	61.3			

AT, aerobic threshold; *CD*, cooldown; *HIIT*, high-intensity interval training; *HRm*, maximum heart rate; *HRp*, peak heart rate; *HRr*, heart rate reserve; *HV*, high volume; *LV*, low volume; *MCT*, moderate continuous training; *NR*, no reported; *PPO*, peak power output achieved in cardiopulmonary exercise test; *R*, recovery; *RCP*, respiratory compensation point; *VO_2peak*, peak oxygen uptake; *W*, work; *WU*, warm-up

Table 3. Quality analysis using PEDro scale

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	MQS
Prado et al. (2016)	N	Y	N	Y	N	N	N	N	N	Y	Y	4
Oliveira et al. (2014)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Aamot et al. (2014)	N	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Conraads et al. (2015)	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7
Blumenthal et al. (2005)	N	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Cardozo et al. (2015)	N	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Choi et al. (2018)	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5
Currie et al. (2015)	Y	Y	N	Y	N	N	N	N	N	Y	Y	4
Eto et al. (2004)	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Ghroubi et al. (2013)	N	Y	N	Y	N	N	N	N	N	Y	Y	4
Giallauria, De Lorenzo, et al. (2006)	Y	Y	N	Y	N	N	N	N	N	Y	Y	4
Giallauria, Lucci, et al. (2006)	Y	Y	N	Y	N	N	N	N	N	Y	Y	4
Giallauria et al. (2011)	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	7
Giallauria et al. (2012)	Y	Y	N	Y	N	N	Y	N	N	Y	Y	5
Giallauria et al. (2013)	Y	Y	N	Y	N	N	Y	N	N	Y	Y	5
Heber et al. (2020)	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Helgerud et al. (2011)	N	Y	N	Y	N	N	N	Y	N	Y	Y	5
Jayo-Montoya et al. (2020)	N	Y	N	Y	N	N	Y	N	Y	Y	Y	6
Keteyian et al. (2014)	N	Y	Y	Y	N	N	Y	N	N	Y	Y	6
Kim et al. (2015)	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5
Lee et al. (2009)	Y	Y	N	Y	N	N	N	N	N	Y	Y	4
Madssen et al. (2014)	N	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Ribeiro et al. (2012)	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7
Rognmo et al. (2004)	Y	Y	Y	Y	N	N	N	N	N	Y	Y	5
Subiela et al. (2018)	N	N	N	Y	N	N	N	N	N	Y	Y	3
Takagi et al. (2016)	Y	N	N	Y	N	N	N	N	N	Y	Y	3
Takeyama et al. (2000)	N	Y	N	Y	N	N	N	N	N	Y	Y	4
Villelabeitia-Jaureguizar et al. (2019)	N	Y	N	Y	N	N	N	N	N	Y	Y	4
Vona et al. (2009)	Y	Y	N	Y	N	N	N	N	N	Y	Y	4

MQS, methodological quality score; *N*, no; *Y*, yes; *Item 1*, eligibility criteria were specified (not included in total score, MQS); *Item 2*, subjects randomly assigned to groups; *Item 3*, allocation concealed; *Item 4*, equivalence of groups at baseline in most important prognostic variables; *Item 5*, blinding of all participants; *Item 6*, therapists who administered the treatment were blinded; *Item 7*, assessors were blinded for at least one key outcome; *Item 8*, data were obtained from at least 85% of the participants initially assigned to the groups; *Item 9*, there were no attrition or, where it was not the case, data for at least one key outcome were analyzed by intention-to-treat; *Item 10*, results of between-group comparisons were reported for at least one key outcome; *Item 11*, the study reports point estimates and variability statistics for at least one key outcome

Effect of aerobic training on VO_2peak

Twenty-six and 14 groups applied MCT and HIIT, respectively. All these pre- and posttest ESs (MDs) together with those of the 14 CGs are presented in the forest plot in Figure 2. The meta-analyzed effects of both training methods showed statistical improvements ($p < .001$) in VO_2peak ($MD_+ = 3.36$; 95% CI [2.96, 3.76] $ml \cdot kg^{-1} \cdot min^{-1}$ for MCT and $MD_+ = 4.61$; 95% CI [4.02, 5.19] $ml \cdot kg^{-1} \cdot min^{-1}$ for HIIT). The change exhibited in the CG ($MD_+ = 0.12$; 95% CI [–0.31, 0.55] $ml \cdot kg^{-1} \cdot min^{-1}$) did not reach statistical significance ($p = .590$). However, tests for subgroup differences among the three average MDs did show statistical significance ($p < .001$) with large heterogeneity explained ($I^2 = 98.9\%$). Therefore, we carried out pairwise comparisons. We performed a Bonferroni correction to control the increase in Type I error (significant at $p \leq .017$). The comparison between the average MD of each training method with the average MD for the CG reached statistical significance ($p < .001$). In addition, the comparison between the average MDs of the MCT and HIIT groups also reached statistical significance in favor of the HIIT groups ($p < .001$). As regards heterogeneity analysis, the 26 ESs of MCT attained statistical significance with moderate heterogeneity ($p < .001$; $I^2 = 67.0\%$), while the 14 ESs of HIIT did not reach statistical significance and no heterogeneity was found ($p = .220$; $I^2 = 22.0\%$). Consequently, we examined the influence of the characteristics of the analysis units, which may explain part of the heterogeneity of the studies that carried out CR based on MCT.

Sensitivity analysis

No outliers were found for MCT and HIIT ESs, indicating that there is no need to assess the overall effect without outlier analysis units. With a lower critical value (MD = –1.95) and an upper critical value (MD = 2.45), we found one outlier for the CG (MD = –3.30; Cardozo et al., 2015), and we carried out the analysis after removing it (see Supplementary Figure 1). Although the overall ES of the CG increased (from $MD_+ = 0.12$; 95% CI [–0.31, 0.55] $ml \cdot kg^{-1} \cdot min^{-1}$ to $MD_+ = 0.25$; 95% CI [–0.13, 0.62] $ml \cdot kg^{-1} \cdot min^{-1}$) and the heterogeneity diminished (from 72.0% to 62.0%), the conclusions were similar to those before removing the outlier, which confirms the validity of our findings. We included two nonrandomized trials in our meta-analysis (Subiela et al., 2018; Takagi et al., 2016). Removing these two studies, the pooled ES and heterogeneity were unchanged for the CG, while the overall ES decreased (from $MD_+ = 3.36$; 95% CI [2.96, 3.76] $ml \cdot kg^{-1} \cdot min^{-1}$ to $MD_+ = 3.23$; 95% CI [2.81, 3.65] $ml \cdot kg^{-1} \cdot min^{-1}$) and the heterogeneity was unchanged for the MCT (see Supplementary Figure 2). The conclusions were similar to before removing nonrandomized studies. All patients were randomly allocated in studies that used HIIT protocols to carry out CR. Therefore, our findings were robust to the decision of the inclusion of nonrandomized trials.

Publication bias

There was no evidence of asymmetry in the funnel plot for MCT and HIIT (Figure 3). However, the Egger test applied for MCT was statistically significant, $t(25) = -2.46$, $p = .022$, but not for HIIT, $t(13) = 0.63$, $p = .529$. Although the Egger test for the MCT groups reached statistical significance, the trim-and-fill method did not impute missing ESs to symmetrize the funnel plot. Therefore, on a reasonable basis, publication bias can be discarded as a threat against the results of the meta-analysis both for the MCT and the HIIT groups.

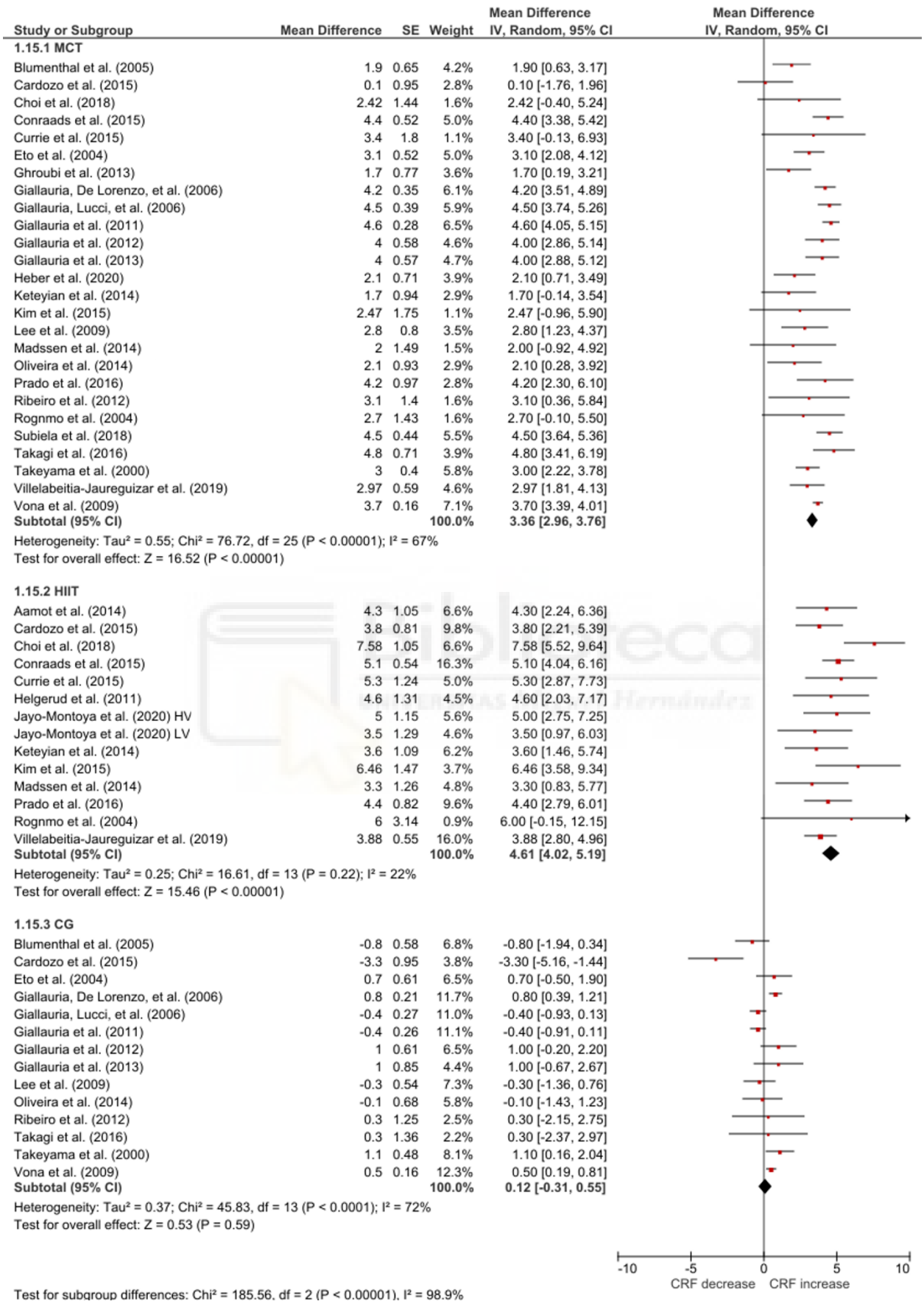


Figure 2. Forest plot grouping the mean difference indices for peak oxygen uptake in MCT, HIIT, and CG. *95% CI*, 95% confidence interval around mean difference; *CG*, control group; *CRF*, cardiorespiratory fitness; *HIIT*; high-intensity interval training; *HV*, high volume; *LV*, low volume *MCT*; moderate continuous training

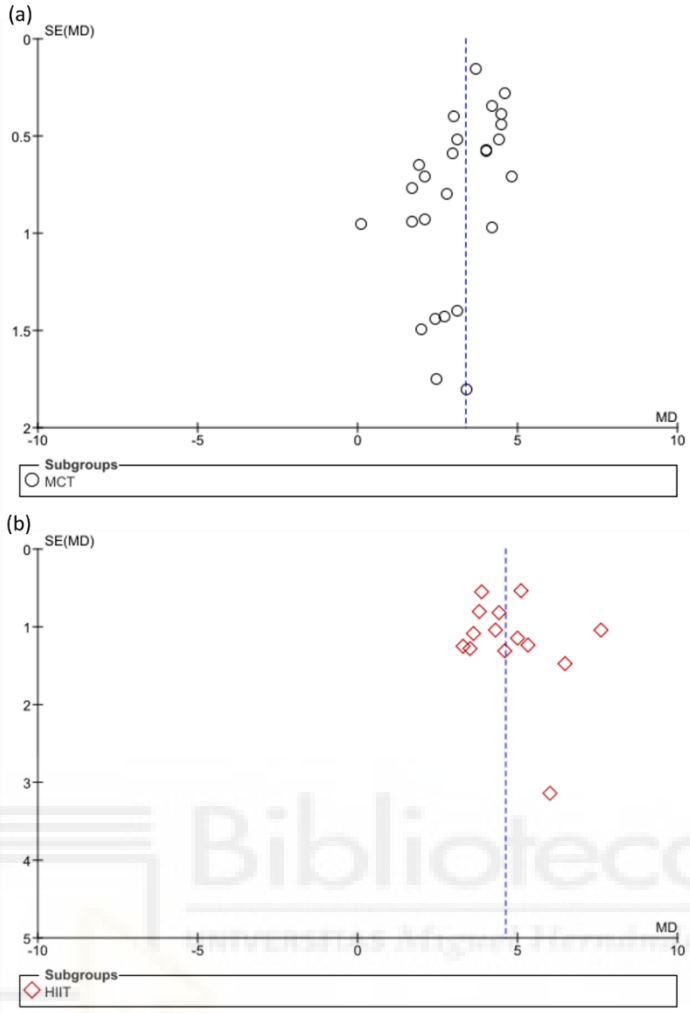


Figure 3. Funnel plot of (a) the 26 MD indices of MCT and (b) the 14 MD indices of HIIT. *MD*, mean difference; *MCT*, moderate continuous training; *HIIT*, high-intensity interval training

Analysis of moderator variables on the ESs of MCT

Table 4 shows the results of analyzing the influence of categorical moderator variables on the effect of MCT. Our subgroup analyses showed significant between-group heterogeneity with high inconsistency for the training mode ($p < .001$; $I^2 = 90.4\%$), the risk of a new event ($p = .010$; $I^2 = 77.4\%$), the type of cardiovascular event ($p = .009$; $I^2 = 84.8\%$), and the wait time to start CR ($p = .010$; $I^2 = 76.6\%$). There were greater CRF increases for patients who carried out CR on a bicycle (n = 469 patients; $MD_+ = 3.71$ ml·kg^{-1}·min^{-1}) or by combining a bicycle and treadmill (n = 84 patients; $MD_+ = 3.42$ ml·kg^{-1}·min^{-1}) compared with a treadmill alone (n = 129 patients; $MD_+ = 1.63$ ml·kg^{-1}·min^{-1}). With regard to the risk of a new event, our findings showed higher CRF increases after CR as the risk of a new event increased (low: n = 111 patients; $MD_+ = 2.40$ ml·kg^{-1}·min^{-1}, moderate: n = 433 patients; $MD_+ = 3.04$ ml·kg^{-1}·min^{-1}, and high: n = 159 patients; $MD_+ = 3.96$ ml·kg^{-1}·min^{-1}). There were greater improvements for patients with AMI (n = 363 patients; $MD_+ = 3.82$ ml·kg^{-1}·min^{-1}) than in the mixed category (n = 287 patients; $MD_+ = 2.60$ ml·kg^{-1}·min^{-1}). In addition, patients who started to receive CR within the first 3 weeks after the event showed

a higher increase (n = 243 patients; MD_+ = 4.05 ml·kg^{-1}·min^{-1}) than those who had to wait between 4 and 12 weeks (n = 284 patients; MD_+ = 3.10 ml·kg^{-1}·min^{-1}) or >12 weeks (n = 63 patients; MD_+ = 2.04 ml·kg^{-1}·min^{-1}). As regards the study quality, a statistically significant relationship with the ESs was found for Item 2 of the PEDro scale (p = .002; I^2 = 89.9%). MCT groups belonging to studies in which participants were randomly assigned to the groups exhibited an average MD lower (n = 676 patients; MD_+ = 3.23 ml·kg^{-1}·min^{-1}) than that of the MCT groups that did not belong to studies that applied an experimental design (n = 27 patients; MD_+ = 4.58 ml·kg^{-1}·min^{-1}). Table 5 presents the results of the simple meta-regressions for the continuous moderator variables. The meta-regression findings revealed that the percentage of patients undergoing revascularization (n = 614 patients; B = –0.022; p = .041) and CRF at baseline (n = 703 patients; B = –0.103; p = .025) were inversely related to the CR-induced effect on the CRF.

Table 4. Results of analyzing the influence of categorical moderator variables on the effect of MCT

				Test for subgroup differences		
Moderator variable	**Category**	***k***	**MD [95% CI]**	χ^2	***p***	I^2
A) Treatment characteristics						
Training mode	Treadmill	6	1.63 [0.82, 2.44]	20.75	<.001	90.4%
	Cycling	16	3.71 [3.32, 4.09]			
	Mixed	3	3.42 [1.72, 5.11]			
Wait time	≤3 weeks	10	4.05 [3.68, 4.42]	8.55	.010	76.6%
	4–12 weeks	7	3.10 [2.16, 4.04]			
	>12 weeks	4	2.04 [0.46, 3.62]			
B) Subject characteristics						
Type of revascularization procedure	CABG	2	3.26 [0.23, 6.30]	0.85	.650	0.0%
	PCI	15	3.74 [3.32, 4.15]			
	Mixed	6	3.28 [2.36, 4.20]			
Risk of a new event	Low	5	2.40 [1.26, 3.54]	8.86	.010	77.4%
	Moderate	14	3.04 [2.40, 3.67]			
	High	7	3.96 [3.46, 4.46]			
Type of cardiovascular event	AMI	15	3.82 [3.42, 4.22]	6.56	.009	84.8%
	Mixed	10	2.60 [1.76, 3.44]			
Sex of the sample	Male	5	3.34 [2.42, 4.26]	0.01	.920	0.0%
	Mixed	20	3.39 [2.94, 3.84]			
C) Methodological quality						
Item 2	Yes	24	3.23 [2.81, 3.65]	9.91	.002	89.9%
	No	2	4.58 [3.85, 5.32]			
Item 3	Yes	7	2.66 [1.62, 3.70]	2.36	.120	57.7%
	No	19	3.54 [3.11, 3.96]			
Item 7	Yes	8	3.13 [2.19, 4.08]	0.28	.600	0.0%
	No	18	3.42 [2.96, 3.76]			
Item 8	Yes	11	2.72 [1.77, 3.66]	3.36	.070	70.3%
	No	15	3.67 [3.27, 4.07]			
Item 9	Yes	7	2.76 [1.61, 3.91]	1.91	.170	47.7%
	No	19	3.61 [3.23, 3.99]			

95% CI, 95% confidence interval around MD; *AMI*, acute myocardial infarction; *CABG*, coronary artery bypass grafting; χ^2, between-categories *Q* statistic for testing the significance of the moderator variable; I^2, heterogeneity index; *k*, number of studies; *MCT*, moderate continuous training; *MD*, mean difference; *p*, probability level associated to the χ^2 statistic; *PCI*, percutaneous coronary intervention. *Item 2*, subjects randomly assigned to groups; *Item 3*, allocation concealed; *Item 7*, assessors were blinded for at least one key outcome; *Item 8*, data were obtained from at least 85% of the participants initially assigned to the groups; *Item 9*, there were no attrition or, where it was not the case, data for at least one key outcome were analyzed by intention-to-treat

Table 5. Results of analyzing the influence of continuous moderator variables on the effect of MCT

Moderator variable	*k*	*B*	*Z*	*p*
(a) Treatment characteristics				
Intensity	25	–0.0140	–0.569	.569
Session duration	26	0.0001	0.045	.964
Treatment duration	26	0.0497	1.747	.081
Number of sessions	26	0.0174	1.572	.116
Total volume	26	0.0001	0.888	.374
Frequency	26	–0.0364	–0.610	.542
(b) Subject characteristics				
Age	26	–0.0191	–0.349	.727
Sample size	26	0.0045	0.398	.691
Patients with AMI (%)	24	0.0169	1.802	.072
Undergoing an intervention (%)	23	–0.0215	–2.047	.041
Male (%)	25	0.0154	0.767	.443
CRF at baseline ($ml \cdot kg^{-1} \cdot min^{-1}$)	26	–0.1029	–2.241	.025
(c) Extrinsic and methodological characteristics				
Publication year	26	–0.0124	–0.272	.786
Methodological quality score	26	–0.2733	–1.907	.057

AMI, acute myocardial infarction; *B*, regression coefficient; *CRF*, cardiorespiratory fitness; *k*, number of studies; *MCT*, moderate continuous training; *p*, probability level associated to the *Z* statistic; *Z*, statistic for testing the significance of the moderator variable

DISCUSSION

According to our findings, both training methods are appropriate for increasing the VO_2peak in patients with CAD. This finding is in line with previous meta-analyses that found a significant effect of HIIT (Ballesta García et al., 2019) and MCT (Kraal et al., 2017) in improving VO_2peak. CRF improvement after aerobic training in patients with CAD could be related to changes in cardiovascular structure and function (Lee et al., 2009).

Although MCT and HIIT seem to be suitable for improving CRF, HIIT seems to be more effective than MCT for improving CRF. This finding is in line with all previous meta-analyses that compared the effect of both training methods on the VO_2peak (Elliott et al., 2015; Gomes-Neto et al., 2017; Hannan et al., 2018; Liou et al., 2016; Pattyn et al., 2014, 2018; Xie et al., 2017). There is some evidence that could explain this superiority. High intensity induces a larger improvement in contractility and hypertrophy of the cardiomyocyte than moderate intensity, which contributes to increasing the contractile cardiac pump function (Kemi et al., 2005). In addition, it also produces an increased activation of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha, which improves mitochondrial function and reduces skeletal muscle fatigue (Tjønna et al., 2008). HIIT allows the accumulation of more time performing at high

intensity and, therefore produces a greater stimulus for cardiovascular and muscular adaptations (Wisløff, Ellingsen, & Kemi, 2009).

Due to the high variability observed in the MCT-induced effect on the CRF (I^2 = 67.0%), we carried out heterogeneity analyses to explain at least part of it. In terms of the characteristics of the subjects, our findings showed the relevance of the type of cardiovascular event, the percentage of patients undergoing revascularization, the preintervention CRF, and the risk of a new event when MCT is applied. These four variables are related to some extent to the health state of the patient just before they began CR.

In regard to the type of cardiovascular event, CRF improvement was greater when the study sample was constituted by patients who had experienced an AMI. The severity of both diagnostics, AMI and angina, is different. While unstable angina is due to a transitory lack of oxygen, in AMI there is a necrosis of the myocardial cells, which affects the myocardial function directly. Thus, patients with AMI had a worse prognosis than patients with angina pectoris (Dudas et al., 2013). Similarly, CRF improvement was higher when the study sample was constituted by patients who had been revascularized. The combined effect of surgical manipulation of the heart and anaesthesia can produce a worse heart condition for several weeks after surgery (Kalisnik et al., 2006). We also found that the effect of MCT is larger when this training method is applied in patients with low CRF or with a high risk of experiencing a new event. Previous studies have also reported that people in poor physical condition experience a higher exercise training effect on CRF (Støren et al., 2017). As we can see, these findings show an increased impact of CR when it is applied to patients with a worse prognosis or in a worse physical condition, and this reinforces the recommendation that all patients with CAD should be included in a CR program.

The wait time to start CR was also related to CRF improvement when MCT was used to carry out CR. We found that the highest gain appeared when CR began within 3 weeks after the event. If the wait time is longer, the increase in VO_2peak is smaller. Despite this variable being a continuous variable, due to the descriptive limitations of empirical studies, we could not analyze it in that way. However, our results are similar to the findings of Collins, Suskin, Aggarwal, and Grace (2015), who found a positive effect on functional capacity when CR initiation occurred within 3 months after the event. More considerable CRF improvement when CR starts early could be explained by an increased exercise training effect on cardiac function in the acute phase of the recovery. Haykowsky et al. (2011) reported that CR has a beneficial impact on left ventricular remodelling after AMI, but the most significant changes were found when CR began ~1 week after the event. Repair of the infarcted myocardium can be described in three phases: inflammatory (hours), proliferative (days), and maturation phase (weeks). Early stimulation of inflammatory signalling is essential for the clearance of dead cells from the infarcted area (Frangogiannis, 2014). Exercise training could help to decrease the inflammatory response and

allow higher adaptations in these acute phases. Therefore, from a clinical point of view, delays in starting CR should be minimized so that patients with CAD can obtain the maximum benefits.

As we have commented previously, it seems that the intensity could explain the difference between MCT and HIIT effect on VO_2peak. Surprisingly, when we carried out heterogeneity analyses to study the heterogeneity across the MCT groups, no other exercise training variables were related to the MCT effect. The only variable that showed differences was the training mode, which showed that the increase in CRF is higher when MCT is carried out on a bicycle. We hypothesized that this could be due to a lower previous adaptation to this training mode in patients with CAD, which limits the muscular capacity of the patients to reach their maximum at baseline in the cardiopulmonary exercise test. Therefore, to know the true effect of CR, a previous adaptation period to baseline assessment should be performed when CR is carried out on a bicycle.

As regards the methodological quality of the studies that used MCT, our findings showed that quasi-experimental studies exhibited larger CRF improvements than experimental studies. The greater CRF improvement found in quasi-experimental studies could be due to selection bias (allocation and concealment) and, therefore, their results should be interpreted with caution. In addition, we also found a residual statistical relationship between the methodological quality score and the effect of MCT (p = .057). In light of both these findings, it may be relevant to only examine randomized studies with higher methodological quality as a means of estimating the confidence-accuracy effect (Cooper, Hedges, & Valentine, 2019). The overestimation of the CRF improvement exhibited by the MCT group from nonrandomized studies leads us to conclude that a better estimate of the real CRF improvement of MCT is that based on randomized studies only, that is, $MD_+ = 3.23$ ml·kg^{-1}·min^{-1} in place of the overall estimate reported in Figure 2, $MD_+ = 3.36$ ml·kg^{-1}·min^{-1}. In addition, future research on this topic should routinely use randomized designs, as it seems that nonrandomized ones overestimate the true effect.

The CR-induced effects on the CRF found in studies that carried out aerobic training based on HIIT produced homogeneous findings (p = .220; I^2 = 22.0%), showing no influence of the potential moderator variables. However, it should be highlighted that our systematic review showed low heterogeneity between HIIT protocols and participant characteristics in the studies that carried out CR based on HIIT. For instance, 65% of the studies (n = 9) that applied HIIT used long intervals (mainly 4-min intervals with 3-min rest between them) to carry out CR, 14% (n = 2) combined long and short intervals, and 21% (n = 3) used short intervals. In addition, only one of the studies that applied short intervals used an intensity above the PPO achieved in the cardiopulmonary exercise test. The low heterogeneity between HIIT protocols implemented in the included studies does not allow us to know the influence of different exercise exposures (e.g., long or short intervals, below or above the PPO). This justifies future research to study the effect of short intervals and intensities above the PPO on the CRF in patients with CAD.

As for patient characteristics, even though the mean age is similar in the MCT and HIIT groups (58.7 vs. 58.1 years, respectively), the age and preintervention CRF for the HIIT groups are more homogeneous than in the MCT groups (min–max: 53–63 years and 18.9–34.7 $ml \cdot kg^{-1} \cdot min^{-1}$; min–max: 52–69 years and 13.0–32.1 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively). The greater homogeneity of these patients' characteristics in HIIT groups could also allow us to explain the absence of heterogeneity found in the results of studies that carried out CR based on HIIT. Moreover, HIIT protocols were only applied in patients with a low-to-moderate risk of a new event. We suppose that the HIIT protocols were not used with high-risk patients for fear that the patient would experience complications. However, this fear seems unjustified because a high intensity above the PPO with short intervals has proven to be less stressful on the heart and severe patients tolerated this high intensity better than moderate continuous efforts (Meyer et al., 1997; Vogiatzis et al., 2005). Therefore, future studies should focus on the effect of HIIT on high-risk older patients with low CRF at baseline.

As we have commented previously, our findings revealed that the MCT-induced effect on the CRF was inversely related to the preintervention VO_2peak, showing a lower CR-induced impact in patients with a higher level of physical fitness. However, despite the fact that the mean CRF at baseline of the included studies that applied HIIT protocols was higher than in the MCT studies (25.6 vs. 21.2 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively), CR based on HIIT was more effective for improving VO_2peak. Therefore, it seems that, in patients with better physical fitness, HIIT protocols should be applied to reach a higher CR-induced effect on the CRF.

Although our findings show a lack of relevance of the exercise training characteristics for the effect of MCT or HIIT, previous studies have reported that proper management of the frequency, intensity, type, and time of training is important to increase the long-term effect of exercise training (Vanhees et al., 2012). Although the aim of our meta-analysis was not to analyse the application of exercise training principles in CR programs, such as individualization, overload, or progression, none of the included studies except one carried out a progression of the training load, even though the duration of this programme was 26 weeks. Readjustment of work rates would have ensured that relative exercise intensity and metabolic stress remained unchanged throughout the training programme (Meyer et al., 1997), thereby suggesting continuity in the CRF improvement. The lack of control of treatment variables and the incorrect manipulation or nonapplication of the exercise training principles could be the reason why the treatment variables were not related to the effect of both training methods on the CRF improvement.

Conclusion

Based on our findings, although current CR programs are sufficient to improve the CRF in patients with CAD, they are not optimized, and the training principles should be reviewed in order

to achieve better short- and long-term effects. In addition, some variables should be taken into account when individualizing and applying an aerobic training program in CR correctly. MCT seems to be more useful for improving CRF in patients with CAD the sooner it starts. In addition, its effectivity is higher in patients with a worse prognosis revealed by lower CRF at baseline, or a higher risk of a new event, and in patients who had experienced AMI or had undergone revascularization. On the other hand, in patients with a better prognosis and a higher level of physical fitness, HIIT protocols should be applied to achieve a more significant CRF improvement as they seem to be more effective in this kind of patient. When carrying out the CR using a cycloergometer, clinicians should consider including an adaptation period and evaluate the performance after this adaptation period to avoid a possible misinterpretation of CRF changes.

Future studies should control and describe the wait time to start CR, the type of event and revascularization, and the risk of a new event to increase our knowledge about the effect of different aerobic training methods in this population. In addition, as the homogeneity of the training programs applied is remarkable, future studies should analyze the impact of varying HIIT setups (i.e., intensity above 100% PPO and short intervals) on different types of patients.

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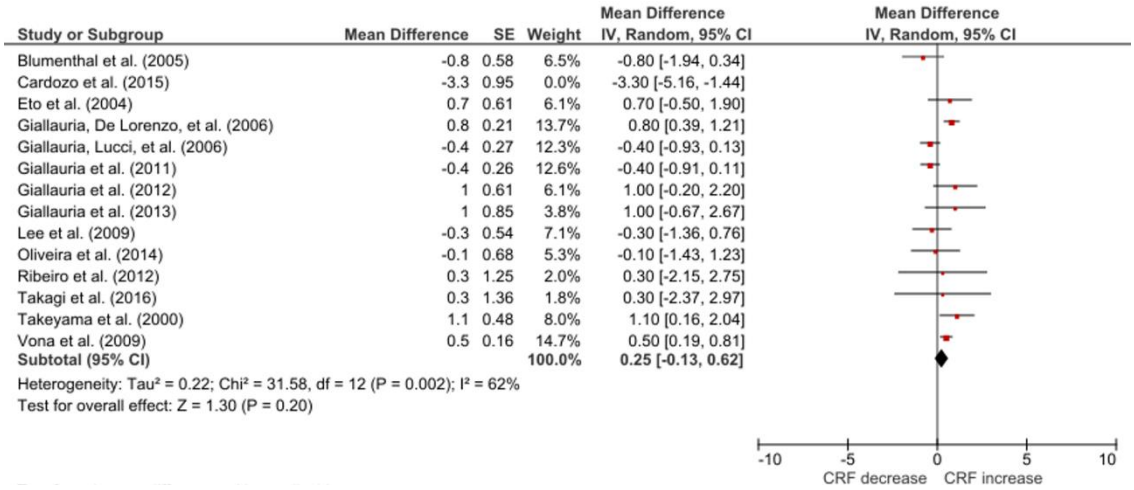
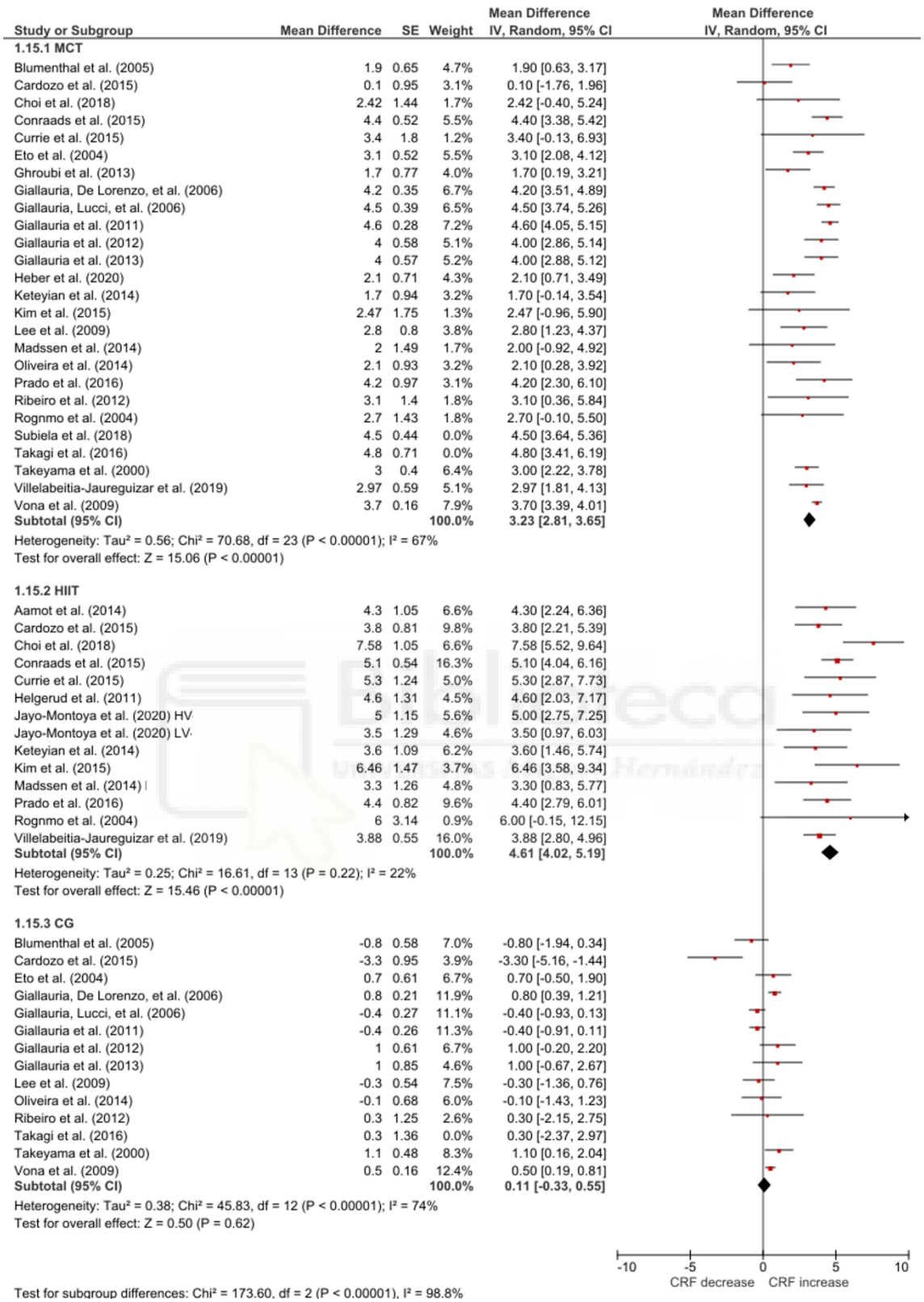
8.3.2. Supplementary material study 3



Supplementary Figure 1. Forest plot grouping the mean difference indices for peak oxygen uptake in control group after removing one outlier. *95% CI*, 95% confidence interval around mean difference; *CRF*, cardiorespiratory fitness



Supplementary Figure 2. Forest plot grouping the mean difference indices for peak oxygen uptake in MCT, HIIT, and CG after deleting nonrandomized trials. *95% CI*, 95% confidence interval around mean difference; *CG*, control group; *CRF*, cardiorespiratory fitness; *HIIT*; high-intensity interval training; *HV*, high volume; *LV*, low volume *MCT*; moderate continuous training

APPENDIX 4

STUDY 4

Heart rate variability-guided training for enhancing cardiac-vagal modulation, aerobic fitness, and endurance performance: a methodological systematic review with meta-analysis

Note. This study was published

Manresa-Rocamora A, Sarabia JM, Javaloyes A, Flatt AA, Moya-Ramón M. Heart rate variability-guided training for enhancing cardiac-vagal modulation, aerobic fitness, and endurance performance: a methodological systematic review with meta-Analysis. *Int J Environ Res Public Health.* 2021 Sep;18(19):10299. https://doi.org/10.3390/ijerph181910299

8.4. Appendix 4

8.4.1. Study 4. Heart rate variability-guided training for enhancing cardiac-vagal modulation, aerobic fitness, and endurance performance: a methodological systematic review with meta-analysis

Abstract

Purpose: This systematic review with meta-analysis was conducted to establish whether heart rate variability (HRV)-guided training enhances cardiac-vagal modulation, aerobic fitness, or endurance performance to a greater extent than predefined training while accounting for methodological factors. Methods*:* We searched Web of Science Core Collection, Pubmed, and Embase databases up to October 2020. A random-effects model of standardized mean difference (SMD) was estimated for each outcome measure. Chi-square and the I^2 index were used to evaluate the degree of homogeneity. Results*:* Accounting for methodological factors, HRV-guided training was superior for enhancing vagal-related HRV indices (SMD_+ = 0.50 (95% confidence interval (CI) = 0.09, 0.91)), but not resting HR (SMD_+ = 0.04 (95% CI = −0.34, 0.43)). Consistently small but non-significant ($p > 0.05$) SMDs in favor of HRV-guided training were observed for enhancing maximal aerobic capacity (SMD_+ = 0.20 (95% CI = −0.07, 0.47)), aerobic capacity at second ventilatory threshold (SMD_+ = 0.26 (95% CI = −0.05, 0.57)), and endurance performance (SMD_+ = 0.20 (95% CI = −0.09, 0.48)), versus predefined training. No heterogeneity was found for any of the analyzed aerobic fitness and endurance performance outcomes. Conclusion*:* Best methodological practices pertaining to HRV index selection, recording position, and approaches for establishing baseline reference values and daily changes (i.e., fixed or rolling HRV averages) require further study. HRV-guided training may be more effective than predefined training for maintaining and improving vagal-mediated HRV, with less likelihood of negative responses. However, if HRV-guided training is superior to predefined training for producing group-level improvements in fitness and performance, current data suggest it is only by a small margin.

Keywords

Autonomic nervous system; parasympathetic activity; heart rate recovery; resting heart rate; cardiorespiratory fitness

INTRODUCTION

Habitual cardiorespiratory endurance exercise improves a variety of markers related to human health and performance [1]. Exercise programs that efficiently stimulate adaptations are therefore of interest to general, clinical, and athletic populations. Traditional exercise prescription methodology involves predefined program parameters in which the intensity, volume, frequency, and timing of training are scheduled in advance. Several predefined training models have been implemented to improve indices of fitness and performance in various populations [2,3]. Though group-level improvements in fitness-related outcomes support predefined training, responses at the individual level are mixed [4]. For instance, Bouchard, An, Rice, Skinner, Wilmore, Gagnon, Pérusse, Leon, Rao [5] reported an average increase in maximal oxygen uptake ($\dot{V}O_2$ max) of 384 ± 202 mL·min^{-1} after a standardized 20-week training program in 720 healthy subjects. However, individual responses ranged from decrements of 100 mL·min^{-1} in some participants to increments of 1000 mL·min^{-1} in others. Thus, individualized exercise prescription that modifies intensity, volume, and timing of exercise according to the evolving status of the participant may increase the effectiveness and efficiency of exercise training [6].

Cardiac-autonomic functioning, as indexed by vagal-mediated heart rate (HR) variability (HRV) indices (i.e., the root-mean-square difference of successive normal R-R intervals (RMSSD), the high frequency (HF), and the standard deviation of the instantaneous beat-to-beat R-R interval variability (SD_1)) [7], is a non-invasive marker of acute and chronic adaptation to endurance exercise. In the short-term (e.g., within 48 h after exercise), recovery of HRV to baseline is thought to coincide with restoration of thermoregulatory, metabolic, hemodynamic, and fluid-balance related processes that are disturbed by physical exertion [8]. In the long-term (e.g., weeks to months), HRV profiles that reflect higher and/or more stable resting values have been associated with greater improvements in post-intervention fitness outcomes among sedentary [9], moderately-trained [9,10], highly-trained [11–13], and clinical populations [14–16]. Recent experiments have compared predefined training versus HRV-guided training, in which high intensity exercise is prescribed when resting HRV is within or above baseline ranges and low intensity exercise (or passive rest) is prescribed when values are suppressed. Some key findings favoring HRV-guided training include similar or greater improvements in selected fitness outcomes despite fewer high intensity sessions, less heterogeneity in fitness changes [17,18], and effectiveness in a variety of populations [17–24].

Recent reviews have aimed to consolidate available findings. Granero-Gallegos, González-Quílez, Plews, Carrasco-Poyatos [25] reported that HRV-guided training had a significantly greater effect on $\dot{V}O_2$ max versus predefined training. However, this meta-analysis included the training group (i.e., HRV-guided training and predefined training) as the analysis unit. Therefore, within-group effect sizes (ESs), which exhibit lower internal validity than between-group ESs

[26], were estimated. Moreover, these results should be interpreted with caution since testing for subgroup comparisons based on the training prescription method used was not performed. Medellin Ruiz, Rubio-Arias, Clemente-Suarez, Ramos-Campo [27] also compared HRV-guided training to predefined training for improving aerobic fitness and performance (i.e., $\dot{V}O_2$ max and maximal power output) in endurance-trained athletes and sedentary subjects and reported no differences between training prescription methods. Nevertheless, heterogeneity analyses to test the influence of methodological approaches and/or individual differences were not performed. Finally, Düking, Zinner, Reed, Holmberg, Sperlich [28] carried out a systematic review on the effectiveness of HRV-guided training and predefined training in healthy runners. The authors reported that both training prescription methods induce physiological adaptations, with effects of HRV-guided training tending to be greater. Thus, collective findings are inconclusive.

Various methodological approaches have been applied in HRV-guided training interventions that may influence outcomes and may possibly explain the lack of consensus in recent reviews [25,27,28]. Differences in HRV assessment (e.g., body position, pre-recording stabilization period, measurement duration, selection of the vagal-related HRV index, and respiration rate) and the criterion to modify training (e.g., use of single or average HRV values, and static or rolling baseline reference ranges) may influence HRV values and, consequently, training prescription. Additionally, the training status of the participants may influence both HRV and the effectiveness of the training program [29]. Highly trained individuals have less room for improvement and a greater tolerance for training stress than recreationally active and sedentary populations. Thus, a more thorough consolidation of the original research that accounts for the aforementioned methodological factors is needed.

Aerobic fitness and performance have been the primary outcomes of interest in recent reviews [25,27,28]. Whether post-intervention changes in markers of cardiac-parasympathetic modulation vary as a function of prescription methodology is unclear. Resting HR and HRV, as well as post-exercise HR recovery (HRR) are various markers of vagal activity, each of which are independent predictors of cardiovascular morbidity and mortality [30]. The ubiquity of mobile devices capable of tracking resting and exercise-related HR metrics has generated widespread interest in these parameters [31], possibly because they are modifiable by lifestyle behaviors [32,33]. HRV in particular exhibits considerable versatility in informing on health and wellbeing [32–34], longevity [35], fitness, and performance [36–40]. Thus, practical and effective interventions that improve HRV are of growing and universal interest [41]. Modification of exercise based on daily HRV is now accessible to the masses, but its efficacy for improving HRV requires clarification.

A comprehensive investigation into the effectiveness of individualized endurance exercise based on daily HRV may be used to guide best practices for future research and inform applied implementation. Therefore, this systematic review with meta-analysis was conducted to establish

whether HRV-guided training enhances cardiac-vagal modulation or aerobic fitness and performance to a greater extent than predefined training while accounting for methodological factors.

METHOD

We conducted and reported a systematic review of the literature and a meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [42]. The systematic review and meta-analysis protocol were prospectively registered in the PROSPERO database (CRD42020218995).

Data search and sources

Potential studies were identified via a comprehensive strategy. A systematic search was performed in the Web of Science Core Collection, PubMed, and Embase databases from inception to October 2020 using free-text terms based on the PIC (participants, interventions, and comparisons) strategy. Language restrictions were not applied during this phase. The electronic search of individual databases was adapted as necessary (the full search strategy is depicted in the supplementary materials, Section 1). Moreover, the reference lists of previous reviews and full-text articles were manually checked to assess for eligibility. Conference proceedings were also searched on the Web of Sciences Core Collection database. Authors of selected studies were contacted via e-mail in an attempt to identify unpublished or ongoing studies that fulfilled our selection criteria. These search strategies were used to minimize the risk of publication bias.

Study selection

Eligibility criteria were established according to the PICOS (participants, intervention, comparison, outcomes, and study design) guideline: (a) sedentary healthy people, physically active, and endurance-trained athletes, regardless of training status or sex (participants); (b) endurance training prescription in the experimental group based on changes in vagal-related HRV indices (intervention); (c) predefined endurance training prescription in the control group (comparison); (d) cardiac-vagal modulation (i.e., vagal-related HRV indices, HRR, and/or resting HR), aerobic fitness parameters (i.e., $\dot{V}O_2$ max, maximal aerobic capacity, aerobic capacity at second ventilatory threshold (VT2), and/or aerobic capacity at first ventilatory threshold (VT1)), and/or endurance performance changes after the intervention (outcomes); and (e) randomized and non-randomized controlled trials (study design) written in English or Spanish.

Data extraction, coding study characteristics, and potential moderator variables

The following information was extracted from included studies: (a) study characteristics (publication year, country, study design (randomized or non-randomized), and journal); (b) baseline participant characteristics (sample size, sex (male, female, or mixed sample), age,

$\dot{V}O_2$ max, weight, athletic status (sedentary, physically active, recreational, or endurance-trained athletes), and sport (if applicable)); (c) exercise characteristics (training mode (endurance training or combined endurance and strength training), intervention length, and predefined training characteristics); (d) methodological approach characteristics (vagal-related HRV index (RMSSD, HF, or SD_1), power spectral density (PSD) method (if applicable), HRV value (single or averaged), number of average HRV values (if applicable), time of the day, device used, body position (sitting, standing, and supine), measurement length, breathing control, smallest worthwhile change (SWC) or reference criterion (fixed or moving), number of average values (if applicable), and criteria for modifying training in the HRV-guided training group).

Risk of bias

The Cochrane Collaboration's core risk of bias tool was uses to assess risk of selection, detection, attrition, and reporting bias, which were classified as high, unclear, or low risk of bias [43].

Two authors (AM and AJ) performed the study selection, data extraction, and risk of bias assessment. Disagreements were settled by consensus and, when consensus was not achieved, a third author (JMS) assessed the study or information to reach an agreement.

Computation of effect size and statistical analyses

The standardized mean difference (SMD) was used as the ES index to assess changes in cardiac-vagal modulation, aerobic fitness parameters, and endurance performance after the intervention. The SMD was calculated by subtracting the mean change in the outcome variables for the HRV-guided training group from the mean change for the predefined training group divided by the pooled standard deviation (SD) at baseline, corrected by a factor for small samples. SMD positive values indicated that it was favorable to HRV-guided training. In multiple-intervention studies with a shared predefined training group, the sample size in the predefined group was split-up [44], allowing us to include several analysis units from the same study. Separate analyses were performed for each SMD index according to the outcome measure when it was reported for at least three analysis units to avoid statistical dependence. A random-effects model was applied for each meta-analysis in which the weighting factor was the inverse variance, defined as the sum of the within-study and the between-studies variance. A conservative value of 0.7 previously proposed by Rosenthal [45] was used to calculate the variance of each study when the studies did not report the correlations between pre- and post-intervention measures. The analysis comprised calculating the mean ES with its 95% confidence interval (CI), a heterogeneity statistical test, chi-square, and the I^2 index to evaluate the degree of homogeneity of the ESs around the average effect. The magnitude of the SMD was classified as trivial (<0.20), small (0.20–0.59), moderate (0.60–1.19), large (1.20–1.99), or very large (≥2.00) [46]. We considered a statistically significant effect when $p \leq 0.05$. Heterogeneity was classified as low, moderate, or high at 25%, 50%, and

75%, respectively. In cases of substantial heterogeneity (chi-square test statistically significant and/or I^2 index > 50%), moderator variables analyses were performed by assessing the relationship between the ESs and the potential categorical and continuous potential moderator variables using subgroup analysis and simple meta-regressions, respectively. All analyses were carried out using weighted least squares and assuming mixed-effects models. In case of substantial heterogeneity in vagal-related HRV results, tests for subgroup comparisons were performed based on the vagal-related HRV index (i.e., RMSSD, HF, and SD_1) and the HRV value (i.e., single HRV value and averaged HRV value) to test the influence of methodological factors. For subgroup comparisons based on the vagal-related HRV index, RMSSD and SD_1 were considered the same index (RMSSD/SD_1), as previously reported [47]. In cases of substantial heterogeneity regardless of the outcome measure, the influence of participant and methodological approach characteristics on our findings were also investigated. Publication bias analyses were performed using a funnel plot with the trim-and-fill method for imputing possible missing ESs [48,49]. Finally, sensitivity analyses were performed to assess the influence of any individual study by removing each study and performing all analyses. Statistical procedures were performed using STATA software (version 16.0; Stata Corp LLC, College Station, TX, USA). For articles that did not report methodological information (e.g., single or averaged HRV values) or outcome data (i.e., mean or SD), authors were contacted via e-mail to obtain this information.

RESULTS

Study selection

From a total of 3260 studies after removing duplicates, 10 were eligible for full text analysis [17–24,50,51], of which we excluded two studies from qualitative and quantitative synthesis as follows: based on the same sample and other outcome measures reported (n = 1) [50] and training not guided by daily HRV values (n = 1) [51]. Out of all the selected studies, Kiviniemi, Hautala, Kinnunen, Nissilä, Virtanen, Karjalainen, Tulppo [21] included three HRV-guided training groups and two predefined training groups, allowing us to include three analysis units. Therefore, a total of 10 analysis units were included in the final qualitative and quantitative synthesis. Although we attempted to locate unpublished studies, all the selected studies had been published in peer-reviewed journals. A Preferred Reporting Items for Systematic Reviews and Meta-analysis flow-chart of our literature search and selection is presented in Figure 1.

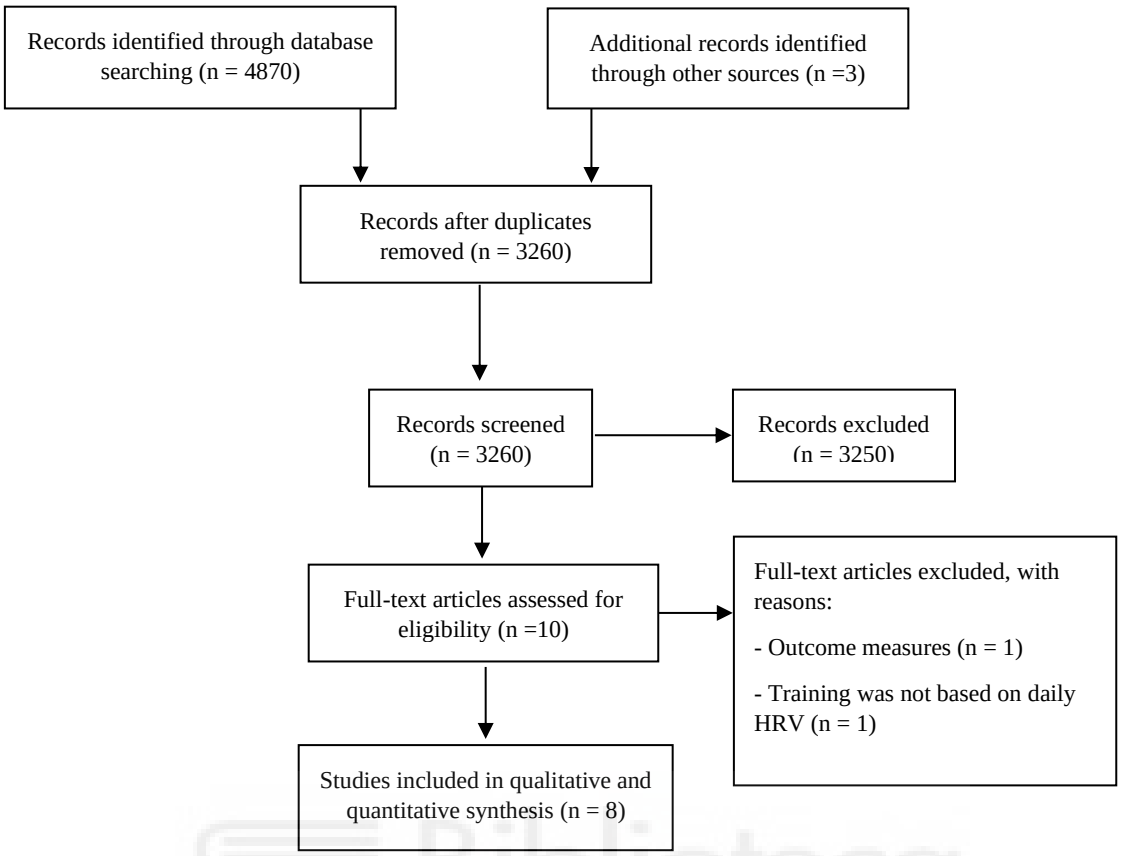


Figure 1. Flow chart of the systematic review process

Study characteristic

Study and participant characteristics are summarized in Table 1. The eight included studies are from four countries and were published between 2007 and 2020. Seven studies (88%) were randomized trials and one (12%) was a non-randomized trial [17]. In total, there were 199 participants (106 participants allocated to the HRV-guided training group and 93 in the predefined training group) with a mean ± SD age of 31.8 ± 4.8 years (min-max: 22.5–38.5 years), of which, 120 were males and 79 were females. Out of the 10 included analysis units, five (50%) were composed exclusively of male participants, three (30%) by female participants, and two (20%) used a mixed sample. Analysis unit sample size at pre-intervention varied from 14 to 40 participants. Based on the authors sample description, one analysis unit (10%) was composed of sedentary participants [19], three (30%) included physically active adults [21], three (30%) recruited recreationally trained athletes [22–24], and three (30%) included well-trained [17,20] and high-level athletes [18]. Out of all the analysis units composed of athletes, two were runners [22,24], two cyclists [17,20], one cross-country and nordic-skiers [18], while one study reported that endurance athletes were included [23]. The average ± SD weight and $\dot{V}O_2$ max at pre-intervention were 71.7 ± 7.1 kg (min–max: 62.1–81.5 kg) and 51.3 ± 9.8 $mL \cdot kg^{-1} \cdot min^{-1}$ (min–max: 35.5–65.2 $mL \cdot kg^{-1} \cdot min^{-1}$), respectively. One study did not report participant weight [24] and another one did not assess $\dot{V}O_2$ max [19].

Intervention and methodological approach characteristics are reported in Table 2. Five studies (62.5%) performed the intervention based on endurance training [17,19–22], two (25%) based on combined endurance and strength training [23,24] and one (12.5%) did not report this information [18]. The intervention length ranged from 2 to 8 weeks. Seven studies (87.5%) carried out daily HRV assessments in the morning after awakening [17,18,20–24] and one (12.5%) performed HRV measurements in the afternoon/evening before performing training sessions [19]. Seven studies (87.5%) explicitly reported that a stabilization period was performed before capturing HRV, ranging from 30 s to 5 min. Three studies (37.5%) carried out daily HRV assessments in the standing position, four (50%) in the supine position, and one (12.5%) in supine and standing positions. The assessment length ranged from 1 to 5 min. Three studies explicitly reported that participants were allowed to breathe spontaneously through HRV assessments [19,21,24], while the remaining studies did not report this information [17,18,20,22,23]. Five studies (62.5%) used RMSSD as the vagal-related HRV index to guide training in participants allocated to HRV-guided training groups [17,19,20,23,24], one (12.5%) SD_1 [21], and two (25%) HF, of which, one used the auto-regressive method to determine power spectral density [22] and another one used Fast-Fourier Transform [18]. Four studies (50%) used a single-day HRV value with a moving reference criterion [18,19,21,22] and four (50%) a rolling averaged HRV value with a fixed reference criterion, of which, three used a 7-day averaged HRV value [17,20,24] and one a 3-day averaged HRV value [23]. Out of the four studies that used a moving reference criterion, three used a 10-day averaged HRV value [19,21,22] and one used the single previous-day HRV value [18], while out of the four studies that used a fixed reference criterion, three updated the reference criterion once at the middle of the intervention [17,20,24] and one used the reference criterion captured at baseline throughout the entire intervention period [23]. Three studies (37.5%) calculated the reference criterion as mean − (1·SD) [19,21,22], three (37.5%) as mean ± (0.5·SD) [17,20,24], one (12.5%) used the 70% of the previous day as reference criterion [18], and one (12.5%) used the mean value measured at baseline [23].

Table 1. Study and participant characteristics

		Study Characteristics		Participant Characteristics	
Study (Author, Year)	**Training Group**	**Country; Study Design; Journal**	**Sample Size; Men Percentage**	**Age; Weight; $\dot{V}O_2$ max**	**Athletic Status; Sport (If Applicable)**
da Silva et al. [19] 2019	HRV-G	Brazil; randomized controlled trial; J Strength Cond Res	15; 0%	25.8 ± 3.1 years; 62.9 ± 10.3 kg; NR	Sedentary; NA
	PRED-G		15; 0%	27.7 ± 3.6 years; 61.3 ± 10.5 kg; NR	
Javaloyes et al. [17] 2020	HRV-G	Spain; non-randomized controlled trial; J Strength Cond Res	7; 100%	28.1 ± 13.2 years; 73.8 ± 4.6 kg; 58.9 ± 5.6 mL·kg^{-1}·min^{-1}	Well-trained; cyclists
	PRED-G		8; 100%	30.8 ± 10.5 years; 72.6 ± 10.4 kg; 59.0 ± 6.2 mL·kg^{-1}·min^{-1}	
Javaloyes et al. [20] 2019	HRV-G	Spain; randomized controlled trial; Int J Sport Physiol Perform	9; 100%	39.2 ± 5.3 years; 76.9 ± 12.5 kg; 55.0 ± 7.6 mL·kg^{-1}·min^{-1}	Well-trained; cyclists
	PRED-G		8; 100%	37.6 ± 7.1 years; 78.7 ± 11.7 kg; 52.2 ± 6.5 mL·kg^{-1}·min^{-1}	
Kiviniemi et al. [21] 2010	HRV-G	Finland; randomized controlled trial; Med Sci Sports Exerc	7; 100%	35.0 ± 4.0 years; 82.0 ± 9.0 kg; 50.0 ± 6.0 mL·kg^{-1}·min^{-1}	Physically active; NA
	PRED-G		7; 100%	37.0 ± 3.0 years; 81.0 ± 14.0 kg; 50.0 ± 7.0 mL·kg^{-1}·min^{-1}	
	HRV-G		7; 0%	33.0 ± 4.0 years; 64.0 ± 5.0 kg; 36.0 ± 4.0 mL·kg^{-1}·min^{-1}	
	HRV-G		10; 0%	35.0 ± 4.0 years; 64.0 ± 9.0 kg; 37.0 ± 5.0 mL·kg^{-1}·min^{-1}	
	PRED-G		7; 0%	34.0 ± 4.0 years; 67.0 ± 6.0 kg; 35.0 ± 5.0 mL·kg^{-1}·min^{-1}	
Kiviniemi et al. [22] 2007	HRV-G	Finland; randomized controlled trial; Eur J Appl Physiol	9; 100%	31.0 ± 6.0 years; 80.0 ± 8.0 kg; 56.0 ± 4.0 mL·kg^{-1}·min^{-1}	Recreationally trained; runners
	PRED-G		8; 100%	32.0 ± 5.0 years; 78.0 ± 8.0 kg; 54.0 ± 4.0 mL·kg^{-1}·min^{-1}	
Nuuttila et al. [23] 2017	HRV-G	Finland; randomized controlled trial; Int J Sports Med	13; 100%	29.0 ± 4.0 years; 76.4 ± 9.4 kg; 53.6 ± 4.2 mL·kg^{-1}·min^{-1}	Recreationally trained; endurance athletes
	PRED-G		11; 100%	31.5 ± 5.0 years; 74.0 ± 5.7 kg; 54.2 ± 4.1 mL·kg^{-1}·min^{-1}	
Schmitt et al. [18] 2018	HRV-G	France, randomized controlled trial; Eur J Appl Physiol	9; 78%	22.4 ± 3.9 years; 65.5 ± 7.2 kg; 66.7 ± 5.9 mL·kg^{-1}·min^{-1}	Highly trained; cross-country and nordic-skiers
	PRED-G		9; 67%	22.6 ± 3.2 years; 66.7 ± 10.1 kg; 63.7 ± 4.4 mL·kg^{-1}·min^{-1}	
Vesterinen et al. [24] 2016	HRV-G	Finland; randomized controlled trial; Me Sci Sports Exerc	20; NR *	34.5 ± 7.5 years [#]; NR; 54.4 ± 6.2 mL·kg^{-1}·min^{-1}	Recreationally trained; runners
	PRED-G		20; NR *	34.5 ± 7.5 years [#]; NR; 53.0 ± 5.8 mL·kg^{-1}·min^{-1}	

HRV-G, heart rate variability guided training group; *NA*, non-applicable; *NR*, no reported; *PRED-G*, predefined training group; *$\dot{V}O_2$ max*, maximal oxygen uptake. Data are reported as mean ± standard deviation, unless otherwise is stated; * 20 males and 20 females were allocated at pre-intervention; [#] Based on all participants

Table 2. Intervention and methodological approach characteristics

	Intervention Characteristics	**Methodological Approach Characteristics**		
Study (Author)	**Type of Exercise; Length; Training Frequency**	**Device; Time of Day; Stabilization Period (min); Recording Posture (Length) *; Breathing Control**	**HRV Index; Single Day vs. Averaged; Number of Averaged Values**	**Fixed vs. Moving; Number of Averaged Values; Range Used**
da Silva et al. [19]	Endurance training; 8 weeks; 3 days a week	Polar RS800cx; afternoon/evening; yes (2 min); standing (3 min); no (spontaneous)	RMSSD; single day; NA	Moving; 5 up to 10 values; mean − (1·SD)
Javaloyes et al. [17]	Endurance training; 8 weeks; NA (habitual training volume)	HRV4training app; morning; yes (30 s); supine (1 min); NR	RMSSD; averaged; 7 values	Fixed [$]; 28 values; mean ± (0.5·SD)
Javaloyes et al. [20]	Endurance training; 8 weeks; NA (habitual training volume)	Polar H7 strap; morning; yes (30 s); supine (1 min); NR	RMSSD; averaged; 7 values	Fixed [$]; 28 values; mean ± (0.5·SD)
Kiviniemi et al. [21]	Endurance training; 8 weeks; at least 5 days a week [#]	Polar RS800; morning; yes (2 min); standing (3 min); no (spontaneous)	SD_1; single day; NA	Moving; 7 up to 10 values; mean − (1·SD)
Kiviniemi et al. [22]	Endurance training; 4 weeks; 6 days a week [#]	Polar S180i; morning; yes (5 min); standing (5 min); NR	HF (auto-regressive method); single day; NA	Moving; 10 values; mean − (1·SD)
Nuuttila et al. [23]	Endurance and strength training; 8 weeks; 6 days a week [#]	Garmin 920XT; morning; supine (3 min); yes (until heart rate became steady); NR	RMSSD; averaged; 3 values	Fixed; 21 values; Mean
Schmitt et al. [18]	NR; 2 weeks; NR	Suunto; morning; yes (3 in supine and 1 in standing); supine and standing (5 + 5 min); NR	HF (Fast-Fourier Transform); single day; NA	Moving; 1 value; 70% of the previous day
Vesterinen et al. [24]	Endurance and strength training; 8 weeks; 2–4 days a week [#]	Omegawave Pro Mobile System; morning; no stabilization; supine (4 min); no (spontaneous)	RMSSD; averaged; 7 values	Fixed [$]; 28 values; mean ± (0.5·SD)

HF, high frequency; *HRV*, heart rate variability; *NA*, non-applicable; *NR*, no reported; *RMSSD*, root-mean-square difference of successive normal R-R intervals; *SD*, standard deviation; SD_1, standard deviation of instantaneous beat-to-beat R-R interval variability. [#] Only in the predefined training group; * analyzed period; [$] Fixed reference criterion was updated

Risk of bias

Details of the author's judgements for each source of bias, and the risk of bias assessment across studies can be found in Table S1 and Table S2 (see supplementary materials, Section 2), respectively. The method of sequence generation and allocation concealment were not reported in the included randomized studies (87.5%), and one non-randomized study was also included (12.5%). Only one study carried out blinded assessments. Therefore, selection and detection biases were judged as unclear-high risk. Attrition bias was judged as low-high risk, while reporting bias was judged as low risk.

Outcomes

Assessment characteristics for measuring cardiac-vagal modulation, aerobic fitness parameters, and endurance performance, as well as outcome details are provided in Table 3. Regarding cardiac-vagal modulation, one study (12.5%) assessed HRR 1 min after an incremental maximal test, five studies (62.5%) reported resting vagal-related HRV indices, and four (50%) resting HR, both indices obtained in several positions. One study (12.5%) used RMSSD as the vagal-related HRV index [19], one (12.5%) used SD_1 [21], two (25%) used HF [18,22], and one (12.5%) measured RMSSD and HF [23]. Four studies (50%) used averaged HR and HRV values [19,21–23] and one (12.5%) captured a single HRV value at pre-intervention and an averaged HRV value at post-intervention [18]. Three studies (37.5%) carried out assessments in the morning [18,21,22], one (12.5%) in the afternoon/evening before training [19], and one (12.5%) measured vagal-related HRV indices at night and in the morning [23]. Nonetheless, incomplete information was reported to calculate the SMD in those studies using vagal-related HRV measured in the morning. All the included studies allowed us to define 19 independent comparisons as follows: HRR 1 min (n = 1) [19], standing vagal-related HRV indices (n = 6) [18,19,21,22], standing HR (n = 5) [18,21,22], sitting vagal-related HRV indices (n = 1) [22], sitting HR (n = 1) [22], supine vagal-related HRV indices (n = 1) [18], supine HR (n = 1) [18], nocturnal vagal-related HRV indices (n = 2) [23], and nocturnal HR (n = 1) [23]. Regarding aerobic fitness parameters and endurance performance, all the included studies performed an incremental test until volitional exhaustion, of which, seven (87.5%) also performed ventilatory gas exchange assessments. Five studies (62.5%) carried out a sport-specific time trial for assessing endurance performance. All the included studies allowed us to define 32 independent comparisons between HRV-guided training and predefined training as follows: $\dot{V}O_2$ max (n = 9) [17,18,20–24], $\dot{V}O_2$ at VT2 (n = 1) [18], maximal aerobic capacity (n = 8) [17,19–23], aerobic capacity at VT2 (n = 5) [17,20,22–24], aerobic capacity at VT1 (n = 4) [17,20,23,24], and endurance performance (n = 5) [17,19,20,23,24]. As previously described, at least three analysis units should report each outcome measure to be pooled for meta-analysis. Otherwise, the results will be qualitatively discussed in the next section.

Table 3. Assessment characteristics and outcome details

Study (Author); N (HRV-G/PRED-G)	Aerobic Fitness Parameters and Endurance Performance		Cardiac-Vagal Modulation	
	Assessment Characteristics	**Parameter Assessed: SMD (95%CI)**	**Assessment Characteristics**	**Parameter Assessed: SMD (95%CI)**
da Silva et al. [19] N (15/15)	Incremental running test until volitional exhaustion	Maximal velocity (MAC): 0.07 (−0.49, 0.63)	Incremental maximal running test; recovery characteristics no reported	[$] HRR 1 min: 0.20 (−0.36, 0.77)
	5 km running performance	Time (EP): 0.31 (−0.26, 0.87)	3-day averaged values measured in standing position in the afternoon/evening	Standing RMSSD: 0.34 (−0.23, 0.90)
Javaloyes et al. [17] N (7/8)	Incremental cardiopulmonary cycling test until volitional exhaustion	$\dot{V}O_2$ max: −0.25 (−1.06, 0.56)		
		Maximal PO (MAC): 0.21 (−0.60, 1.02)		
		PO at VT2 (AC_VT2): 0.42 (−0.41, 1.24)		
		PO at VT1 (AC_VT1): 1.77 (0.67, 2.87)		
	40 min all-out time trial	Mean PO (EP): 0.55 (−0.29, 1.39)		
Javaloyes et al. [20] N (9/8)	Incremental cardiopulmonary cycling test until volitional exhaustion	$\dot{V}O_2$ max: 0.20 (−0.55, 0.96)		
		Maximal PO (MAC): 0.39 (−0.38, 1.15)		
		PO at VT2 (AC_VT2): 0.32 (−0.44, 1.09)		
		PO at VT1 (AC_VT1): 0.19 (−0.56, 0.95)		
	40 min all-out time trial	Mean PO (EP): 0.23 (−0.53, 0.98)		
Kiviniemi et al. [21] I N (7/7)	Incremental cardiopulmonary cycling test until volitional exhaustion	$\dot{V}O_2$ max: 0.14 (−0.69, 0.98)	7-day averaged values measured in standing position in the morning	Standing SD_1: 0.50 (−0.36, 1.37)
		Maximal PO (MAC): 0.39 (−0.46, 1.24)		Standing HR: 0.48 (−0.38, 1.34)
Kiviniemi et al. [21] II N (7/3)		$\dot{V}O_2$ max: 0.21 (−0.89, 1.31)		Standing SD_1: 0.57 (−0.57, 1.71)
		Maximal PO (MAC): −0.12 (−1.22, 0.97)		Standing HR: −0.24 (−1.34, 0.86)
Kiviniemi et al. [21] III N (10/3)		$\dot{V}O_2$ max: 0.19 (−0.85, 1.22)		Standing SD_1: 1.10 (−0.05, 2.26)
		Maximal PO (MAC): −0.07 (−1.10, 0.96)		Standing HR: −0.15 (−1.18, 0.88)

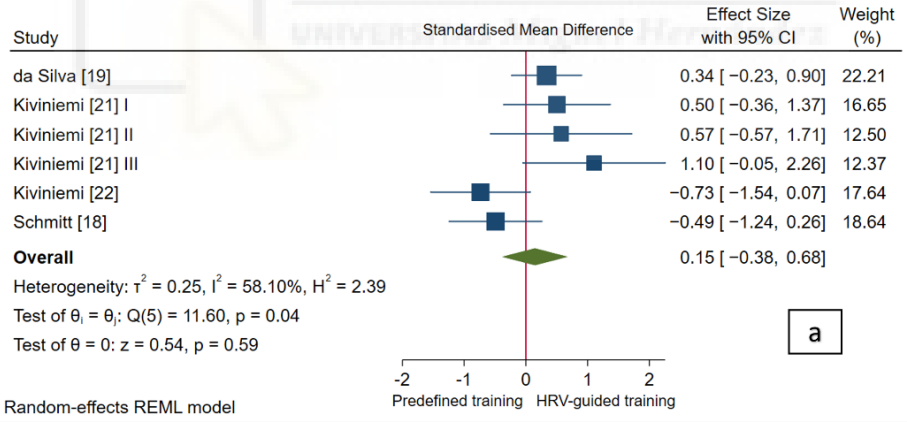
Table 3. Continued

Study (Author); N (HRV-G/PRED-G)	Aerobic Fitness Parameters and Endurance Performance		Cardiac-Vagal Modulation	
	Assessment Characteristics	**Parameter Assessed: SMD (95%CI)**	**Assessment Characteristics**	**Parameter Assessed: SMD (95%CI)**
Kiviniemi et al. [22] N (9/8)	Incremental cardiopulmonary running test until volitional exhaustion	$\dot{V}O_2$ max: 0.71 (−0.09, 1.51)	3-day averaged values measured in sitting and standing position in the morning	[$] Sitting HF: 0.66 (−0.14, 1.45)
		Maximal velocity (MAC): 0.25 (−0.51, 1.01)		[$] Sitting HR: 0.00 (−0.75, 0.75)
		Velocity at VT2 (AC_VT2): 0.38 (−0.39, 1.14)		Standing HF: −0.73 (−1.54, 0.07)
				Standing HR: −0.21 (−0.97, 0.55)
Nuuttila et al. [23] N (13/11)	Incremental cardiopulmonary running test until volitional exhaustion	$\dot{V}O_2$ max: 0.21 (−0.42, 0.84)	Averaged 3-control weeks (11 days, measured every other night) and averaged last training week (4 days, measured every other night)	[$] Night RMSSD: −0.05 (−0.68, 0.58)
		Maximal velocity (MAC): 0.32 (−0.32, 0.96)		[$] Night HF: 0.10 (−0.53, 0.73)
		Velocity at VT2 (AC_VT2): 0.30 (−0.33, 0.94)		[$] Night HR: 0.14 (−0.49, 0.77)
		Velocity at VT1 (AC_VT1): 0.14 (−0.49, 0.77)	21-day averaged (pre-intervention) and 7-day averaged (post-intervention) measured in supine position the morning	No reported
	3 km running performance	Time (EP): 0.00 (−0.63, 0.63)		
Schmitt et al. [18] N (9/9)	Incremental cardiopulmonary running test until volitional exhaustion	$\dot{V}O_2$ max: 0.11 (−0.62, 0.84)	Single day (pre-intervention) and 21-day averaged (post-intervention) values measured in supine and standing position in the morning	[$] Supine HF: −0.17 (−0.90, 0.57)
				[$] Supine HR: 0.44 (−0.31, 1.18)
		[$] $\dot{V}O_2$ at VT2: 0.24 (−0.49, 0.98)		Standing HF: −0.49 (−1.24, 0.26)
				Standing HR: 0.19 (−0.55, 0.92)
Vesterinen et al. [24] N (13/18)	Incremental cardiopulmonary running test until volitional exhaustion	$\dot{V}O_2$ max: −0.08 (−0.64, 0.48)		
		Velocity at VT2 (AC_VT2): 0.06 (−0.49, 0.62)		
		Velocity at VT1 (AC_VT1): 0.15 (−0.41, 0.71)		
	3 km running performance	Mean velocity (EP): 0.06 (−0.50, 0.62)		

AC_VT1, aerobic capacity at first ventilatory threshold; *AC_VT2*, aerobic capacity at second ventilatory threshold; *EC*, endurance capacity; *EP*, endurance performance; *HF*, high frequency; *HR*, heart rate; *HRR 1 min*, heart rate recovery 1 min; *HRV-G*, heart rate variability guided training group; *MAC*, maximal aerobic capacity, *N*, number of participants included to calculate SMD; *PO*, power output; *PRED-G*, predefined training group; *RMSSD*, root-mean-square difference of successive normal R-R intervals; SD_1, standard deviation of instantaneous beat-to-beat R-R interval variability; *SMD*, standardized mean difference; $\dot{V}O_2$, oxygen uptake; *VT1*, first ventilatory threshold; *VT2*, second ventilatory threshold. [$] Excluded from meta-analysis as the minimal number of studies needed to perform pooled analyses was not reached; I, II, III refer analysis units from the same study

Cardiac-vagal modulation

Pooled analysis revealed no statistically significant difference in standing vagal-related HRV indices (p = 0.59) and standing HR (p = 0.82) between HRV-guided training and predefined training, and the overall SMDs reached a trivial effect (SMD_+ = 0.15 (95% CI = −0.38, 0.68), and SMD_+ = 0.04 (95% CI = −0.34, 0.43), respectively; Figure 2). The heterogeneity test reached statistical significance (p = 0.04) and inconsistency was moderate (I^2 = 58.1%) for standing vagal-related HRV indices, while the heterogeneity test did not reach statistical significance (p = 0.74) and no inconsistency was found (I^2 = 0.0%) for standing HR. Therefore, analyses of the influence of methodological factors on the pooled findings for standing vagal-related HRV indices were carried out. Our subgroup analyses showed significant between-group heterogeneity for the vagal-related HRV index (i.e., RMSSD/SD_1 and HF) (p < 0.01). There were greater increases in RMSSD/SD_1 (SMD_+ = 0.50 (95% CI = 0.09, 0.91) and greater decrements in HF (SMD_+ = −0.60 (95% CI = −1.15, −0.05)) after HRV-guided training compared to predefined training (see Figure 3). Subgroup analysis based on the HRV value (i.e., single and averaged HRV values) was not performed since none of the included studies used a single HRV value at pre- and post-intervention. Within-group heterogeneity, based on the vagal-related HRV index (i.e., RMSSD/SD_1 and HF), was not found (I^2 = 0%). Thus, the influence of participant and methodological approach characteristics on vagal-related HRV indices was not studied.



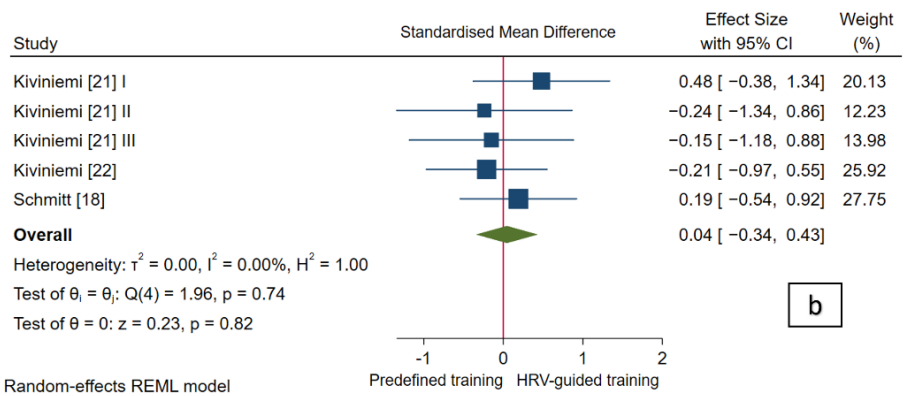


Figure 2. Forest plot of standardized mean difference indices for cardiac-vagal modulation: (**a**) standing vagal-related heart rate variability indices, and (**b**) standing heart rate. I, II, III refer analysis units from the same study

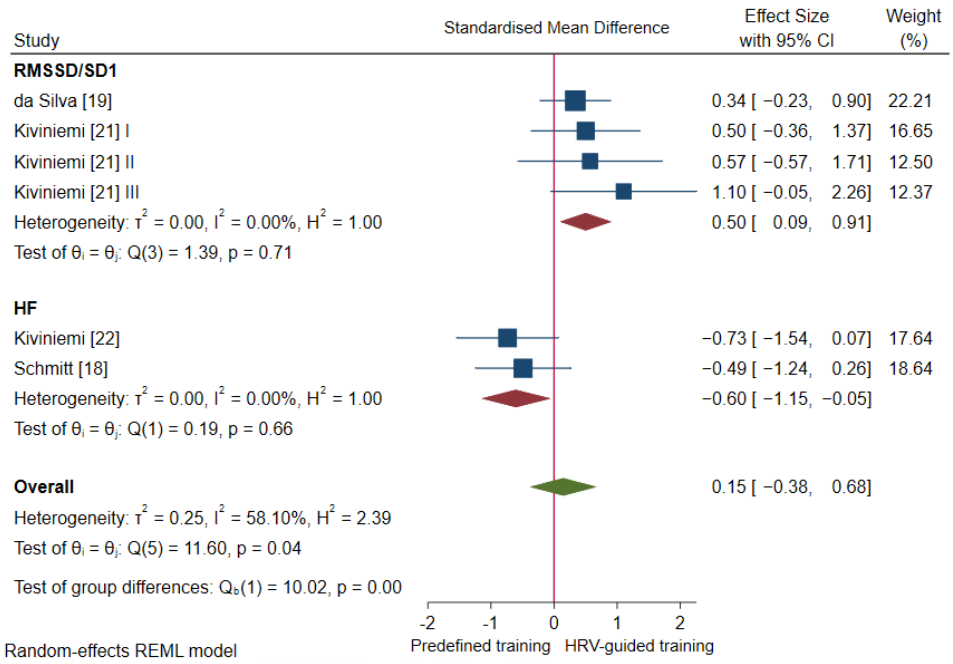


Figure 3. Test for subgroup comparisons for standing vagal-related HRV indices based on the HRV index used. I, II, III refer analysis units from the same study

Aerobic fitness parameters and endurance performance

Pooled analysis revealed no statistically significant difference in $\dot{V}O_2$ max (p = 0.30) between HRV-guided training and predefined training, and the overall SMD reached a trivial effect (SMD_+ = 0.13 (95% CI = −0.12, 0.39); Figure 4). The heterogeneity test did not reach statistical significance (p = 0.89) and no inconsistency was found (I^2 = 0.0%). Therefore, the influence of moderator variables on $\dot{V}O_2$ max changes after HRV-guided training vs. predefined training was not analyzed.

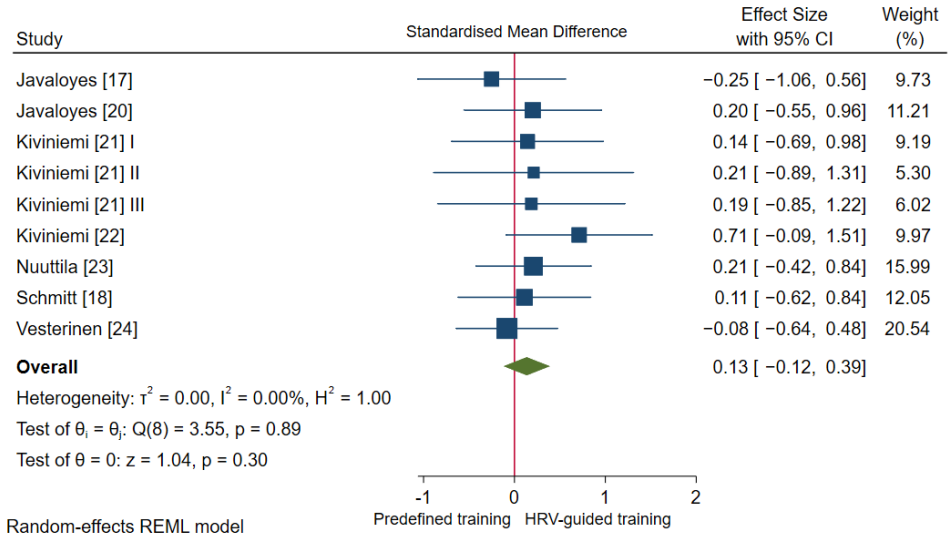


Figure 4. Forest plot of standardized mean difference indices for $\dot{V}O_2$ max. I, II, III refer analysis units from the same study

Pooled analyses showed no statistically significant differences in maximal aerobic capacity (p = 0.14), aerobic capacity at VT2 (p = 0.10), and aerobic capacity at VT1 (p = 0.16) between both training prescription methods. Nevertheless, the overall SMDs reached a small effect in favor of HRV-guided training (SMD_+ = 0.20 (95% CI = −0.07, 0.47), SMD_+ = 0.26 (95% CI = −0.05, 0.57), and SMD_+ = 0.44 (95% CI = −0.17, 1.05), respectively; Figure 5) compared to predefined training. Heterogeneity tests did not reach statistical significance (p > 0.05) and no inconsistency was found (I^2 = 0.0%) for maximal aerobic capacity and aerobic capacity at VT2, showing no influence of potential moderator characteristics on these variables. Despite the existence of a non-significant heterogeneity test (p = 0.06), inconsistency was moderate for aerobic capacity at VT1 (I^2 = 64.5%). However, due to the low number of studies, the influence of potential moderator variables was not performed.

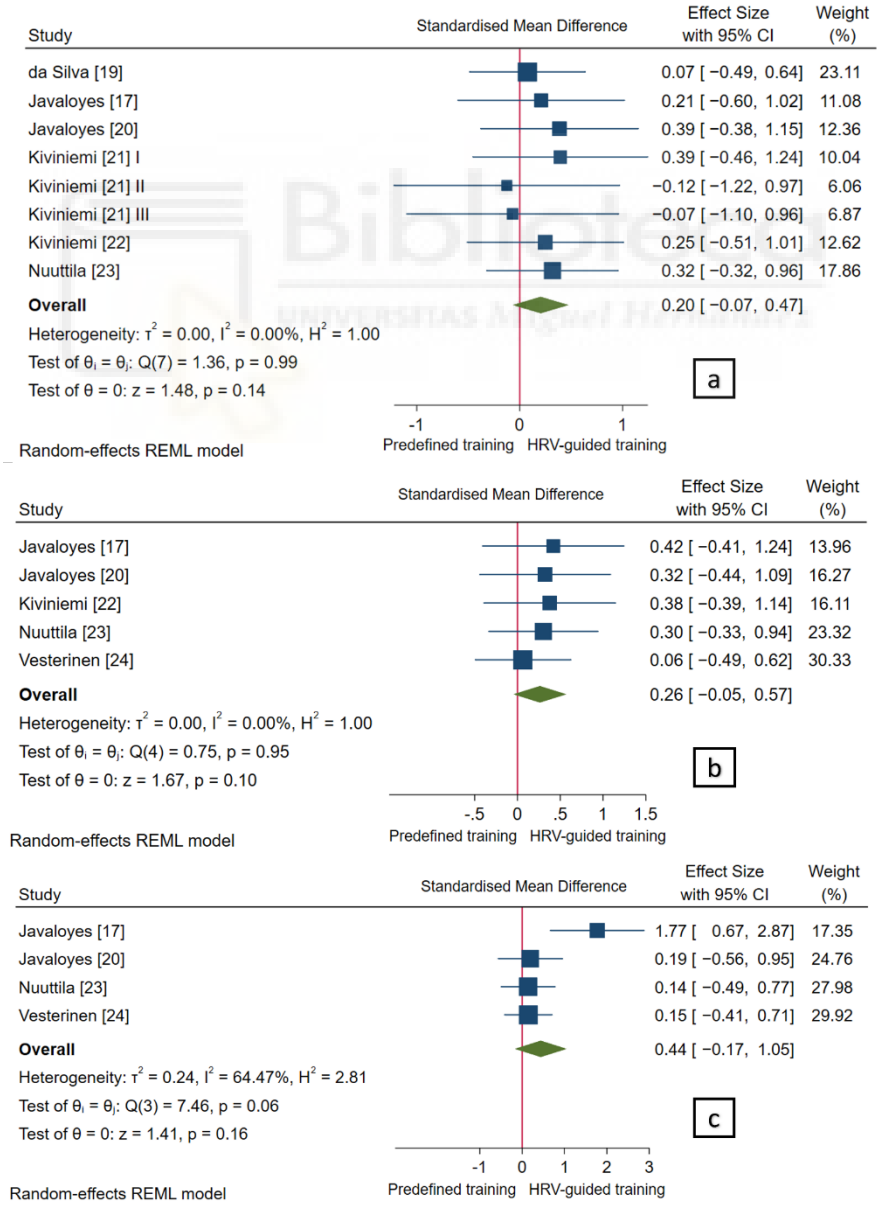


Figure 5. Forest plot of standardized mean difference indices for (a) maximal aerobic capacity, (b) aerobic capacity at second ventilatory threshold, and (c) aerobic capacity at first ventilatory threshold. I, II, III refer analysis units from the same study

Publication bias

There was no evidence of asymmetry in the funnel plots for any of the analyzed variables and the trim-and-fill method imputed no ESs to symmetrize the funnel plots (see supplementary materials, Section 3, Figures S1–S7). Therefore, on a reasonable basis, publication bias can be discarded as a threat against the validity of our findings.

Sensitivity analysis

Our sensitivity analyses showed no influence of any individual study for cardiac-vagal modulation, $\dot{V}O_2$ max, maximal aerobic capacity, aerobic capacity at VT2, and endurance performance. Nonetheless, the overall SMD and heterogeneity for aerobic capacity at VT1 diminished (from $SMD_+ = 0.44$ (95% CI = −0.17, 1.05) to $SMD_+ = 0.16$ (95% CI = −0.21, 0.52), and from 64.5% to 0.0%, respectively) after removing Javaloyes, Sarabia, Lamberts, Plews, Moya-Ramon [17].

DISCUSSION

This systematic review with meta-analysis investigated the effects of HRV-guided training versus predefined training for improving cardiac-vagal modulation, aerobic fitness, and endurance performance in sedentary healthy people, physically active, and endurance-trained athletes. Results showed that the effect of training prescription style on cardiac-vagal activity was index-dependent, such that greater increases in $RMSSD/SD_1$ were observed for HRV-guided training and vice-versa for HF. Our findings further showed that HRV-guided training was not significantly greater than predefined training for improving maximal aerobic capacity, aerobic capacity at VT2, and endurance performance, though small ESs consistently favored HRV-guided training. No heterogeneity was found for any aerobic fitness and performance parameters included in our pooled analyses. This indicates that there was no influence of potential moderator variables (e.g., baseline participant characteristics and methodological approach characteristics) on the difference between training prescription methods for improving these outcomes.

This is the first systematic review with meta-analysis to investigate the effectiveness of HRV-guided training versus predefined training for enhancing cardiac-vagal modulation. Although pooled analyses showed no significant differences between training approaches, significant heterogeneity was observed for the vagal-related HRV index used to reflect autonomic adaptation (Figure 2). Follow-up subgroup analysis revealed that HRV-guided training was superior to predefined training for increasing $RMSSD/SD_1$, whereas the opposite was found for HF (Figure 3). Certain methodological factors may account for the inconsistent responses among the vagal-related HRV indices. For instance, HF is more influenced by breathing rate than $RMSSD/SD_1$

[52,53], but whether respiration was standardized in studies using HF was not disclosed [18,22]. Moreover, Schmitt, Willis, Fardel, Coulmy, Millet [18] compared single time-point HF values obtained pre-intervention with a 21-day averaged value obtained post-intervention. Isolated values inadequately represent autonomic status [12,54–56] and averaged values from such a lengthy follow-up are likely influenced by alterations in training (i.e., cessation, resumption, or variation not specified) and thus may not suitably reflect effects of the intervention [18]. The remaining studies used pre- and post-intervention RMSSD or SD_1 values averaged across 3–7 days in accordance with recent findings [12,54–58]. Finally, previous studies have reported potential bias of spectral indices due to non-stationarities [59]. Thus, methodological factors from studies that used HF [18,22] may explain the heterogeneity found in our pooled analysis for vagal-related HRV indices.

Most studies in our analysis recorded vagal-related HRV indices in the standing position, whilst two studies also included seated [22] and supine [18] measures (Table 3). A subgroup analysis based on the assessment position was not performed to avoid statistical dependence (i.e., inclusion of participants twice for multiple positions). The original rationale for adopting standing measures was to counteract the effects of parasympathetic saturation [22], commonly observed during traditional supine recordings [60]. This results in reduced HRV concurrent with reduced resting HR due to saturation of myocardial cholinergic receptors from parasympathetic predominance, reflecting a quadratic relationship between parasympathetic activity and HRV [61,62]. Thus, HRV-guided training prescription in such instances would be unmatched (i.e., low intensity or rest due to low HRV) with the true status of the autonomic nervous system (high parasympathetic activity). Orthostatic stress during standing provokes baroreflex-mediated cardiac-autonomic and hemodynamic adjustments to maintain cardiac output and overcome blood-pooling in the lower extremities. Accordingly, supine and standing positions represent distinct physiological conditions that have demonstrated varying timeframes of post-exercise HRV recovery [63]. In addition, daily standing RMSSD patterns are generally lower and more variable relative to supine values [58,64], and whether they are correlated (i.e., provide similar intra-individual HRV trends despite different absolute values) is unclear. Thus, it is possible that exercise prescription on the basis of daily HRV would vary depending on the recording position and potentially impact adaptations. One recent review paper identified standing measures as being more sensitive to changes in parasympathetic activity than other positions [56]. However, the optimal HRV assessment position for guiding daily training prescription and reflecting autonomic adaptation remains unclear.

Though post-intervention improvements in HRV are of interest, responses observed amid training may be of similar or greater relevance. Several investigations and one case study reported greater reductions in vagal-mediated HRV relative to baseline throughout predefined training versus

better maintenance of values with HRV-guided training [17,18,65]. Moreover, observational studies frequently report greater aerobic fitness improvements among individuals who exhibit higher and more stable vagal HRV values throughout predefined training [37,66–71]. Contrastingly, greater day-to-day fluctuations in HRV are often observed in fatigued athletes and can occur with [58,68,72] or without [66,73] purposeful overload. Importantly, acute reductions in training stress enables suppressed HRV to revert to baseline [58,72]. Thus, it seems that HRV responses associated with improved adaptation and greater health (i.e., higher and more stable values) may be intentionally facilitated by adjusting training based on HRV. This strategy may support adaptations by matching the training stimulus with the current adaptive state of the autonomic nervous system [74], and by limiting wear-and-tear from excessive training load [19,20,22]. To improve our understanding of how training approaches impact cardiac-autonomic activity, we encourage future comparison studies to report inter-group HRV trend characteristics (e.g., averages and coefficient of variation) from before, during, and after the intervention.

Regarding other HR-based indices, da Silva, Ferraro, Adamo, Machado [19] measured HRR 1 min post-maximal incremental running tests in sedentary females. Characteristics of the recovery such as position or standardization of respiratory rate were not reported. Greater improvements in HRR 1 min were observed for HRV-guided training; however current results were non-significant and underpowered. Previous studies have reported that HRR 1 min is a sensitive index for reflecting autonomic adaptation [75] and may carry clinically-relevant implications related to cardio-metabolic morbidity and mortality [76]. Thus, future studies should investigate whether HRV-guided training is superior to predefined training for enhancing HRR 1 min. Pooled findings for resting HR showed no differences between training methods with no heterogeneity for improving resting HR assessed in the standing position. Studies that were not pooled because resting HR measurements were performed in other positions (i.e., sitting or supine) [18,22] or times of the day (i.e., night) [23], also failed to show differences between HRV-guided training and predefined training for changing resting HR (see Table 3).

No significant differences between training prescription methods were observed for improving aerobic fitness and endurance performance. These findings agree with Medellin Ruiz, Rubio-Arias, Clemente-Suarez, Ramos-Campo [27]. Albeit non-significant, our pooled analyses showed small ESs in favor of HRV-guided training for improving maximal aerobic capacity, aerobic capacity at VT2, and endurance performance versus predefined training. Unlike the current and previous findings [27,28], Granero-Gallegos, González-Quílez, Plews, Carrasco-Poyatos [25] reported a significant effect for $\dot{V}O_2$ max favoring HRV-guided training. We noted that between-group comparisons to compare the effectiveness of both training prescription methods for improving $\dot{V}O_2$ max was not reported, and the overall training effect result seems to be reported in their forest plot instead [25]. Therefore, the conclusion of this study should be considered with

caution. Length of training intervention may help explain the small magnitude of the ES for HRV-guided training versus predefined training. The longest training intervention from studies included herein was 8-weeks (75% of studies). Short-term predefined endurance training programs (i.e., 6 to 10 weeks) enhance aerobic fitness and endurance performance in sedentary and endurance-trained individuals [77,78], with plateaus in $\dot{V}O_2$ max often observed with longer-term training [79]. The short duration of the reviewed training interventions may help explain why ESs favoring HRV-guided training were only small in magnitude. Moreover, HRV-guided regulation of exercise volume and intensity over chronic training periods may support performance and fitness gains by limiting maladaptions. For example, fatigue-related decrements in HRV left unabated may reflect heightened risk of infection, overuse, or overreaching [12,80]. Thus, future research should determine if longitudinal HRV-guided training offers any direct or indirect fitness or performance advantages over predefined training.

No heterogeneity was found when comparing training methods for enhancing aerobic fitness or endurance performance, despite inclusion of samples varying in training status and history (i.e., sedentary to well-trained), age, and sex. These descriptive characteristics often impact responsiveness to training interventions [81]. Nevertheless, we noted that only da Silva, Ferraro, Adamo, Machado [19] included exclusively sedentary people. In agreement with our findings, Kiviniemi, Hautala, Kinnunen, Nissilä, Virtanen, Karjalainen, Tulppo [21] found no sex-related differences in response to HRV-guided training compared to predefined training. Thus, our findings apply to healthy adult males and females between the ages of 22 to 39 years. Future studies should compare HRV-guided versus predefined training for improving aerobic fitness and endurance performance in young, elderly, and clinical populations. Initial evidence among the latter suggests that HRV-guided training may be more effective than predefined training in cardiac-rehabilitation [82].

Our systematic review showed between-study variability in the use of the daily versus rolling averaged HRV values and in the fixed versus rolling reference criteria used to guide prescription in the HRV-guided training group. All the studies that used a rolling averaged HRV value also used a fixed reference criterion (i.e., 3- or 4-week baseline period), which was maintained throughout the training [23] or updated mid-training period [17,20,24]. Studies that used a single day HRV value used a moving reference criterion (i.e., 10 values) [19,21,22]. The use of rolling averaged HRV values results in less frequent training modifications relative to using daily values. Additionally, rolling reference criteria reflect current responses while fixed values reflect the initial baseline profile. It remains unclear which approach may be superior for improving training adaptations. Future studies are therefore needed to compare HRV-guided training methodologies to further establish best practices.

Changes in aerobic fitness and endurance performance following predefined training may be more heterogeneous [6,83] than changes observed following HRV-guided training. Javaloyes, Sarabia, Lamberts, Plews, Moya-Ramon [17] found a post-training performance decrement in only one cyclist allocated to the HRV-guided training group (14.3%) versus three athletes in the predefined training group (37.5%). Kiviniemi, Hautala, Kinnunen, Tulppo [22] reported a more homogeneous positive response in maximal running velocity for the HRV-guided training group. Similarly, $\dot{V}O_2$ max decreased in only one runner after HRV-guided training (11.1%) versus four runners after predefined training (50.0%). Nevertheless, the low number of athletes included in these studies limits the scope of the findings. Therefore, future studies should analyze and report individual participant changes to investigate heterogeneity in adaptations to the training prescription method used.

This systematic review with meta-analysis is the first to investigate the effects of HRV-guided versus predefined training on cardiac-vagal modulation in sedentary healthy people, physically active, and endurance-trained athletes. Consideration of methodological factors in regard to HRV index selection, recording position, and approaches for establishing baseline reference values and daily changes (i.e., fixed or rolling HRV averages) are key strengths of the current study. However, a limited number of overall investigations, in addition to inconsistent methodological approaches, limit our ability to perform sufficient subgroup analyses to make strong conclusions. Similarly, the low number of studies included in the subgroup analysis for vagal-related HRV index selection limits the scope of our findings. Limitations notwithstanding, our review identified numerous unresolved research questions pertaining to methodological approaches to HRV-guided training that warrant further investigation.

Conclusions

Our results generated a novel insight regarding the effects of HRV-guided training on cardiac-vagal activity and adds clarification about its impact on fitness and performance relative to predefined training. HRV-guided training demonstrated a small advantage over predefined training for improving vagal-mediated HRV (i.e., RMSSD/SD_1) measured in standing position when averaged between 3–7 days. Similar findings were not observed for HF, possibly due to methodological factors related to standardization of respiratory rate and use of insufficient (i.e., isolated) or excessive (i.e., 3-week) periods of comparison. Effects on supine and seated HRV and post-exercise HRR were indeterminate. Qualitative review of available data further indicated that HRV-guided training facilitates greater maintenance of HRV values throughout an intervention relative to predefined training. By design, this training method prevents sustained decrements in HRV that may occur with excess training and fatigue, and which are often associated with smaller or negative changes in fitness markers. HRV-guided training did not produce significantly greater fitness and performance outcomes relative to pre-planned training,

though ESs that were small in magnitude consistently favored HRV-guided training. Qualitative reviews of studies reporting individual changes in fitness and performance indicate that responses were more homogenous among HRV-guided training groups with fewer negative responders relative to predefined training. Lastly, despite our observation of high heterogeneity for methodological characteristics among studies, no inconsistency was found for any of the aerobic fitness and endurance performance parameters analyzed. In sum, HRV-guided training is an accessible individualized exercise prescription strategy that may be more effective than predefined training for maintaining and improving vagal-mediated HRV, with less likelihood of negative responses. However, if HRV-guided training is superior to predefined training for producing group-level improvements in fitness and performance, current data suggest it is only by a small margin.

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8.4.2. Supplementary material study 4

Section 1. Electronic database search

- Participants. Healthy OR active OR sedentary OR trained OR untrained OR recreational OR fit OR young OR runn* OR swimm* OR cycli* OR triathl* OR athlete* OR rower* OR cross-countr* OR canoeist* OR kayak* OR skier* OR endurance

- Interventions. “Heart rate variability” OR HRV OR “HR variability” OR “training guided” OR “prescription guided” OR “individually guided” OR “individualized recovery”

- Comparison. Traditional OR predefined OR standard* OR periodization OR predetermined OR “fixed recovery”

Section 2. Risk of bias assessment

Table S1. Risk of bias assessment criteria

Bias	Authors' judgements	Support for judgement
Da Silva et al. [19]		
Random sequence generation (selection bias)	Unclear risk	States participants were "randomly assigned". No further details given
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding of outcome assessment (detection bias)	High risk	Quote: "This is a non-blinded, randomised controlled trial"
Incomplete outcome data (attrition bias)	Low risk	Less than 20% missing outcome data, losses balanced, and reasons reported
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes in the method section were reported
Javaloyes et al. [17]		
Random sequence generation (selection bias)	High risk	Non-randomised controlled study
Allocation concealment (selection bias)	High risk	Non-randomised controlled study
Blinding of outcome assessment (detection bias)	High risk	Quote: "This is a non-blinded, controlled trial"
Incomplete outcome data (attrition bias)	High risk	More than 20% missing outcome data, losses balanced, and reasons reported
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes in the method section were reported
Javaloyes et al. [20]		
Random sequence generation (selection bias)	Unclear risk	States participants were "randomly assigned". No further details given
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of outcome assessment blinding
Incomplete outcome data (attrition bias)	Unclear risk	Initial and final sample sizes were not reported
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes in the method section were reported
Kiviniemi et al. [21]		
Random sequence generation (selection bias)	Unclear risk	States participants were "randomised into". No further details given
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of outcome assessment blinding
Incomplete outcome data (attrition bias)	Low risk	Less than 20% missing outcome data, losses balanced, and reasons reported
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes in the method section were reported
Kiviniemi et al. [22]		
Random sequence generation (selection bias)	Unclear risk	States participants were "randomised into". No further details given
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Ventilatory threshold was analysed blindly from the…"
Incomplete outcome data (attrition bias)	Low risk	Less than 20% missing outcome data, losses balanced, and reasons reported
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes in the method section were reported

Table S1. Continued

Bias	Authors' judgements	Support for judgement
Nuuttila et al. [23]		
Random sequence generation (selection bias)	Unclear risk	States participants were "randomly assigned". No further details given
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of outcome assessment blinding
Incomplete outcome data (attrition bias)	High risk	More than 20% missing outcome data and losses were reported regardless of the allocated groups
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes in the method section were reported
Schmitt et al. [18]		
Random sequence generation (selection bias)	Unclear risk	States participants were "randomly matched". No further details given
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of outcome assessment blinding
Incomplete outcome data (attrition bias)	Unclear risk	Initial and final sample sizes were not reported
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes in the method section were reported
Vesterinen et al. [24]		
Random sequence generation (selection bias)	Unclear risk	States participants were "randomised into". No further details given
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding of outcome assessment (detection bias)	Unclear risk	No mention of outcome assessment blinding
Incomplete outcome data (attrition bias)	High risk	More than 20% missing outcome data and losses were reported regardless of the allocated groups
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes in the method section were reported

Table S2. Risk of bias across studies

Risk of bias item	Low risk n/N (%)	Unclear risk n/N (%)	High risk n/N (%)
Random sequence generation (selection bias)	0/8 (0)	7/8 (87.5)	1/8 (12.5)
Allocation concealment (selection bias)	0/8 (0)	7/8 (87.5)	1/8 (12.5)
Blinding of outcome assessment (detection bias)	1/8 (12.5)	5/8 (62.5)	2/8 (25)
Incomplete outcome data (attrition bias)	3/8 (37.5)	2/8 (25)	3/8 (37.5)
Selective reporting (reporting bias)	0/8 (0)	0/8 (0)	8/8 (100)

Section 3. Publication bias assessment

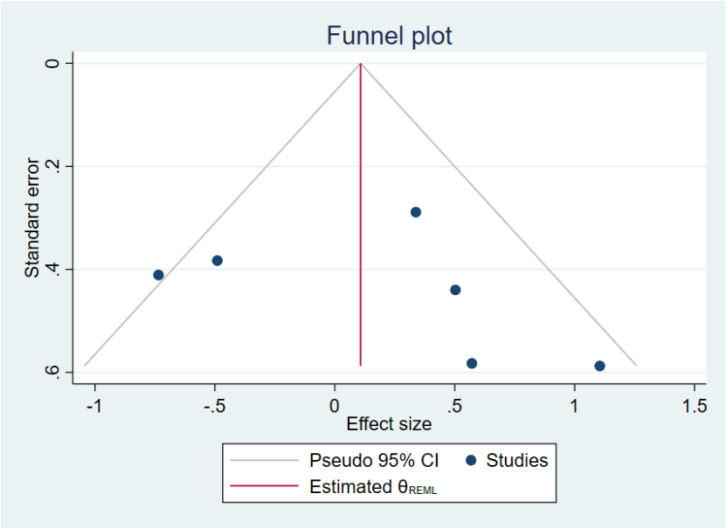

Figure S1. Funnel plot with trim-and-fill method for standing vagal-related heart rate variability indices

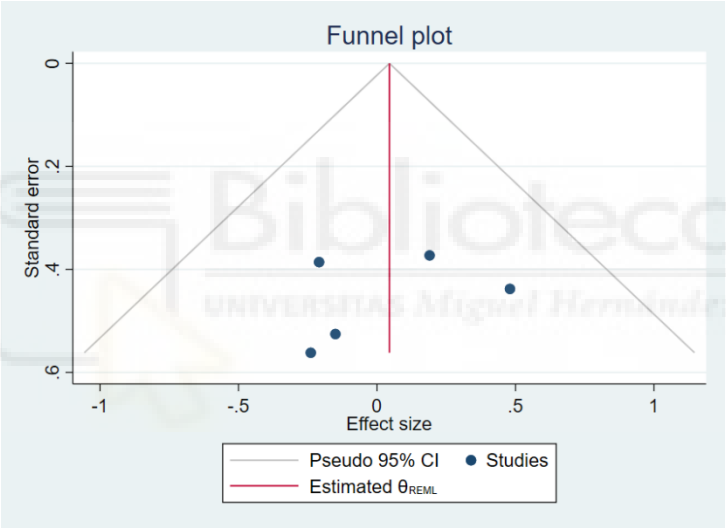

Figure S2. Funnel plot with trim-and-fill method for standing heart rate

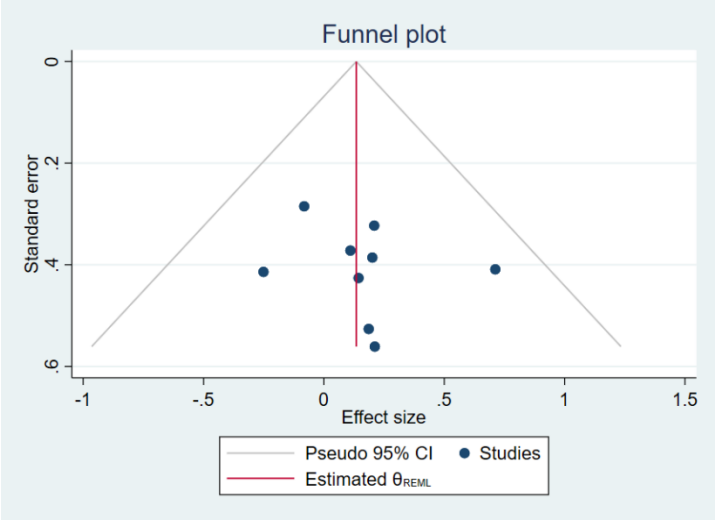

Figure S3. Funnel plot with trim-and-fill method for $\dot{V}O_2$ max

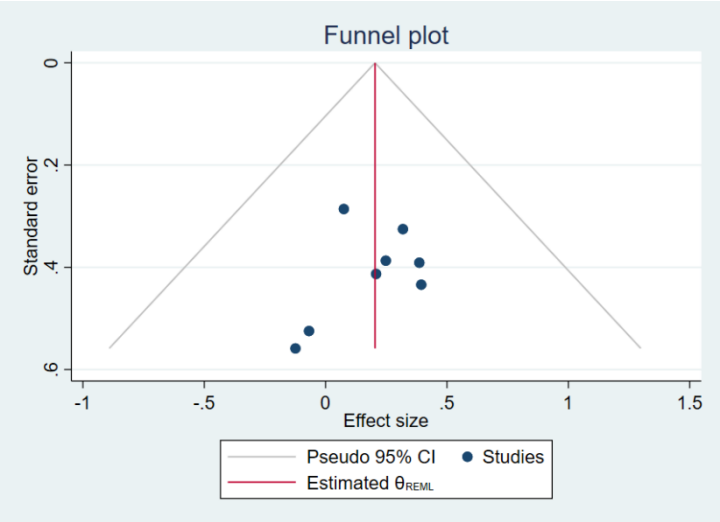

Figure S4. Funnel plot with trim-and-fill method for maximal aerobic capacity

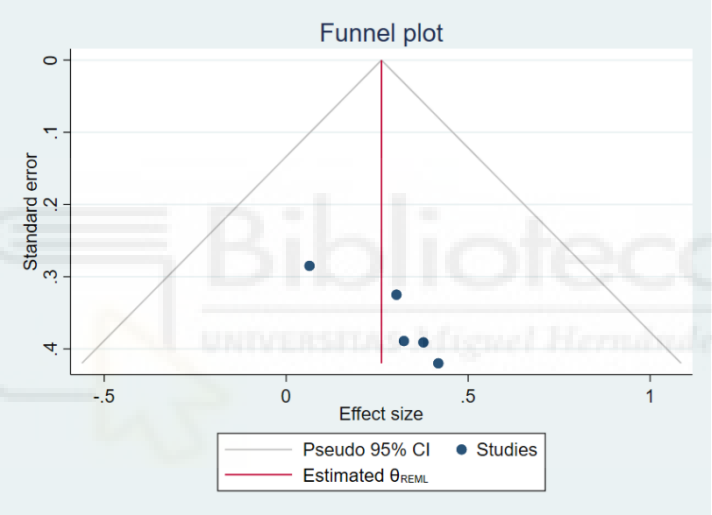

Figure S5. Funnel plot with trim-and-fill method for aerobic capacity at second ventilatory threshold

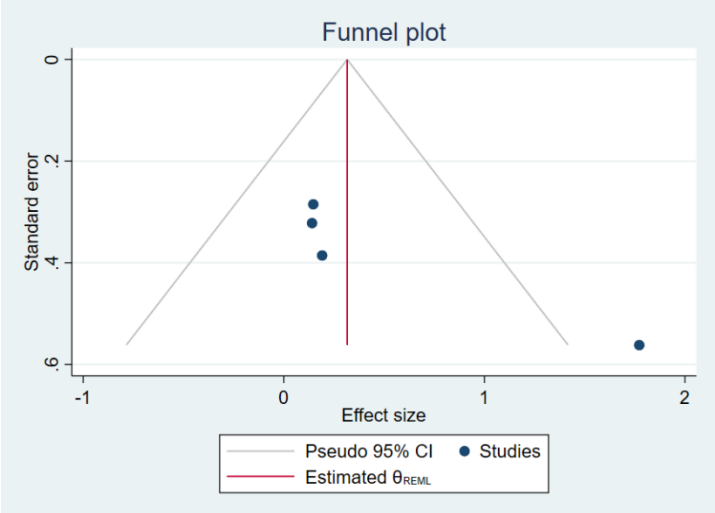

Figure S6. Funnel plot with trim-and-fill method for aerobic capacity at first ventilatory threshold

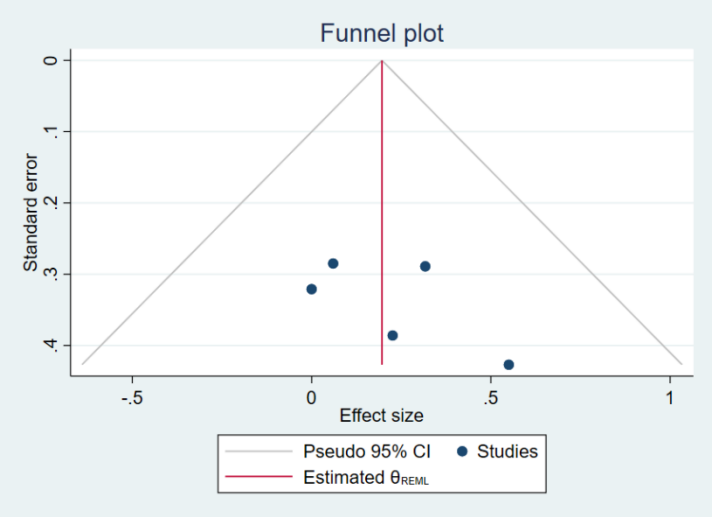

Figure S7. Funnel plot with trim-and-fill method for endurance performance

APPENDIX 5

STUDY 5

Is heart rate variability-guided training superior to predefined training for improving mortality predictors in patients with coronary artery disease?

Note. This study was under review in *Med Sport*

Manresa-Rocamora A, Sarabia JM, Guillen-Garcia S, Pérez-Berbel P, Miralles-Vicedo B, Roche E, Vicente-Salar N, Moya-Ramón M. Is heart rate variability-guided training superior to predefined training for improving mortality predictors in patients with coronary artery disease? Under review in *Med Sport*

8.5. Appendix 5

8.5.1. Study 5. Is heart rate variability-guided training superior to predefined training for improving mortality predictors in patients with coronary artery disease?

Abstract

Background: Heart rate variability (HRV)-guided training enhances mortality predictors in chronic heart failure patients. Nonetheless, no studies have been performed in coronary artery disease (CAD) patients. The main objective of this research was to investigate whether HRV-guided training enhances mortality predictors to a greater extent than predefined training in patients with CAD while accounting for methodological factors. Moreover, the effect of exercise training, regardless of the training prescription method, was also investigated.

Methods: Patients were randomly allocated into the HRV-guided training group (HRV-G) or the predefined training group (PRED-G). All patients trained 3 days a week for 6 weeks. Mortality predictors (i.e., resting heart rate, vagal-related HRV indices, heart rate recovery, and peak oxygen uptake) were assessed before and after the intervention period.

Results: There was a statistically significant difference (p = .034) between HRV-G and PRED-G in averaged vagal-related HRV changes (i.e., the root-mean-square difference of successive normal R-R intervals [RMSSD]). HRV-guided training increased averaged RMSSD values (p = .039; mean change [MC] = 7.57 [95% CI = 0.48 – 14.64] ms), while predefined training did not change averaged RMSSD values (p = .416; MC = -2.79 [95% CI = -10.13 – 4.55] ms). There were no statistically significant differences (p > .050) between the two groups in the remaining analyzed variables. Regardless of the training prescription method, exercise training enhanced resting heart rate (p = .001; MC = -4.10 [95% CI = -6.37 – -1.82] beats per minute [bpm]), heart rate recovery 2 min (p = .010; MC = 4.33 [95% CI = 1.15 – 7.52] bpm), and peak oxygen uptake (p < .001; MC = 3.04 [95% CI = 1.70 – 4.37] $mL \cdot kg^{-1} \cdot min^{-1}$). Our findings showed that, accounting for methodological factors, HRV-guided training is superior to predefined training for improving vagal-related HRV, what could reduce mortality risk in CAD patients.

Clinical trial registration: https://www.clinicaltrials.gov. Unique identifier: NCT04930939

Keywords

Cardiac rehabilitation; cardiorespiratory fitness; heart rate-based indices; methodological issues

INTRODUCTION

Coronary artery disease (CAD) is one of the deadliest diseases worldwide. Thus, the development of cost-efficient treatments to reduce mortality within CAD patients is mandatory. Accumulating evidence has demonstrated that exercise-based cardiac rehabilitation (CR) programs reduce mortality rates in patients with CAD [1]. In this regard, parasympathetic nervous system (PNS) activity and cardiorespiratory fitness (CRF), assessed by heart rate (HR)-based indices and peak oxygen uptake ($\dot{V}O_2$ peak), respectively, are considered independent predictors of mortality [2]. Martinez et al. [3] and Medeiros et al. [4] reported an improvement in the PNS activity after an exercise-based CR program. In a recent systematic review and meta-analysis, Manresa-Rocamora et al. [5] showed that exercise-based CR programs enhance $\dot{V}O_2$ peak. Thus, the reduction of mortality rates could be explained in part by the training-induced effect on mortality predictors (i.e., HR-based indices and $\dot{V}O_2$ peak).

Within HR-based indices, resting HR, resting HR variability (HRV), and post-exercise HR recovery (HRR) are commonly used as non-invasive reliable tools to indirectly measure the PNS status [6, 7]. HRV is defined as the oscillation in the interval between heartbeats and it depends on the continuous modulation of the autonomous nervous system (ANS) branches [8]. Within HRV indices, the root-mean-square difference of successive normal R-R intervals (RMSSD), the high frequency (HF; 0.15 – 0.40 Hz), and the standard deviation of instantaneous beat-to-beat R-R interval variability (SD_1) are considered as vagal-related HRV indices, while the interpretation of other HRV indices is more difficult [6, 9]. On the other hand, the first fall of the HR after the exercise peak occurs mainly due to PNS reactivation [7, 10]. Although there is evidence that shows that exercise-based CR allows to improve vagal-related HRV and HRR indices in patients with CAD [11], there are contradictory findings about the training-induced effect on PNS modulation based on the vagal-related HRV index used [11]. In this regard, previous studies showed the influence of methodological issues on the sensitivity of vagal-related HRV indices for inferring PNS modulation [12]. For instance, there is evidence that shows that averaged RMSSD values seem to be more suitable than other isolated vagal-related HRV indices to reflect PNS activity due to the fact that averaged values reduce the natural day-to-day lability of HRV indices [13].

On the other hand, even though important benefits have been reported after an exercise-based CR program, the inter-individual responsiveness after the same training program varies considerably among patients [14]. This variability in the training responses could be due to factors such as age, gender, initial CRF or race [5, 15]. Moreover, the PNS function could also play a determinant role in the responsiveness to exercise training. For instance, Hedelin et al. [16] and Compostella et al. [17] found diminished vagal-related HRV indices at baseline associated with lower CRF enhancement in sedentary subjects and in chronic heart failure (CHF) patients, respectively. Moreover, HRV is considered a valid maker to reflect training-induced status [18]. For these reasons, HRV has also

been used to carry out aerobic training prescription, known as HRV-guided training, in endurance-trained athletes [19, 20], sedentary people [21], and CHF patients [22].

The basic idea behind HRV-guided training is to adjust the training stimulus when PNS activity differed meaningfully from the reference values [23]. Previous studies reported that HRV-guided training is superior to predefined training for improving PNS activity or CRF [21, 22, 24]. Moreover, the individual response to HRV-guided training seems to be less heterogeneous [24, 25]. Nevertheless, the effect of HRV-guided training on mortality predictors has not been tested in CAD patients. Therefore, the main objective of this research was to determine whether HRV-guided training increases HR-based indices or $\dot{V}O_2$ peak to a greater extent than predefined training. Ancillary to the main objective, other objectives were to test the effect of HRV-guided training versus predefined training on secondary outcomes (e.g., body composition, quality of life), and to study the effect of exercise-based CR, regardless of the training prescription method, on mortality predictors and secondary endpoints. Based on previous evidence, it was hypothesized that HRV-guided training is superior to predefined training for improving mortality predictors in CAD patients. Moreover, regardless of the training prescription method, exercise-based CR enhances mortality predictors.

METHOD

Study design, randomization, and implementation

This study was a parallel-group, double-blind, randomized controlled trial that was performed from October 2018 to July 2019. Before taking part in the study, patients were interviewed and signed a written informed consent. In brief, patients were instructed to properly carry out day-to-day HRV measurements. The study protocol was divided into two periods: a 2-week baseline period (BP) and a 6-week training period (TP). A baseline assessment week (PRE) and a final assessment week (POST) were conducted before and after the TP, respectively. The patients were matched into pairs according to their $\dot{V}O_2$ peak, wait time to start CR, gender, and peak power output at PRE. Afterwards, the patients were randomly allocated to an HRV-guided training group (HRV-G) or predefined training group (PRED-G) (Figure 1). An allocation sequence was computer-generated following a non-blocked strategy and delivered by a researcher not involved in the trial. A researcher who was aware of the study design conducted the enrolment and assignment of the patients. Throughout the 6-week TP, patients allocated to the PRED-G carried out a predefined training program, while patients that were assigned to the HRV-G trained based on their day-to-day HRV measurements. At PRE and POST, each patient took part in several assessments which were carried out in the same sequence and at the same period of the day. Patients and assessors recording the outcome measurements were blinded to the group allocations. This study was approved by the ethical committee of the local University (Ref. DPS.JSM.01.17)

and was conducted conforming to the recommendations of the Declaration of Helsinki. Informed consent was obtained from all subjects involved in the study.

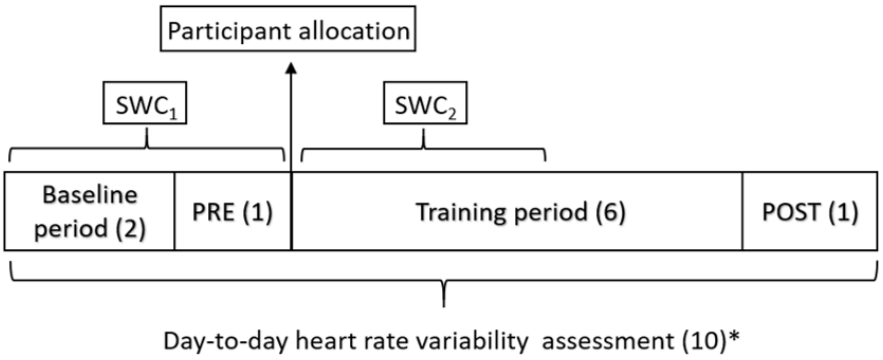

Figure 1. Experimental design. *PRE*, baseline assessment week; *POST*, final assessment week*; SWC1*, smallest worthwhile change during the first three weeks of the study protocol; *SWC2*, smallest worthwhile change during the first three weeks of the training period; * denotes number of weeks

Participants

Eligible patients were men and women with low-risk and age ≥ 18 years, who had experienced an acute myocardial infarction, angina pectoris, had undergone revascularization (percutaneous transluminal coronary angioplasty or coronary artery bypass grafting) or suffered a coronary heart disease which was documented by angiography, up to one year before to the enrolment in the study. Exclusion criteria included unstable angina, atrial fibrillation, cardiac implantable electronic devices, complex ventricular arrhythmias, uncontrolled hypertension, conditions limiting participation in exercise training and/or symptom-limited cardiopulmonary exercise test (CPET) at PRE. All participants maintained their medication regimen throughout the intervention.

Measurements

Day-to-day HRV assessment

All patients were instructed to assess their HRV in the morning at home for 10 weeks. The HRV recordings were attained via a photoplethysmography smartphone application (HRV4Ttraining) previously validated. HRV assessments were done at rest, as patients lay supine for 90 s with spontaneous breathing in a semi-dark room, and the last 60 s were captured. The validity of ultra-short-term HRV indices (i.e., 60 s) has been previously reported, allowing the assessment of daily HRV. Patients were asked to avoid talking or moving through the assessment. Measurement errors and ectopic beats were automatically deleted by the smartphone application. The record was discarded and repeated immediately in cases of erroneous signals. RMSSD was selected as the vagal-related HRV index since previous studies have reported that it is more adequate to reflect the PNS status than other indices [23, 26]. In addition, the RMSSD data was logarithmically transformed to correct skewness (LnRMSSD). A 7-day rolling average of RMSSD ($LnRMSSD_{7\text{-}day}$) was calculated to carry out training prescription in patients allocated to the HRV-G [27]. During

the first three weeks of the study protocol (BP and PRE), the smallest worthwhile change (SWC) of LnRMSSD was calculated as mean ± 0.5 x standard deviation (*SD*) [27, 28] (SWC_1). SWC_1 was used to prescribe exercise training for the first three weeks of the TP in HRV-G patients. SWC was updated after the first three weeks of TP (SWC_2) and used to carry out training prescription for the remaining TP weeks (Figure 1), as previous studies have reported a relationship between ANS status and performance [29].

Cardiorespiratory fitness

CRF was evaluated using a medically supervised maximal graded cycle ergometer exercise test (Excite Bike Med, Technogym, Cesena, Italy). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were assessed at resting condition before starting the CPET. Moreover, a 10-min resting assessment was performed in seated position in the ergometer. Patients were instructed to avoid talking or moving throughout the resting assessment. The last 5 min were captured to obtain results at resting condition. Afterwards, a 3-min warm-up at 10 W was carried out before starting a 1-min stage incremental exercise test to volitional exhaustion with 10 W work increments [30]. The pedaling frequency was fixed between 60 and 70 rpm. At the end of the test, a 3-min cool-down at 10 W was performed. Respiratory gas exchange was measured by MasterScreen CPX (Jaeger, Hoechberg, Germany) and HR was monitored continuously using a 12-lead electrocardiogram (Jaeger, Hoechberg, Germany) throughout the test. The criteria to consider the test as maximal was to reach a respiratory exchange ratio (RER) > 1.15. Breath-by-breath gas exchange measurements allowed the determination of oxygen uptake ($\dot{V}O_2$) and carbon dioxide production (VCO_2). These data were averaged every 15 s. The $\dot{V}O_2$ peak was defined as the highest $\dot{V}O_2$ mean value measured at the end of the test. First ventilatory threshold (VT1) and second ventilatory threshold (VT2) were analyzed blindly using the ventilatory equivalents method [31]. Variables were obtained at exercise peak, VT2 and resting condition. $\dot{V}O_2$ peak was included as primary endpoint, while the remaining variables (i.e., workload, HR, $\dot{V}O_2$, SBP and DBP) were included as secondary outcomes.

Heart rate-based indices

Each patient underwent HRV assessment at the same hour of the day (7 to 9 a.m.) on repeated testing to avoid bias due to circadian rhythms. Before carrying out the assessment, patients were familiarized with the material and protocol to increase the validity of the measurement [32]. Patients were informed to avoid eating or drinking anything in the previous eight hours to the assessment and not to perform any type of exercise for at least 48 hours. The assessments were performed in a quiet room with an average temperature of 22ºC. Polar H7 chest strap (Polar Electro OY, Kempele, Finland) and Elite HRV app [33] were used to capture HRV measurements. Patients were informed to avoid talking and sleeping, controlling their breathing pace to 12 breaths per min.

The length of the recording was 20 min, and the last 5 min were selected to calculate isolated vagal-related HRV indices. Kubios HRV Software 2.0 for Windows (The Biomedical Signal Analysis Group, Kuopio, Finland) was used to analyze time and frequency domain indices. Data was detrended using a smoothness method. Fast-Fourier transform was used to calculate power spectral density. On the other hand, day-to-day RMSSD values across the assessment weeks (PRE and POST) were averaged to obtain 7-day weekly averaged RMSSD values. Finally, as it has been aforementioned, resting HR was measured before the start of the CPET in seated position. HRR was defined as the reduction in HR from exercise peak to the HR after 1 min (HRR 1 min) and 2 min (HRR 2 min), respectively.

Secondary outcomes

A detailed description of other analyzed secondary outcomes (i.e., body composition, blood analysis, quality of life and dietary intake) are available in the Supplementary digital material.

Exercise training programs

During the 2 weeks of the BP, all the patients carried out 2 low-intensity sessions per week (4 sessions) to familiarize themselves with the cycle ergometer and obtain a baseline HRV measurement. The length of the familiarization sessions ranged from 20 to 30 min. Throughout 6 weeks of the TP, an individualized exercise training was prescribed according to the workload at VT1 (WVT1) and workload at VT2 (WVT2) obtained in the CPET at PRE. The intensity of moderate continuous training (MCT) sessions ranged between WVT1 and WVT2, and the session length increased from 30 to 40 min. High intensity interval training (HIIT) sessions were composed by four repetitions of 4 min above WVT2 with 4 min of active recoveries below WVT1. Each session started and finished with 5 min of warm-up and cool-down below WVT1. The training frequency in both groups was three times per week (18 sessions). The first session was always in the form of MCT, regardless of the training group. The frequency of HIIT sessions in the PRED-G increased every two weeks (1 – 2 weeks: 3 MCT / 0 HIIT; 3 – 4 weeks: 2 MCT / 1 HIIT; 5 – 6 weeks: 1 MCT / 2 HIIT). The patients allocated in the HRV-G carried out MCT or HIIT sessions on the basis of their daily HRV assessments following a decision schema (Figure 2). Patients allocated in the HRV-G did not accumulate more than 2 consecutive HIIT exercise sessions. All training sessions were performed under the supervision of qualified instructors.

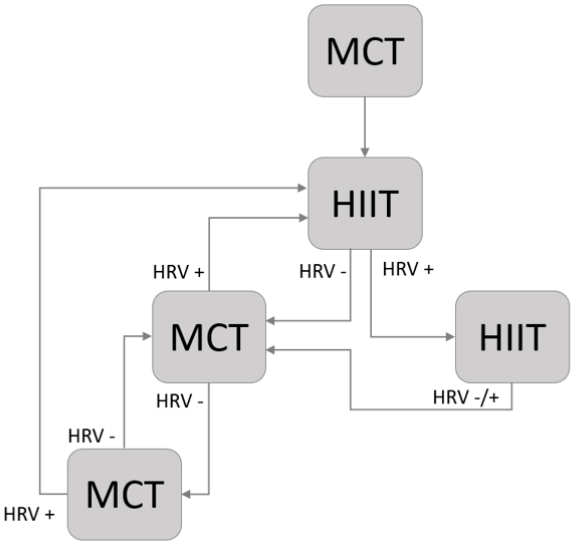

Figure 2. HRV-guided training schema. *HRV* -, $LnRMSSD_{7\text{-day}}$ fell outside SWC; *HRV* +, $LnRMSSD_{7\text{-day}}$ fell inside SWC; *MCT*, moderate continuous training; *HIIT*, high intensity interval training

Statistical analyses

The Shapiro-Wilk test and the Levene test were used to test the normality of the data and the equality of the group variances (homoscedasticity), respectively. Besides, the normal distribution of the data was graphically verified by box plot and Q-Q graphs. Categorical variables are presented as number of cases (percentage). Normally distributed continuous variables are reported as mean ± *SD*, and those that were non-normally distributed are reported as median (25^{th} and 75^{th} percentiles). Percentiles were calculated by the weighted average method. The Student's independent *t*-test, the Mann-Whitney *U* test and the Fisher's exact test were used for between-group comparisons in normally distributed continuous variables, non-normally distributed continuous variables, and categorical variables, respectively. The Student's paired *t* test and the Wilcoxon's signed-rank test were carried out for within-group comparisons in normally and non-normally distributed variables, respectively. Any changes in the outcomes following the intervention were quantified by subtracting the pre-intervention values from the post-intervention values, including 95% confidence interval (CI) for the mean or median change based on the normality assumption [34]. All analyses were considered statistically significant at critical level of $p \leq .050$. Within-group comparisons, regardless of the training group, were carried out if between-group differences in changes at follow-up did not reach statistical significance ($p > .050$). The intention-to-treat principle was applied in the sense that data were analyzed for all randomized patients for whom post-intervention data were available. G*Power was used to estimate the required sample size a priori ($\alpha = .050$, $1 - \beta = .080$), which yielded a total of 24 participants with an effect size of $d = 1.2$, based on the results of a previous study about the effect of HRV-guided

training on resting vagal-related HRV indices [20]. STATA software was used to perform statistical analyses (version 16.0; Stata Corp LLC, College Station, TX, USA).

RESULTS

Twenty-five patients were recruited to participate in this study. After baseline assessments, two patients were not allocated because they showed exercise limitations. Therefore, 23 patients were randomized to the HRV-G (n = 11) or PRED-G (n = 12) of which two patients (9%, one in the HRV-G and one in the PRED-G) dropped out of the study. Thus, a total of 21 patients, comprising 10 patients in the HRV-G and 11 patients in the PRED-G, completed a 6-week CR program, carrying out 18 exercise sessions (Figure 3). No events happened throughout the intervention. Demographic and clinical characteristics of the study patients at baseline are reported in Table 1. The proportion of the diabetic patients was statistically significantly lower (p = .035) in the HRV-G (0.0%) than in the PRED-G (45.5%), while no between-group statistically significant differences (p > .050) were found in the remaining baseline characteristics.

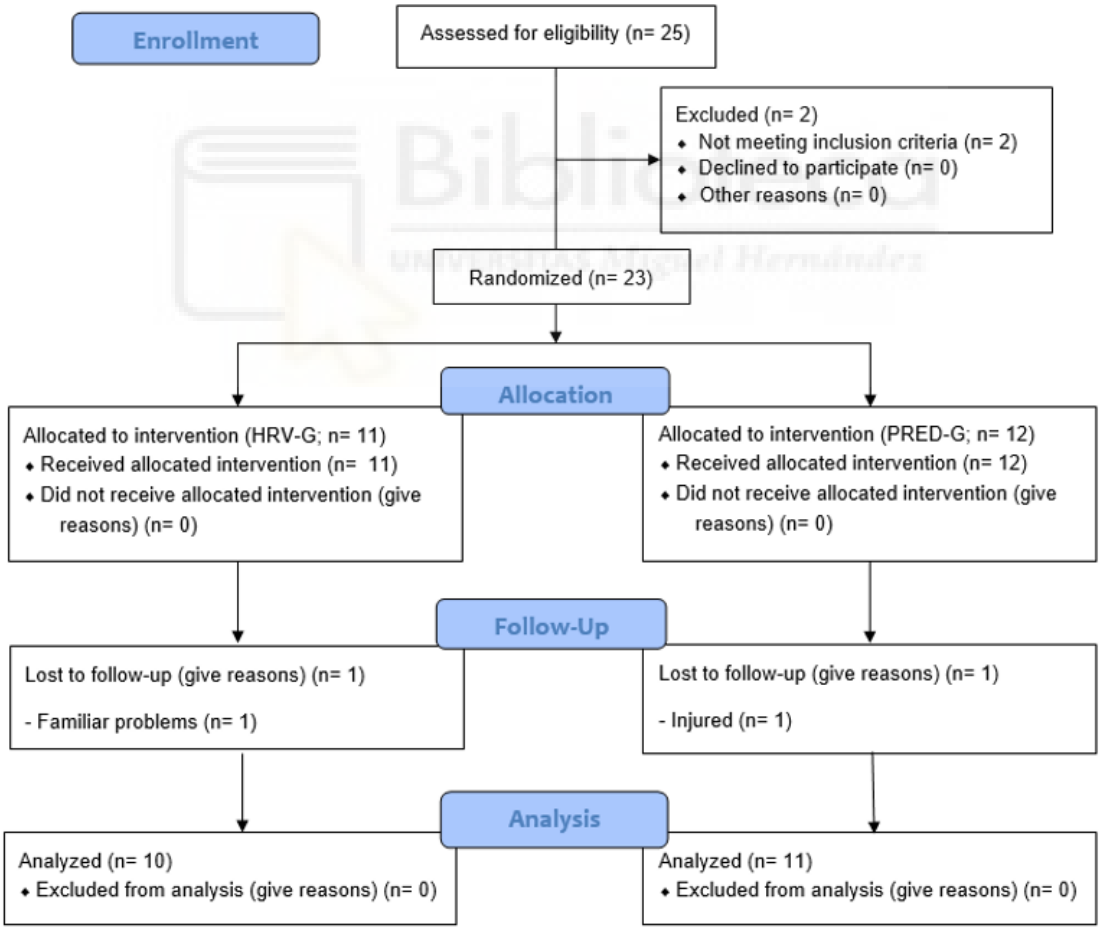

Figure 3. CONSORT 2010 flow diagram. *HRV-G*, heart rate variability-guided trainng group; *PRED-G*, predefined training group

Table 1. Demographic and clinical characteristics of the study patients at baseline

	PRED-G (n = 11)	**HRV-G (n = 10)**	***p***
Age (years)	59.2 ± 6.9	56.9 ± 5.6	.418
Sex (male)	10 (90.9)	9 (90.0)	.999
Body weight (kg)	78.2 ± 7.7	77.1 ± 15.5	.852
Body mass index (kg/m^2)	29.1 (27.7, 29.7)	26.8 (26.0, 30.6)	.569
Wait time (days)	215.4 ± 84.9	169.2 ± 57.8	.166
No. of infarcted patients	7 (63.6)	7 (70.0)	.999
Site of infarction (anterior)	7 (63.6)	5 (50.0)	.670
No. of vessels involved (1 vessel)	8 (72.7)	7 (70.0)	.999
No. of events (first)	10 (90.9)	9 (90.0)	.999
No. PTCA intervention surgery	10 (90.9)	9 (90.0)	.999
Diabetes mellitus	5 (45.5)	0 (0.0)	.035*
Hypertension	5 (45.5)	3 (30.0)	.659
Smoker	5 (45.5)	4 (40.0)	.999
Hyperlipidaemia	6 (54.5)	5 (50.0)	.999
Overweight / obesity	3 (27.3)	1 (10.0)	.586
Family history	2 (18.2)	3 (30.0)	.635
Personal history	2 (18.2)	1 (10.0)	.999
β-Blockers	9 (81.8)	9 (90.0)	.999
ACE inhibitors	4 (36.4)	5 (50.0)	.670
Antiplatelets	11 (100)	9 (90.0)	.476
Diuretics	4 (36.4)	1 (10.0)	.311
Nitrates	11 (100)	10 (100)	N/A
ARBs	6 (54.5)	2 (20.0)	.183
Calcium-channel blockers	3 (27.3)	0 (0.0)	.214
Lipid-lowering drugs	11 (100)	10 (100)	N/A

ACE, angiotensin-converting enzyme; *ARB*, angiotensin II receptor blocker; *CR*, exercise-based cardiac rehabilitation; *HRV-G*, heart rate variability-guided training group; *p*, probability associated to the statistic; *PRED-G*, predefined training group; *PTCA*, percutaneous transluminal coronary angioplasty; wait time: time from procedure or event to start of exercise-based cardiac rehabilitation

Data are delivered as number of cases (percentage), mean ± *SD* or median (25th and 75th percentiles). *p* values refer to differences between the randomized groups at baseline in patients completing the intervention

Mortality predictors

Pre- and post-intervention values, and changes in HR-based indices (i.e., vagal-related HRV indices, resting HR and HRR indices) and $\dot{V}O_2$ peak are reported in Table 2. There were no between-group statistically significant differences in any of the analyzed variables at baseline ($p > .050$). A between-group statistically significant difference was found for the change reached at follow-up in the averaged RMSSD ($p = .034$). A statistically significant increase in averaged RMSSD after HRV-guided training ($p = .039$; mean change [MC] = 7.57 [95% CI = 0.48 – 14.64] ms) was found, while no significant change in averaged RMSSD was found after predefined training ($p = .416$; MC = -2.79 [95% CI = -10.13 – 4.55] ms). No between-group statistically significant differences were found in the remaining analyzed variables ($p > .050$). Regardless of the training prescription method, statistically significant changes in resting HR ($p = .001$; MC = -4.10 [95% CI = -6.37 – -1.82] beats per minute [bpm]), HRR 2 min ($p = .010$; MC = 4.33 [95% CI = 1.15 – 7.52] bpm), and $\dot{V}O_2$ peak ($p < .001$; MC = 3.04 [95% CI = 1.70 – 4.37] $mL \cdot kg^{-1} \cdot min^{-1}$) were found.

Table 2. Effect of exercise-based cardiac rehabilitation on mortality predictors

		Based on the training group (PRED-G, n = 11; HRV-G, n = 10)					All patients (n = 21)			
Variable	**Group**	**Pre**	**Post**	p^A	**Change (95% CI)**	p^B	**Pre**	**Post**	p^A	**Change (95% CI)**
RMSSD (ms)	PRED-G	28.4 ± 11.8	29.4 ± 10.2	.774	1.07 (-7.12 – 9.26)	.431	35.1 ± 25.7	34.3 ± 21.8	.721	-0.86 (-5.83 – 4.11)
	HRV-G	41.9 ± 34.0	39.1 ± 29.1	.398	-2.79 (-9.90 – 4.32)					
HF (ms^2)	PRED-G	272.0 (151.3, 663.0)	480.5 (188.5, 670.3)	.846	-27.0 # (-313.0 – 259.0)	.770	374.0 (175.3, 745.0)	357.5 (207.5, 649.8)	.202	-66.00 # (-236.59 – 53.53)
	HRV-G	649.5 (190.3, 1269.0)	353.5 (197.5, 627.0)	.065	-111.5 # (-599.1 – 376.1)					
SD_1 (ms)	PRED-G	20.1 ± 8.3	20.7 ± 7.1	.824	0.61 (-5.42 – 6.64)	.430	24.9 ± 18.2	24.1 ± 15.4	.654	-0.78 (-4.34 – 2.79)
	HRV-G	29.7 ± 24.1	27.5 ± 20.7	.346	-2.16 (-7.07 – 2.75)					
Averaged RMSSD (ms)	PRED-G	57.6 ± 20.0	54.8 ± 19.8	.416	-2.79 (-10.13 – 4.55)	.034*	NA	NA	NA	NA
	HRV-G	49.7 ± 16.0	57.3 ± 18.3	.039*	7.57 (0.48 – 14.64)					
Resting HR (bpm)	PRED-G	64.7 ± 5.0	62.2 ± 7.3	.068	-2.55 (-5.32 – 0.23)	.140	63.9 ± 7.1	59.8 ± 9.1	.001*	-4.10 (-6.37 – -1.82)
	HRV-G	63.0 ± 9.1	57.2 ± 10.6	.009*	-5.80 (-9.74 – -1.86)					
HRR 1 min (bpm)	PRED-G	17.6 ± 6.8	19.1 ± 5.7	.108	1.45 (-0.38 – 3.29)	.235	20.0 ± 9.9	20.9 ± 9.1	.163	0.81 (-0.36 – 1.98)
	HRV-G	22.7 ± 12.3	22.8 ± 11.8	.893	0.10 (-1.53 – 1.73)					
HRR 2 min (bpm)	PRED-G	28.4 ± 9.2	34.4 ± 7.3	.014*	6.00 (1.19 – 10.51)	.263	32.0 ± 12.6	36.3 ± 10.9	.010*	4.33 (1.15 – 7.52)
	HRV-G	36.0 ± 15.0	38.5 ± 14.0	.300	1.00 (-2.35 – 7.38)					
$\dot{V}O_2$ peak ($ml \cdot kg^{-1} \cdot min^{-1}$)	PRED-G	25.0 ± 5.7	28.1 ± 6.0	.005*	3.16 (1.21 – 5.11)	.851	24.9 ± 5.4	28.0 ± 6.0	<.001*	3.04 (1.70 – 4.37)
	HRV-G	24.9 ± 5.3	28.0 ± 6.4	.017*	2.91 (0.67 – 5.15)					

CI, confidence interval; *HF*, high-frequency; *HR*, heart rate; *HRR 1 min*; heart rate recovery 1 min; *HRR 2 min*; heart rate recovery 2 min; *HRV-G*, heart rate variability-guided training group; *NA*, non-applicable; *PRED-G*, predefined training group; *RMSSD*, the root mean square of the differences between successive R-R intervals; SD_1, the standard deviation of instantaneous beat-to-beat R-R interval variability; $\dot{V}O_2$ *peak*, peak oxygen uptake

Data at pre- and post-intervention are delivered as mean ± *SD* or median (25th and 75th percentiles); p^A and p^B values refer to within-group and between-group differences, respectively; * denotes $p \leq .050$; # denotes median change instead of mean change

Secondary outcomes

Pre- and post-intervention values, and changes at follow-up in CPET variables, body composition, biochemical and hematological variables, and quality of life are reported in Tables S1 – S4 (Supplementary digital material), respectively. There were no between-group statistically significant differences at baseline ($p > .050$). No between-group statistically significant differences were found for the change reached at follow-up in any of the secondary outcomes ($p > .050$). The effect of exercise-based CR on secondary outcomes are shown in the Supplementary digital material.

Regarding dietary intake, pre- and post-intervention values of the 4-day recording of energy, water, and macronutrients are shown in Table S5 (Supplementary digital material). There were no between-group statistically significant differences at pre- and post-intervention for any of the analyzed variables ($p > .050$). Within-group analyses showed a significant decrease at follow-up in eicosapentaenoic acid and docosahexaenoic acid for the PRED-G, and in cholesterol intakes for the HRV-G ($p \leq .050$).

DISCUSSION

This research was aimed to investigate whether HRV-guided training enhances mortality predictors (i.e., HR-based indices and $\dot{V}O_2$ peak) to a greater extent than predefined training prescription in patients with CAD. Additionally, if no differences were found between HRV-guided training and predefined training, the effects of exercise-based CR, regardless of the training prescription method, on mortality predictors were also investigated. In line with our hypothesis, we found that HRV-guided training is superior to predefined training for improving PNS modulation, assessed by averaged RMSSD values. Although dietary intake has been associated with ANS function changes [35], diet does not seem to have an influence on the results of this study because it is very similar in both groups of participants. On the other hand, in contrast to our hypothesis, HRV-guided training is not superior to predefined training for improving other mortality predictors (i.e., resting HR, HRR indices and $\dot{V}O_2$ peak). Interestingly, there is evidence that shows that predefined exercise-based CR programs enhance HRR indices and $\dot{V}O_2$ peak [5, 11], while the training-induced effect on vagal-related HRV indices seems to be more controversial [11]. The efficacy of predefined exercise-based CR programs on these mortality predictors may help explain the lack of superiority of HRV-guided training for improving HRR indices and $\dot{V}O_2$ peak. Nonetheless, HRV-guided training seems to be a suitable training prescription method to overcome limitations of predefined exercise-based CR programs for enhancing vagal-related HRV indices. Regardless of the training prescription method, the findings of this study showed that exercise-based CR enhances resting HR, HRR 2 min and $\dot{V}O_2$ peak.

To the best of our knowledge, this is the first study that has examined the superiority of HRV-guided training for improving mortality predictors (i.e., HR-based indices and $\dot{V}O_2$ peak) compared to predefined training in CAD patients. As has been mentioned above, previous studies have been carried out with CHF patients, sedentary healthy people and endurance-trained athletes, showing high methodological heterogeneity for applying HRV-guided training, such as RMSSD [19, 21, 28] vs HF [24], isolated HRV values [20, 21, 24] vs averaged HRV values [19, 28], standing position [20, 21, 24] vs supine position [19, 28] or morning [19, 20, 24, 28] vs afternoon/evening measurements [21]. We decided to use a 7-day rolling average of RMSSD values as their sensitivity to training status is higher than isolated HRV values [23]. Additionally, the patients in this study carried out daily HRV assessments in supine position in the morning. Assessments of HRV performed in the morning allow to control daily stressors easily [24]. Moreover, there is evidence that shows that standing position is more suitable than supine position in endurance-trained athletes to avoid saturation of acetylcholine receptors due to heightened PNS tone (i.e., bradycardia) [26], which diminishes vagal-related HRV indices [36]. Nonetheless enhanced PNS tone is not common in CAD patients. Future studies carried out with CAD patients should test the influence of these methodological approaches on the applicability of HRV-guided training for enhancing the effectiveness of exercise-based CR on mortality predictors.

The findings of this study showed that HRV-guided training is superior to predefined training for enhancing resting PNS modulation, assessed by averaged RMSSD values. However, no differences were found between both training prescription methods when isolated vagal-related HRV indices (i.e., RMSSD, HF or SD_1) were used for inferring PNS modulation. These controversial findings could be due to the influence of methodological issues on the sensitivity of vagal-related HRV indices to detect PNS status, such as the influence of breathing patterns on HRV values and the natural day-to-day HRV lability. In this regard, Buchheit [26] and Saboul et al. [37] reported that RMSSD have lower sensitivity to breathing patterns than HF, while Plews et al. [13] found that averaged HRV values appear to be a better method for assessing training-induced PNS adaptation compared to isolated HRV values due to the reduction of day-to-day HRV lability. In the same line, Le Meur et al. [38] revealed that isolated HRV measurements may not detect training-induced PNS modulation in athletes after an overload training period, while Manresa-Rocamora et al. [12] reported that averaged HRV values provide the best evidence of PNS modulation. This evidence supports our idea that averaged RMSSD values may be a more suitable vagal-related HRV index to obtain information of the PNS modulation. Nonetheless, the influence of methodological issues (i.e., isolated vs averaged HRV values) on the sensitivity of vagal-related HRV indices to detect PNS hyperactivity in patients with CAD should be addressed in future studies. In line with the findings of the present study, da Silva et al. [21] and Kiviniemi et al. [20] only found an increase of resting PNS modulation (i.e., RMSSD or SD_1) in the HRV-guided

training groups, while no changes were found in the predefined training groups. Therefore, based on our findings and this previous evidence, as we hypothesized, it seems that HRV-guided training is superior to predefined training for improving resting PNS modulation in patients with CAD, which could help to reduce mortality rates in these patients [39]. Nevertheless, averaged RMSSD values should be used for increasing the sensitivity of HRV measurements to detect CR-induced PNS adaptation.

As it has been commented previously, the individual response to the same exercise-based CR program varies among patients. Individual changes in averaged RMSSD values after exercise-based CR, based on the training prescription group, are shown in Figure 4. Most of the patients who carried out HRV-guided training increased averaged RMSSD values (70%), while individual changes in this vagal-related HRV index in response to predefined training were more heterogeneous (27% showed increased averaged RMSSD values). These findings are in line with those previously reported by Kiviniemi et al. [24] and Javaloyes et al. [25] about the effect of HRV-guided training on CRF and endurance performance, respectively. In this regard, there is evidence that shows the influence of the PNS status, which is the physiological criterion used to carry out HRV-guided training, on the response to aerobic training [17], which may explain lower heterogeneity in the response to HRV-guided training compared to predefined training. Nonetheless, the heterogeneity in the response to training based on the training prescription method used requires future study.

Figure 4. Individual changes in the averaged root-mean-square difference of successive normal R-R intervals (RMSSD) based on the training prescription group. *HRV*, heart rate variability

Regarding other HR-based indices, in contrast to our hypothesis, there was not an increase of HRR 1 min after exercise-based CR. There is evidence that shows that exercise-based CR is a non-pharmacological treatment for enhancing HRR 1 min, which is primarily PNS mediated [40].

For instance, Manresa-Rocamora et al. [11] reported an increase of 5.35 (95% CI = 4.08 – 6.61) bpm in HRR 1 min after exercise-based CR compared to usual care. Nonetheless, HRR 1 min at baseline in the studies included in this meta-analysis (mean ± *SD*: 10.88 ± 5.17 bpm) was lower than HRR 1 min at pre-intervention shown by the participants (mean ± *SD*: 20.00 ± 9.90 bpm), even though this HR-based index was measured during an active recovery period, which diminishes HRR 1 min [41, 42]. Therefore, the controversial finding of the present study could be due to the high HRR 1 min shown by the included patients at baseline, which could limit the possibility of improving PNS reactivation in these patients after exercise-based CR. On the other hand, the results of the present study showed an increase of 4.33 (95% CI = 1.15 – 7.52) bpm in HRR 2 min after exercise-based CR. The recovery of HR at 2 minutes after exercise is affected by PNS reactivation and sympathetic nervous system withdrawal as reported by Perini et al. [10], who found a plasma norepinephrine concentration reduction during the second minute of the recovery. In line with the present findings, Wang et al. [43] found an enhancement in HRR 2 min after a 4-week multimedia CR program compared to usual care in cardiac patients. The improvement of HRR 2 min after exercise-based CR could be also due to a faster clearance of metabolites, that diminishes metaboreflex stimulation and, therefore, increases HRR 2 min [44]. The enhancement of HRR 2 min also could help to reduce mortality in CAD patients [45]. Finally, this study also showed that exercise-based CR diminishes resting HR, which shows an increase of the PNS tone [46].

Finally, the current study showed that HRV-guided training is not superior to predefined training for improving $\dot{V}O_2$ peak, which is in line with the results of previous systematic reviews with meta-analyses which included studies carried out with healthy people and endurance-training athletes [47, 48]. As it has been previously commented, predefined exercise-based CR enhances $\dot{V}O_2$ peak [5], which may explain the lack of superiority of HRV-guided training for improving this mortality predictor compared to predefined training. In contrast to the finding of the present study, Behrens et al. [22], who performed a 4-week exercise-based CR program, found that HRV-guided training enhances $\dot{V}O_2$ peak in CHF patients, while no changes were noticed after predefined training. Nonetheless, there is evidence that shows that the effect of predefined exercise-based CR programs on $\dot{V}O_2$ peak in patients with CHF is lower in shorter interventions [49], while no influence of the intervention length on the training-induced effect on $\dot{V}O_2$ peak has been reported in patients with CAD [5, 50]. Therefore, it seems that in CHF patients, whose hallmark is exercise intolerance, HRV-guided training could induce faster CRF adaptations than predefined training. Based on these controversial findings, future studies should test the influence of training characteristics (e.g., intervention length, training frequency) on the applicability of HRV-guided training for improving mortality predictors. Regardless of the training prescription method, the

present study showed an improvement of 3.04 (95% CI = 1.70 – 4.37) $mL \cdot kg^{-1} \cdot min^{-1}$ in $\dot{V}O_2$ peak after a 6-week CR program, which is in line with previously reported results [5].

Strengths and Limitations

This is a randomized double-blind study, and it has been the first study that has tested the superiority of HRV-guided training for improving PNS function and CRF compared to predefined training in patients with CAD. All sessions were performed under supervision of qualified instructors on previously established weekdays (Monday, Wednesday, and Friday) at the same time of the day, which allows to enhance the control of the training sessions and avoids variations from the exercise session to the following HRV assessment. Moreover, averaged RMSSD was also included as vagal-related HRV index, which increases the validity of our findings about the training-induced effect on vagal-related HRV indices. Nevertheless, there are also some limitations that should be highlighted. No patients were included in a usual care group, which does not allow to discard the influence of confounding factors against the validity of our results. However, the main objective of this study was to compare the effects of both training prescription methods for improving the analyzed variables. Most of the patients included in the present study were men (90%). Therefore, these findings should be limited to CAD male patients, and future studies should test the efficacy of HRV-guided training in CAD female patients. Finally, day-to-day HRV assessments were performed at home since it is more convenient for the patients. For this reason, to increase the applicability of this model, it was decided to allow patients to breathe spontaneously, which did not allow to analyze the effect of exercise-based CR on averaged HF values, since it is affected by breathing patterns.

Conclusions

According to the findings of the present study, HRV-guided training is superior to predefined training for improving resting PNS modulation, assessed by averaged RMSSD values, in patients with CAD. However, it should be highlighted that contradictory findings were found based on the vagal-related HRV indices used, which could be due to the influence of methodological issues on the sensitivity of isolated vagal-related HRV indices for inferring PNS modulation. Moreover, HRV-guided training is not superior to predefined training for enhancing other mortality predictors (i.e., resting HR, HRR indices and $\dot{V}O_2$ peak). However, improved PNS modulation is likely relevant given the independent association between vagal-related HRV indices and cardiovascular morbidity and mortality. Regardless of the training prescription method used to prescribe aerobic training, exercise-based CR enhances resting HR, HRR 2 min, and $\dot{V}O_2$ peak.

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8.5.2. Supplementary material study 5

Secondary outcomes

Body composition

All anthropometrical variables were measured by a Level 2 anthropometrist certified by the International Society for the Advance of Kinanthropometry (ISAK) with an individual technical error of measurement (TEM) of 0.76–0.39% for skinfolds and of 0.12% for the remaining parameters. The errors were considered acceptable for ISAK standards (<7.5% for skinfolds and <1.5% for the remaining measurements). All measurements were made following the guidelines stated by ISAK [1]. The total body mass of each participant was measured in kilograms using a digital scale (Tanita, TBF 300 A, Tokyo, Japan), breadths with a Holtain bicondylar caliper (Holtain, UK), girths with a metallic non-extensible tape (Lufkin, USA), and skinfolds with a Holtain Tanner/Whitehouse skinfold caliper (Holtain, UK). The following four breadths were measured: humerus, wrist, femur, and ankle. Regarding girths, four were measured: relaxed arm, flexed and tensed arm, thigh, and medial calf. Finally, eight skinfolds were also measured: triceps, biceps, subscapular, ileocrestal, supraspinale, abdominal, thigh, and medial calf. Percentage of body fat mass was calculated using Durnin-Womersley equation [2]. Percentage of bone mass was calculated according to Martin's equation [3]. The percentage of muscle mass was calculated from Lee's equation [4]. In addition, the sums of the eight skinfolds were considered for fat content calculations.

Blood collection

Blood samples were obtained from the median cubital vein at PRE and POST after at least a 10-hour fast. Venipuncture (Höfer, Doering, Rumpold, Oldridge, & Benzer, 2006). Blood was centrifuged (2500 ×g for 15 min at 4 °C) to obtain serum or plasma, and frozen at −80 °C until further analysis. Measurement of glucose, urea, creatinine, uric acid, LDH, CK, sodium, potassium, total cholesterol, HDL-C, LDL-C, triglycerides, haemoglobin A1c, platelet, red blood cells and haemoglobin was performed using standardized methods.

Quality of life

The MacNew heart disease health-related quality of life (HRQL) instrument was used as a disease-specific HRQL questionnaire [5]. MacNew consists of 27 items that fall into three domains (a 13-item physical limitations domain scale, a 14-item emotional function domain scale, and a 13-item social function domain scale). The maximum possible score in any domain is 7 (high HRQL) and the minimum is 1 (poor HRQL).

Dietary intake

Patients were indicated to follow the dietetic instructions they received during the time they stayed at the hospital. No personal diet was provided. Patients recorded their food and beverage consumption during 4 consecutive days, including Sunday, before and after the intervention. Data from records was analyzed using the ST-Nutrition software (Servitux, Elche, Spain). Macro- and micro-nutrient intakes were evaluated paying attention to the recommendations established by the Portfolio dietary pattern for the National Cholesterol Education Program (NECP) Step II [6]. Recommendations from FESNAD (Spanish Federation of Nutrition, Food and Dietetics Associations)-SEEDO (Spanish Association for the Study of Obesity) were considered as well, taking into account the strong relation of overweight and obesity as risk factors to develop cardiovascular disease [7]. Basal metabolic rate of participants was estimated according to FAO/WHO recommendations (http://www.fao.org/3/y5686e/y5686e07.htm#bm07). Physical activity level was expressed as a multiple of 24-h basal metabolic rate, considering 1.53 for light activity lifestyle.

Table S1. Effect of exercise-based cardiac rehabilitation on the cardiopulmonary exercise test variables at exercise peak, second ventilatory threshold and resting condition

		Based on the training group (PRED-G, n = 11; HRV-G, n = 10)					All patients (n = 21)			
Variable	**Group**	**Pre**	**Post**	p^A	**Change (95% CI)**	p^B	**Pre**	**Post**	p^A	**Change (95% CI)**
- Exercise peak										
Workload (Watts)	PRED-G	173.0 (120.0, 203.0)	216.5 (145.0, 226.4)	.002*	28.50 # (7.97 – 45.00)	.540	173.0 (123.0, 203.0)	211.5 (136.3, 236.8)	<.001*	27.50 # (12.12 – 37.00)
	HRV-G	156.5 (124.5, 221.3)	198.8 (131.3, 239.1)	.020*	25.00 # (8.96 – 36.35)					
HR peak (bpm)	PRED-G	141.3 ± 19.0	144.9 ± 21.2	.283	3.60 (-3.54 – 10.74)	.797	139 ± 18.2	143.5 ± 19.8	.057	4.15 (-0.14 – 8.44)
	HRV-G	137.4 ± 18.2	142.1 ± 19.3	.125	4.70 (-1.58 – 10.98)					
- Second ventilatory threshold										
Workload (Watts)	PRED-G	128.6 ± 32.0	147.5 ± 50.0	.043*	18.85 (0.77 – 36.93)	.465	124.2 ± 32.8	146.6 ± 43.9	<.001*	22.35 (12.65 – 32.05)
	HRV-G	119.8 ± 34.8	145.7 ± 39.6	<.001*	25.85 (14.74 – 36.95)					
HR (bpm)	PRED-G	120.0 (105.0, 126.0)	127.0 (108.0, 133.0)	.122	2.00 # (-0.29 – 9.57)	.987	113.0 (101.5, 132.0)	123.0 (105.0, 133.5)	.038*	2.00 # (0.01 – 7.55)
	HRV-G	109.0 (100.3, 134.0)	121.5 (100.0, 134.3)	.275	4.00 # (-0.68 – 8.68)					
$\dot{V}O_2$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	PRED-G	18.9 ± 4.7	23.5 ± 6.6	.003*	4.56 (1.97 – 7.15)	.432	19.4 ± 4.5	23.3 ± 6.3	<.001*	3.94 (2.32 – 5.55)
	HRV-G	19.9 ± 4.4	23.2 ± 6.4	.012*	3.31 (0.93 – 5.69)					
- Resting condition										
$\dot{V}O_2$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	PRED-G	3.3 ± 0.4	3.7 ± 0.4	.003*	0.36 (0.16 – 0.56)	.135	3.4 ± 0.5	3.7 ± 0.6	.007*	0.24 (0.07 – 0.41)
	HRV-G	3.5 ± 0.6	3.7 ± 0.7	.372	0.12 (-0.17 – 0.41)					
SBP (mmHg)	PRED-G	133.0 ± 13.9	129.2 ± 15.1	.393	-3.82 (-13.34 – 5.70)	.767	129.3 ± 15.7	126.3 ± 14.8	.293	-3.00 (-8.80 – 2.80)
	HRV-G	125.2 ± 17.3	123.1 ± 14.6	.584	-2.10 (-10.46 – 6.26)					
DBP (mmHg)	PRED-G	80.5 ± 10.4	81.7 ± 8.7	.719	1.18 (-5.93 – 8.30)	.324	81.1 ± 9.3	80.1 ± 10.0	.655	-1.05 (-5.86 – 3.77)
	HRV-G	81.8 ± 8.4	78.3 ± 11.5	.322	-3.50 (-11.05 – 4.04)					

CI, confidence interval; *DBP*, diastolic blood pressure; *HR*, heart rate; *HRV-G*, heart rate variability-guided training group; *PRED-G*, predefined training group; *SBP*, systolic blood pressure; $\dot{V}O_2$, oxygen uptake

Data at pre- and post-intervention are delivered as mean ± *SD* or median (25th and 75th percentiles); p^A and p^B values refer to within-group and between-group differences, respectively; * denotes $p \leq .050$; # denotes median change instead of mean change

Table S2. Effect of exercise-based cardiac rehabilitation on the body composition

		Based on the training group (PRED-G, n = 11; HRV-G, n = 10)					All patients (n = 21)			
Variable	**Group**	**Pre**	**Post**	p^A	**Change (95% CI)**	p^B	**Pre**	**Post**	p^A	**Change (95% CI)**
Weight (kg)	PRED-G	78.2 ± 7.7	78.2 ± 8.1	.962	0.02 (-0.82 – 0.85)	.560	76.9 ± 11.5	76.8 ± 12.2	.635	-0.14 (-0.72 – 0.45)
	HRV-G	75.4 ± 15.4	75.1 ± 16.3	.482	-0.32 (-1.33 – 0.69)					
BMI ($kg \cdot m^{-2}$)	PRED-G	28.05 ± 2.42	28.22 ± 2.41	.344	0.16 (-0.20 – 0.53)	.442	27.60 ± 3.42	27.67 ± 3.59	.598	0.07 (-0.20 – 0.34)
	HRV-G	27.03 ± 4.45	26.99 ± 4.74	.840	-0.04 (-0.54 – 0.45)					
∑8Sk	PRED-G	125.0 ± 23.9	119.3 ± 27.6	.009*	-5.68 (-9.63 – -1.73)	.581	121.6 ± 35.0	116.7 ± 37.4	.005*	-4.90 (-8.07 – -1.72)
	HRV-G	117.5 ± 46.4	113.6 ± 48.5	.180	-3.93 (-10.10 – 2.24)					
Waist-hip ratio	PRED-G	0.99 ± 0.06	0.98 ± 0.06	.124	-0.01 (-0.03 – 0.00)	.447	0.98 ± 0.08	0.97 ± 0.08	.151	-0.01 (-0.02 – 0.00)
	HRV-G	0.96 ± 0.09	0.95 ± 0.10	.701	-0.00 (-0.02 – 0.02)					
Percent body fat (%)	PRED-G	31.1 ± 4.6	30.6 ± 5.1	.129	-0.59 (-1.38 – 0.20)	.655	30.1 ± 5.4	29.3 ± 6.0	.022*	-0.71 (-1.30 – -0.11)
	HRV-G	28.7 ± 6.3	27.9 ± 6.9	.111	-0.85 (-1.95 – 0.24)					
Percent muscle mass (%)	PRED-G	36.5 (34.5, 37.9)	36.3 (33.0, 38.8)	.965	-0.07 # (-1.17 – 0.50)	.304	36.5 (35.1, 38.0)	36.8 (34.7, 39.0)	.615	0.20 # (-0.14 – 0.44)
	HRV-G	36.6 (35.5, 38.8)	37.4 (35.3, 39.1)	.359	0.27 # (-0.53 – 0.93)					

BMI, body mass index; *CI*, confidence interval; *HRV-G*, heart rate variability-guided training group; *PRED-G*, predefined training group; ∑8Sk, the sum of subscapular, triceps, biceps, ileocrestal, supraspinale, abdominal, thigh, and calf skinfolds

Data at pre- and post-intervention are delivered as mean ± *SD* or median (25^{th} and 75^{th} percentiles); p^A and p^B values refer to within-group and between-group differences, respectively; * denotes $p \leq .050$; # denotes median change instead of mean change

Table S3. Effect of exercise-based cardiac rehabilitation on the biochemical and hematology variables

		Based on the training group (PRED-G, n = 11; HRV-G, n = 10)					All patients (n = 21)			
Variable	**Group**	**Pre**	**Post**	p^A	**Change (95% CI)**	p^B	**Pre**	**Post**	p^A	**Change (95% CI)**
Glucose ($mg \cdot dL^{-1}$)	PRED-G	111.7 ± 15.0	112.5 ± 14.5	.838	0.73 (-6.98 – 8.43)	.240	107.6 ± 15.6	111.7 ± 17.6	.203	4.10 (-2.40 – 10.60)
	HRV-G	102.6 ± 15.6	110.8 ± 21.7	.164	8.22 (-4.14 – 20.58)					
Urea ($mg \cdot dL^{-1}$)	PRED-G	41.0 (34.0, 52.0)	39.0 (35.0, 51.0)	.333	-1.00 # (-10.29 – 5.57)	.500	41.0 (35.5, 50.5)	39.0 (35.5, 48.0)	.615	-1.00 # (-5.00 – 2.55)
	HRV-G	40.5 (36.3, 50.0)	40.5 (35.8, 47.3)	.999	0.00 # (-5.00 – 5.70)					
Creatinine ($mg \cdot dL^{-1}$)	PRED-G	1.0 (0.9, 1.0)	1.0 (0.8, 1.1)	.999	-0.01 # (-0.07 – 0.07)	.117	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)	.316	0.03 # (-0.02 – 0.11)
	HRV-G	0.9 (0.7, 1.0)	0.9 (0.8, 1.0)	.168	0.10 # (-0.05 – 0.18)					
Uric acid ($mg \cdot dL^{-1}$)	PRED-G	5.3 (4.6, 5.9)	4.9 (4.5, 6.4)	.562	0.10 # (-0.66 – 0.33)	.499	5.1 (4.5, 6.6)	5.2 (4.4, 6.7)	.999	0.10 # (-0.51 – 0.35)
	HRV-G	4.9 (4.1, 6.8)	5.9 (4.1, 7.1)	.625	0.10 # (-0.67 – 0.90)					
LDH ($IU \cdot L^{-1}$)	PRED-G	326.0 (292.0, 368.0)	338.0 (309.0, 378.0)	.054	15.00 # (-3.16 – 35.59)	.877	317.0 (270.0, 362.5)	334.0 (288.5, 368.5)	.069	15.00 # (-1.10 – 32.10)
	HRV-G	293.0 (154.5, 360.8)	319.5 (277.0, 369.0)	.420	18.00 # (-46.40 – 195.73)					
CK ($IU \cdot L^{-1}$)	PRED-G	98.0 (84.0, 253.0)	115.0 (77.0, 180.0)	.700	8.00 # (-34.74 – 48.84)	.876	98.0 (76.0, 156.5)	100.0 (63.0, 162.5)	.702	10.00 # (-21.10 – 23.20)
	HRV-G	77.5 (53.0, 135.5)	100.0 (65.8, 145.8)	.902	12.00 # (-34.16 – 88.50)					
Sodium	PRED-G	142.0 (140.0, 143.0)	142.0 (139.0, 144.0)	.654	1.00 # (-3.29 – 4.00)	.353	141.0 (139.5, 143.0)	142.0 (142.0, 144.0)	.101	2.00 (-0.88 – 2.88)
	HRV-G	140.5 (139.0, 143.0)	144.0 (142.0, 144.0)	.027*	2.00 # (0.08 – 4.77)					
Potassium	PRED-G	4.7 (4.4, 4.7)	4.5 (4.4, 4.6)	.812	0.10 # (-0.46 – 0.30)	.358	4.6 (4.4, 4.9)	4.5 (4.4, 4.7)	.240	-0.05 # (-0.39 – 0.20)
	HRV-G	4.6 (4.4, 5.1)	4.5 (4.3, 4.7)	.203	-0.10 # (-0.59 – 0.19)					

Table S4. Continued

		Based on the training group (PRED-G, n = 11; HRV-G, n = 10)					All patients (n = 21)			
Variable	**Group**	**Pre**	**Post**	p^A	**Change (95% CI)**	p^B	**Pre**	**Post**	p^A	**Change (95% CI)**
Cholesterol ($mg \cdot dL^{-1}$)	PRED-G	129.2 ± 36.0	128.2 ± 27.3	.827	-1.00 (-10.93 – 8.93)	.339	135.6 ± 122.4	130.9 ± 25.7	.250	-4.76 (-13.14 – 3.62)
	HRV-G	142.7 ± 18.1	133.8 ± 24.8	.228	-8.90 (-24.48 – 6.67)					
Triglycerides ($mg \cdot dL^{-1}$)	PRED-G	100.0 (55.0, 131.0)	85.0 (69.0, 128.0)	.783	-1.00 # (-33.08 – 15.45)	.340	91.0 (51.0, 143.5)	79.0 (53.5, 128.0)	.109	-11.00 # (-28.86 – 4.55)
	HRV-G	90.5 (45.0, 187.8)	65.0 (41.0, 146.3)	.065	-14.50 # (-75.13 – 4.68)					
HDL-C ($mg \cdot dL^{-1}$)	PRED-G	39.7 ± 7.3	44.4 ± 8.0	.006*	4.64 (1.69 – 7.58)	.817	42.3 ± 10.8	47.3 ± 11.3	.008*	5.05 (1.47 – 8.63)
	HRV-G	45.0 ± 13.5	50.5 ± 13.8	.140	5.5 0 (-2.19 – 13.20)					
LDL-C ($mg \cdot dL^{-1}$)	PRED-G	67.5 ± 23.9	65.7 ± 25.7	.561	-1.73 (-8.13 – 4.68)	.419	70.7 ± 19.5	66.0 ± 20.2	.205	-4.71 (-12.22 – 2.79)
	HRV-G	74.3 ± 13.4	66.3 ± 13.3	.278	-8.00 (-23.67 – 7.67)					
Hemoglobin A1c ($mmol \cdot mol^{-1}$)	PRED-G	46.0 ± 6.7	40.5 ± 4.1	<.001*	-5.45 (-8.03 – -2.88)	.835	44.6 ± 6.2	39.3 ± 4.2	<.001*	-5.29 (-6.99 – -3.58)
	HRV-G	43.1 ± 5.7	38.0 ± 4.1	.002*	-5.10 (-7.85 – -2.35)					
Platelet	PRED-G	210.4 ± 46.2	204.1 ± 50.5	.292	-6.27 (-18.83 – 6.28)	.671	222.6 ± 48.9	214.0 ± 51.0	.128	-8.52 (-19.72 – 2.67)
	HRV-G	236.0 ± 50.6	225.0 ± 51.8	.286	-11.0 (-32.96 – 10.96)					
Red blood cells	PRED-G	5.0 ± 0.2	4.9 ± 0.3	.339	-0.06 (-0.19 – 0.07)	.524	4.9 ± 0.3	4.8 ± 0.3	.122	-0.10 (-0.22 – 0.03)
	HRV-G	4.8 ± 0.4	4.7 ± 0.3	.241	-0.14 (-0.39 – 0.11)					
Hemoglobin ($g \cdot dL^{-1}$)	PRED-G	15.2 (14.3, 15.7)	15.0 (14.1, 15.5)	.062	0.00 # (-0.60 – 0.19)	.542	14.7 (14.1, 15.6)	14.6 (13.9, 15.4)	.104	0.00 # (-0.25 – 0.25)
	HRV-G	14.4 (13.8, 15.2)	14.0 (13.7, 15.1)	.586	0.10 # (-0.84 – 0.77)					

CI, confidence interval; *CK*, creatine kinase; *HDL-C*, high-density lipoprotein cholesterol; *HRV-G*, heart rate variability-guided training group; *LDH*, lactate dehydrogenase; *LDL-C*, low-density lipoprotein cholesterol; *PRED-G*, predefined training group

Data at pre- and post-intervention are delivered as mean ± *SD* or median (25^{th} and 75^{th} percentiles); p^A and p^B values refer to within-group and between-group differences, respectively; * denotes $p \leq .050$; # denotes median change instead of mean change

Table S5. Effect of exercise-based cardiac rehabilitation on the quality of life

		Based on the training group (PRED-G, n = 11; HRV-G, n = 10)					All patients (n = 21)			
Variable	**Group**	**Pre**	**Post**	p^A	**Change (95% CI)**	p^B	**Pre**	**Post**	p^A	**Change (95% CI)**
Emotional score	PRED-G	5.9 (5.3, 6.6)	6.5 (5.5, 6.7)	.898	0.14 [#] (-0.02 – 0.75)	.173	6.2 (5.5, 6.6)	6.3 (5.6, 6.6)	.999	0.14 [#] (-0.09 – 0.35)
	HRV-G	6.3 (5.9, 6.6)	6.1 (5.8, 6.5)	.867	0.03 [#] (-0.56 – 0.31)					
Physical score	PRED-G	6.1 ± 0.6	6.5 ± 0.3	.085	0.32 (-0.05 – 0.70)	.398	6.1 ± 0.6	6.4 ± 0.4	.058	0.23 (-0.01 – 0.47)
	HRV-G	6.1 ± 0.7	6.2 ± 0.5	.432	0.13 (-0.22 – 0.47)					
Social score	PRED-G	6.4 ± 0.5	6.6 ± 0.3	.087	0.27 (-0.05 – 0.59)	.390	6.3 ± 0.6	6.5 ± 0.4	.025*	0.20 (0.03 – 0.37)
	HRV-G	6.3 ± 0.7	6.4 ± 0.5	.124	0.12 (-0.05 – 0.30)					
Global score	PRED-G	6.1 ± 0.7	6.4 ± 0.4	.067	0.33 (-0.03 – 0.69)	.187	6.1 ± 0.7	6.3 ± 0.5	.056	0.20 (-0.01 – 0.41)
	HRV-G	6.2 ± 0.7	6.2 ± 0.5	.565	0.06 (-0.17 – 0.30)					

CI, confidence interval; *HRV-G*, heart rate variability-guided training group; *PRED-G*, predefined training group

Data at pre- and post-intervention are delivered as mean ± *SD* or median (25^{th} and 75^{th} percentiles); p^A and p^B values refer to within-group and between-group differences, respectively; * denotes $p \leq .050$; [#] denotes median change instead of mean change

Table S5 Dietary intake

	PRED-G, n = 11		HRV-G, n = 10	
Variable	**Pre**	**Post**	**Pre**	**Post**
Energy (Kcal)	1325.8 (1245.1, 1406.4)	1278.3 (1116.8, 1576.7)	1264.9 (1134.6, 1466.3)	1221.5 (1185.4, 1489.1)
Water (mL)	2211.4 (1020.9, 2363.9)	2208.9 (1931.4, 2588.6)	1701.3 (996.7, 2443.3)	2270.0 (1812.2, 3239.3)
Protein (g)	83.4 (78.1, 90.0)	79.7 (69.6, 88.3)	81.4 (67.8, 89.3)	71.1 (62.8, 85.3)
Total fat (g)	41.9 (32.1, 54.8)	44.3 (34.3, 54.4)	47.3 (38.9, 54.0)	42.7 (34.8, 57.0)
Saturated (g)	10.7 (5.6, 13.4)	9.9 (8.0, 12.5)	10.3 (7.1, 12.9)	9.0 (7.5, 12.6)
Monounsaturated (g)	13.5 (9.4, 20.7)	15.2 (12.4, 18.2)	18.7 (11.9, 20.7)	17.4 (9.5, 21.0)
Polyunsaturated (g)	6.1 (5.2, 14.1)	7.4 (5.6, 15.8)	6.4 (4.8, 15.0)	6.1 (4.7, 16.4)
EPA (g)	0.28 ± 0.25	0.18 ± 0.22*	0.16 ± 0.12	0.18 ± 0.14
DHA (g)	0.49 (0.08, 0.86)	0.32 (0.08, 0.49)*	0.27 (0.21, 0.47)	0.31 (0.13, 0.49)
Cholesterol (mg)	283.1 ± 122.7	298.9 ± 101.2	297.7 ± 112.0	209.6 ± 74.9*
Carbohydrates (g)	155.2 ± 49.7	153.5 ± 40.5	158.9 ± 61.0	161.0 ± 37.2
Fiber (g)	19.6 ± 9.9	20.2 ± 11.5	21.0 ± 8.8	20.5 ± 8.6

DHA, docosahexaenoic acid; *EPA*, eicosapentaenoic acid; *HRV-G*, heart rate variability-guided training group; *PRED-G*, predefined training group

Data at pre- and post-intervention, as well as changes at follow-up are delivered as mean ± *SD* or median (25^{th} and 75^{th} percentiles); * and $ refer to within-group and between-group differences, respectively

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