Research Letters

Relationship between ankle–brachial index and carotid intima-media thickness in HIV-infected patients

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Both low and high ankle–brachial index are considered as indicators of systemic atherosclerosis in older HIV-negative adults. Whether those ankle–brachial index values are predictors of atherosclerosis in HIV-positive subjects remains unknown. We measured ankle–brachial index in 139 HIV-infected patients and compared the results obtained with carotid intima-media thickness, a well established marker of subclinic atherosclerosis. Ankle–brachial index was associated with carotid intima-media thickness. Patients with low ankle–brachial index, but not those with high ankle–brachial index, had high carotid intima-media thickness.

Cardiovascular disease (CVD) is of growing concern in HIV-infected patients receiving antiretroviral therapy [1]. Given the usual late onset of clinical events in the course of systemic atherosclerosis, clinicians caring for HIV-infected patients with significant cardiovascular risk would welcome disease surrogate markers. In the general population, carotid intima-media thickness (IMT) measured by ultrasonography has shown to correlate with coronary atherosclerosis [2], and it has been directly associated with an increased risk of myocardial infarction and stroke in older adults without a history of cardiovascular disease [3]. Carotid IMT measurement, however, is fairly expensive and not readily available. An alternative noninvasive imaging modality is ankle–brachial index (ABI), a simple and inexpensive diagnostic test that is a powerful indicator of systemic atherosclerosis and peripheral vascular disease and a strong predictor of death from cardiovascular causes in HIV-negative adults [4,5]. However, most previous studies validating ABI were performed in older adults with a high prevalence of diabetes [6–8]. Therefore, the significance of the cut-off points derived from those populations for younger patients with a lower prevalence of diabetes, such as HIV-infected subjects, remains unknown.

We investigated subclinic atherosclerosis by measuring both ABI and carotid IMT in HIV-infected patients. We studied the association between both techniques and the relationship of the abnormal values with cardiovascular risk factors and with factors associated with HIV infection.

Study participants were HIV-infected patients who were cared for in our HIV clinic from January 2006 to October 2007. The investigation was approved by the Ethics Committee for Clinical Research. A total of 139 patients gave their informed consent to perform both techniques. Clinical and laboratory data were obtained at the visit. Cardiovascular risk factors were defined according to the National Cholesterol Education Program [9].

To calculate the ABI, measurements of systolic arterial pressure (SAP) were obtained from bilateral brachial, dorsalis pedis, and posterior tibial arteries using a blood pressure cuff and a Doppler probe (SmartdopTM 30; Hayashi Denki Co. Ltd, Kawasaki, Japan). When the two brachial SAP differed, the highest reading was used as the denominator. To calculate the ABI of each leg, the ABI numerator used was the highest pressure measured (dorsalis pedis or posterior tibial) from that leg. The lowest ABI value was used to classify the patient into an ABI category. For determining the carotid IMT, B-mode high-resolution ultrasound was used following a standard procedure as described previously [10]. To quantify the degree of carotid artery wall thickening, the mean of six measures performed in the posterior wall of the left common carotid artery was taken.

We used the Mann–Whitney *U*-test to compare continuous variables and Fisher's exact test or χ^2 test for categorical variables. The cut-off point of greater than 0.8 mm was used to define a high IMT [3,11]. For ABI, the currently accepted cut-off point of less than 0.90, which is associated with a two- to three-fold increased risk of cardiovascular morbidity and mortality [4,5], was used to define an abnormal (low) value. As an increased cardiovascular disease mortality with ABIs greater than 1.40 has recently been demonstrated [6], an analysis of patients with ABI greater than 1.40 was also conducted. The discriminative power of other ABI cut-off points was also explored using receiver operating characteristic (ROC) curves and the IMT values as gold standard. The association of abnormal values of both techniques with cardiovascular risk factors and with factors associated with HIV infection was examined by univariate analysis. Correlations between HIV-1 plasma viral load and either IMT and ABI measurements were described using the Spearman correlation coefficient. Forward stepwise multiple linear regression models were constructed to estimate the prediction of IMT values by traditional cardiovascular risk factors, HIV-1 plasma viral load, and ABI measurements. Statistical analyses were performed using SPSS, version 12.0 (Chicago, Illinois, USA).

Table 1. Carotid intima media thickness (IMT) by ankle-brachial index (ABI) category in 139 HIV-infected patients.

	ABI < 0.90 (n = 4)	ABI 0.90–1.40 (n = 131)	ABI > 1.40 (n = 4)
Carotid IMT (mm), mean/median (interquartile range)	0.95/0.95 (0.83–1.07)[a,b]	0.68/0.66 (0.58–0.58)	0.75/0.72 (0.68–0.86)
Carotid IMT > 0.8 mm; n (%)	4 (100)[c]	25 (19.08)	1 (25)

[a]$P = 0.005$ (as compared with ABI ≥ 0.90).
[b]$P = 0.05$ (as compared with ABI ≥ 1.40).
[c]$P = 0.032$ (as compared with ABI ≥ 0.90).

The main baseline characteristics [mean (SD) unless otherwise indicated] of the 139 patients included in the study were: age, 45.8 (10.6) years; sex male [n (%)], 101 (72.7); current antiretroviral therapy [n (%)], 110 (79.1); time of exposure to antiretroviral therapy, 6.5 (4.25) years; HIV-RNA viral load less than 50 copies/ml [n (%)], 80 (57.5); CD4 cell count, 503.2 (287.45) cells/μl; lipodystrophy [n (%)], 31 (22.3); body mass index, 24.92 (3.85) kg/m^2; LDL cholesterol, 122.2 (37.36) mg/dl; HDL cholesterol, 46.5 (15.3) mg/dl; current smoking [n (%)], 85 (61.1); type 2 diabetes mellitus [n (%)], 14 (10.1); hypertension [n (%)], 40 (28.8); family history of early coronary disease [n (%)], 15 (10.8); low risk Framingham score (<10%) [n (%)], 91 (65.47%), moderate risk Framingham score (10–20%) [n (%)], 23 (16.55), high risk Framingham score (>20%) [n (%)], 25 (17.99). Fifty-eight (41.73%) patients had 0–1 cardiovascular risk factors, 22 (15.83%) had two risk factors, and 59 (42.45%) had three or more risk factors. No significant correlations were found between HIV-1 plasma viral load and IMT or ABI measurements, either in all patients ($r = 0.173$, $P = 0.063$; and $r = -0.078$, $P = 0.406$, respectively) or in those with 0–1 cardiovascular risk factor ($r = -0.084$, $P = 0.539$; $r = -0.13$, $P = 0.103$, respectively).

Thirty (21.58%) of the 139 patients had a carotid IMT greater than 0.8 mm. Patients with carotid IMT greater than 0.8 mm were older [median, interquartile range (IQR)], 57.65 (47.34–70.68) years vs. 43.28 (37.67–47.42) years; $P < 0.001$], had a higher frequency of hypertension (73 vs. 20%; $P < 0.001$) and dyslipidaemia (80.7 vs. 25.71%; $P < 0.001$), a higher Framingham score [17 (6–20) vs. 4 (1–10); $P < 0.001$], were less likely to be current smokers (46.15 vs. 68.57%; $P = 0.019$), and tended to have a lower CD4 cell count [410 (227–582) vs. 460 (307–740) cells/ml; $P = 0.164$] than those with lower IMT. Considering the IMT as the dependent variable, multiple linear regression analysis that included age, hypertension, dislipidemia, current smoker status, ABI, Framingham score, and HIV-1 plasma viral load indicated ABI (standardized beta, -0.175), hypertension (standardized beta, $+0.277$), and age (standardized beta, $+0.411$) as the best predictors (adjusted $r^2 = 0.362$; $P < 0.001$). When only patients with two or more cardiovascular risk factors were included in the analyses, ABI (standardized beta, -0.231), hypertension (standardized beta, $+0.433$), current smoker status (standardized

beta, $+0.339$), and age (standardized beta, $+0.542$) were also the best predictors of IMT (adjusted $r^2 = 0.312$; $P < 0.001$).

Associations between ABI and carotid IMT are shown in Table 1. According to ROC analysis, the ABI cut-off point of less than 0.90 had the best discriminatory power between patients with normal and abnormal carotid IMT. All patients with ABI less than 0.90 were men, they had higher carotid IMT [0.95 (0.83–1.07) vs. 0.66 (0.58–0.78) mm; $P = 0.005$], more traditional cardiovascular risk factors [4 (2.5–4.7) vs. 2 (1–3); $P = 0.015$], and lower CD4 cell count [220 (54.7–267.5) vs. 450 (310–710) cells/μl; $P = 0.009$] than those with ABI greater than 0.90.

No differences were seen in the carotid IMT between patients with high (>1.40) and normal (0.90–1.39) ABI. When patients with two or more cardiovascular risk factors were analysed separately, those with high (>1.40) ABI had lower total cholesterol levels [160.5 (102.2–196.2) vs. 207 (174.2–243.5) mg/dl; $P = 0.024$], lower LDL cholesterol levels [80.5 (48.7–120.5) vs. 135 (102.5–155.5) mg/dl; $P = 0.01$], and a lower Framingham score [6.5 (3.7–10) vs. 11 (7–20); $P = 0.02$] than subjects with normal ABI.

We found that patients with low ABI, according to the accepted cut-off point value for general population (<0.90), had a high carotid IMT, suggesting that, in HIV-infected patients, this value may indeed be a surrogate marker of subclinical atherosclerosis. Despite having a very low sensitivity, its high specificity makes it a clinically meaningful predictor for indicating patients with high IMT. In contrast, we did not find an association between high (>1.40) ABI and carotid IMT measurements. Moreover, patients with two or more cardiovascular risk factors and ABI greater than 1.40 had lower LDL cholesterol levels and lower Framingham score than those with normal ABI. That cut-off point was associated with increased cardiovascular disease mortality among the Strong Heart Study in which the participants were American Indians, older, and with a much higher prevalence of diabetes than the HIV-infected patients included in the present study [6].

Our present study did not address the clinical impact of the ABI measurements but, given its simplicity and high

positive predictive value, we believe that they might have implications for management of individual HIV-infected patients with cardiovascular risk factors. Although our observations need to be confirmed in large longitudinal studies with clinical endpoints, the data support the current recommendation for HIV-negative patients with an ABI less than 0.90 to be implemented in HIV-infected patients [9]; an aggressive approach to risk factors modification aimed to delay the progression of subclinical atherosclerosis is warranted in those patients.

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Impact of antiretroviral therapy on chemokine (C-C motif) receptor 5 expression in HIV patients followed for over 2 years

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Suppression of HIV replication using highly active antiretroviral therapy (HAART) might influence chemokine (C-C motif) receptor 5 expression on infected cells and therefore modulate the activity of chemokine (C-C motif) receptor 5 antagonists. Chemokine (C-C motif) receptor 5 expression was examined longitudinally in 26 HIV-infected adults who initiated HAART. Long-term suppression of plasma HIV-RNA did not significantly influence chemokine (C-C motif) receptor 5 expression on T lymphocytes. Therefore, the activity of chemokine (C-C motif) receptor 5 antagonists should not differ before and following HIV suppression on HAART.

The chemokine (C-C motif) receptor 5 (CCR5) acts as coreceptor for HIV entry into target cells and therefore plays a major role in HIV pathogenesis [1−4]. Expression of CCR5 on the surface of T lymphocytes varies among individuals [4]. CCR5 expression has been directly associated with disease progression in HIV-infected patients; those who express high number of CCR5 molecules at the surface of CD4+ T lymphocytes tend to show high viral load, increased immune activation and low CD4 cell counts [5−7]. Scarce and controversial data are available about the effect of highly active antiretroviral therapy (HAART) on CCR5 expression on T lymphocytes. If CCR5 upregulation is linked to immune activation, a decrease of CCR5 expression could be expected following diminished immune activation as a result of HIV suppression under HAART [8,9]. By contrast, similar CCR5 expression before and after HAART could suggest that CCR5 expression is not influenced by viral replication and it could be more inherent to each individual [5]. CCR5 antagonists are a