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# Markers of preclinical vascular disease and left ventricular diastolic dysfunction in patients with HIV infection.

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**Abstract**

**Background:** HIV infected patients have an increased cardiovascular risk that may be linked not only to the infection itself but also to the metabolic side effects of the antiretroviral therapy.

**Aim:** The aim of our study was to determine markers of aortic arterial stiffness, carotid intima-media thickness (IMT) and parameters of left ventricular diastolic function and to establish the relationship between these vascular and cardiac parameters in HIV infected patients.

**Material and method:** In this cross sectional case control study 43 patients with HIV infection and 25 healthy controls, matched for age and sex were enrolled. Aortic pulse wave velocity (PWV) and augmentation index (AIx) using an oscillometric method were measured. Carotid IMT and left ventricular systolic and diastolic function were determined by ultrasonography. Clinical status, laboratory parameters (glucose and lipid metabolism), and markers of disease activity were also recorded.

**Results:** In patients with HIV infection PWV was increased when compared to controls (p=0.02), but there were not significant differences in carotid IMT (p= 0.17). There were no differences for classical risk factors between HIV infected patients and controls with the exception of triglycerides level (p<0.001). HIV infected patients had a significant reduction in E/A ratio when compared to controls (p= 0.03). Significant differences were found for age (p=0.001), PWV (0.002) and carotid IMT (p=0.02) between patients with and without left ventricular diastolic dysfunction (LVDD). In multiple regression analyze only PWV remained correlated with LVDD (OR = 2.90, 95%CI: 1.41-5.97, p=0.004)

**Conclusions:** In patients with HIV infection, without overt cardiovascular disease, arterial stiffness was increased. This finding is correlated with markers of LVDD. Increased arterial stiffness may be one of the mechanisms implicated in the alteration of left ventricular diastolic function in HIV infected patients.

**Keywords:** arterial stiffness, left ventricular diastolic dysfunction, HIV infection

## Introduction

It has been reported that patients with HIV infection have an increased cardiovascular morbidity and mortality [1]. The increased cardiovascular risk was initially found among patients without antiretroviral treatment (ART) [2]. In the last two decades the introduction of efficient antiviral therapy transformed HIV infection into a chronic disease but, at the same time, a positive correlation between this therapy and an increased cardiovascular risk was also reported. Patients with HIV infection have the same classical cardiovascular risk factors as the general population but in addition to HIV infection itself, the state of chronic inflammation and ART may increase their cardiovascular risk [3].

Arterial stiffness is now considered to be an independent predictor factor for cardiovascular events and mortality [4-6]. Aortic pulse wave velocity (PWV), marker of arterial stiffness, was strongly correlated with the risk of cardiovascular events [7]. Increased arterial stiffness has been reported in both treated [8] and naïve HIV infected patients [9].

Left ventricular diastolic dysfunction (LVDD) may be the first pathological finding of an underlying cardiac

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disease [10]. It was associated with an increased risk of cardiovascular events and death [11]. In HIV infected patients a highly prevalence of diastolic dysfunction compared to the general population was reported [12,13]. Association between brachial-ankle PWV, as a measure of arterial stiffness and parameters of LVDD, was found in patients with hypertension [14] and in the general population [15].

Carotid IMT has been suggested to be used as an early indicator of preclinical atherosclerosis and as a predictor of cardiovascular risk [16]. It was reported that IMT is increased in HIV infected patients compared to normal controls [8].

The aim of our study was to evaluate the association of arterial stiffness parameters and of carotid IMT with LVDD in patients with HIV infection.

## Material and methods

The study group consists of 43 consecutive patients, 17 women (40%) and 26 men (60%), with documented HIV infection enrolled at the Infectious Diseases Hospital, Cluj- Napoca, Romania between 2009-2010. Patients with chronic renal diseases, malignancies, concomitant hepatitis C virus infection, systemic infections, and known cardiac or respiratory diseases were excluded. The control group consists of 25 healthy controls matched for age, gender and smoking status, tested to be HIV-antibody negative. Patients and controls were not under vasoactive medication.

All participants gave their informed consent and the study was approved by the institution's Ethics Committee.

### Clinical and laboratory assessment

Clinical assessment of subjects included physical examination and 12-lead electrocardiography. History of smoking was noted, patients being divided in two groups smokers and non-smokers. Body mass index (BMI = weight/height$^2$, kg/m$^2$), was calculated. Fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG) and blood creatinine levels were determined. Normal values fasting plasma glucose were < 120 mg/dl. Hyperlipidemia was considered for total cholesterol > 200 mg/dl and triglycerides > 140 mg/dl. Obesity was defined at a BMI ≥30kg/m².

The metabolic syndrome was defined according to the National Cholesterol Education Programme–Adult Treatment Panel (NCEP-ATP) [17].

Disease activity was evaluated by the determination of CD4+ cell count and of the viral load (copies/ml).

Depending on the therapy the patients group was formed by untreated patients, defined as no ART in the preceding 6 months, and treated patients divided in two groups, one group with reverse transcriptase inhibitors (RTI) therapy and the other with combined RTI and protease inhibitors (PI) therapy. Cumulative exposure to ART and to specific drug classes was noted.

Treated patients were divided into to groups: with detectable viremia, defined as >24 weeks antiretroviral therapy with the most recent two HIV RNA levels > 75 copies/ml, and treated patients with undetectable viremia defined as >24 weeks antiretroviral therapy with the most recent two HIV RNA levels < 75 copies/ml.

### Vascular parameters

*Parameters of arterial stiffness*

PWV and augmentation index (AIx) were measured using an oscillometric device (Arteriograph, TensioMed, Budapest, Hungary). Patients were examined in the morning, in the supine position, after 5 min of bed rest at a room temperature of 22° C. Subjects have to refrain, for at least 3 h before measurements, from drinking beverages containing caffeine and from smoking, and 10 h before measurements from drinking alcohol. Values of PWV (m/s) and AIx (%) were calculated automatically by the apparatus after the introduction of the distance measured between the sternal notch and the symphsis pubica. Concomitantly, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP) and pulse pressure (PP) were registered with the same device. All examinations were done by a single experienced physician.

Normal systemic arterial pressure was considered for values equal or inferior to 140 mmHg for the systolic pressure and 90 mmHg for the diastolic pressure.

*Carotid ultrasound examination*

Carotid B-mode ultrasonographic examination was performed using Aloka Prosound alpha 10, Tokyo, Japan ultrasound machine using 7.5 to 13 MHz linear probe by the same examiner. The common carotid, the bifurcation and at least the first 2 cm of the internal and external carotids arteries were examined in the short and long axes. Common carotid artery IMT was measured using images of the far wall at 10 mm proximal to the bifurcation. We defined as plaques a focal echogenic structure with IMT > 1.2 mm; pathological IMT was considered with values > 0.9 mm. The intraobserver reproducibility was assessed in 6 healthy patients who were examined by the same observer twice, one week apart. The median intersession coefficient was: 2.28.

*Assessment of diastolic function*

Transthoracic echocardiography was performed using the same ultrasound machine and a 2.5 MHz transducer. Left ventricular diastolic function was assessed with

pulsed-wave Doppler obtained with the transducer in the apical 4-chamber view, with the Doppler beam aligned perpendicular to the plane of the mitral annulus and the Doppler sample volume between the tips of the mitral leaflets. Color M-mode Doppler echocardiography was done in the apical 4-chamber view, with the M-mode cursor aligned parallel with left ventricular inflow, in order propagation velocity (Vp) - the slope of the first aliasing velocity from the mitral annulus in early diastole to 4 cm distally into the left ventricular cavity. Three consecutive cardiac cycles were analyzed and average values were calculated. Normal left ventricular function was considered for the following parameters: E wave deceleration time (EDT) <220 ms, E/A wave velocity ratio between 1and 2, IVRT <100ms, Vp > 45 cm/s.

Diastolic dysfunction was evaluated according to the following classification: grade 1 (delayed relaxation) – EDT > 220 ms, E/A <1, IVRT>100ms; Vp < 45 cm/s; grade 2 (pseudonormal filing) – EDT between 150 and 200 ms, E/A: 1-2, IVRT between 60 and 100 ms; Vp < 45 cm/s; grade 3 (restrictive filing) – EDT < 150 ms, E/A > 2, IVRT<60 ms; Vp < 45 cm/s [18].

Left ventricular systolic function was determined using modified Simpson method. Left ventricular systolic dysfunction was defined as left ventricular ejection fraction <50%. Cardiac measurements were made in accordance with the recommendations of The American Society of Echocardiography [19].

**Statistical analysis**

For continuous variable mean ± standard deviations (SD) were given and frequencies for qualitative variables. To test normal distribution we used the Shapiro-Wilk test; for comparing two means of a continuous variable we used the t-test or Mann-Whitney Rank Sum Test. Chi-square test were used to evaluate the relation between qualitative variables. Spearman or Pearson correlation coefficient was used to evaluate the correlation between two variables. The diastolic dysfunction as dependent variable and all other studied parameters as an independent variable were included in a logistic regression model (Forward LR). The error threshold was considered 0.05. The analyses were performed in SPSS 13.0.

**Results**

Clinical and laboratory parameters of the patients and control groups are summarized in Table I. Mean age of the patients was 37.8±13.9 years and mean disease duration 58.8±45.6 months. There were no differences between patients and healthy controls for BMI, TC, HDL–cholesterol, fasting plasma glucose and creatinine levels.

Table I. Clinical and biological parameters in HIV infected patients.

| | **Patients with HIV infection N=43** | **Healthy controls N=25** | **P** |
|---|---|---|---|
| Age (years) | 37.8±13.9 | 37.8±12.7 | 0.79 |
| Sex: males/females (%) | 26 (60.5%)/17(39.5%) | 15(60%)/10(40%) | 0.98 |
| BMI (kg/m²) | 23.6±3.7 | 22.84±1.2 | 0.32 |
| Current smokers (%) | 14 (32.5%) | 5 (20%) | 0.32 |
| Duration of HIV infection (month) | 58.8±45.6 | - | - |
| Fasting plasma glucose (mg/dl) | 88.4±9.2 | 88.68±88.7 | 0.52 |
| Total cholesterol (mg/dl) | 186.8±52.2 | 173.4±33.5 | 0.21 |
| Triglycerides (mg/dl) | 163.5±83.2 | 87.9±30.1 | **<0.001** |
| High-density lipoprotein cholesterol (mg/dl) | 44.8±4 | 45.7±5 | 0.68 |
| Creatinine (mg/dl) | 0.87±0.17 | 0.84±0.12 | 0.58 |
| Viral load (copies/ml) | 200055±77684.9 | - | - |
| CD4+ (cells/mm³) | 402.6±232.9 | - | - |
| HIV specific treatment, n (%) | 37 (86%) | | |
| ARVT exposure (month) | 55.2±45.6 | - | - |
| RTI exposure (month) | 55.2±45.2 | - | - |
| PI exposure (month) | 32±20.4 | - | - |

Data are means ± standard deviation or number (%)
*Abbreviations:* BMI = body mass index; ARVT = antiretroviral treatment; RTI = reverse transcriptase inhibitors; PI = protease inhibitors

Only triglycerides levels were significantly higher in patients than in controls.

All patients and controls had normal values for fasting plasma glucose and their BMI < 30 kg/m². None of them full fulfilled the criteria of metabolic syndrome. There were 14 patients (32.5%) with hyperlipidemia. All subjects from the control group had normal values of lipids.

A total of 37 patients (86%) had ARV therapy: 18 patients (41.8%) were under RTI therapy and 19 (44.2%) received combined RTI and PI therapy. Detectable viremia was found in 39 patients (90.7%).

Vascular and cardiac parameters are listed in table II.

All patients had normal values of arterial pressure. We found significant differences for PWV and E/A ratio between patients and controls. Carotid IMT was increased in patients more than in controls but differences were not statistically significant. No carotid plaques were found in the study group.

Aortic PWV correlated with some of the classical cardiovascular risk factors, such as age (p<0.001), BMI (p=0.005), MBP (p=0.04), FPG (P=0.01) and TC (p=0.04), but it did not correlate with the male gender (p=0.45) and smoking status (p=0.73). We found an inverse correlation of PWV with E/A ratio (p=0.04), peak E (p=0.008), and a direct correlation with IVRT (p=0.001), and with left atrial diameter (p<0.001). No correlation with viral infection or antiretroviral treatment exposure was found (table III).

Carotid IMT correlated with age (p<0.001), BMI (p<0.001) and TC (p=0.04). No correlation was found with current CD4+ values, viral load, and duration HIV infection, exposure to ARV therapy or to different types of treatment (IRT or IP). Carotid IMT inversely correlated with E/A ratio (p=0.002), peak E (<0.001) and left atrial diameter (p<0.001) (Table 3). We found no correlation for carotid IMT with male gender (p= 0.35) and current smoking status (p= 0.63).

There were 16 patients (37%) with LVDD grade I EDT > 220 ms, E/A <1, IVRT>100ms; Vp < 45 cm/s. None of the subjects from the control group had diastolic dysfunction.

Clinical, biological and vascular parameters in HIV patients with diastolic dysfunction compared with those without diastolic dysfunction are listed in table IV.

There was significant increase for age, PWV and carotid IMT in patients with diastolic dysfunction compared to patients without diastolic dysfunction.

In multivariate regression analysis, after adjusting for age, only PWV velocity was correlated with diastolic dysfunction (OR: 2.90, 95%CI: 1.41-5.97, p=0.004).

Table II. Vascular and cardiac parameters in patients with HIV infection

| | **Patients with HIV infection N= 43** | **Healthy controls N=25** | **P** |
|---|---|---|---|
| Systolic blood pressure (mmHg) | 122±14.1 | 118.6±11.5 | 0.49 |
| Diastolic blood pressure (mmHg) | 72.7±10.9 | 74±8.9 | 0.47 |
| Mean blood pressure (mmHg) | 88.7±10.6 | 88.9±9.9 | 0.94 |
| Brachial pulse pressure (mmHg) | 48.1±10.8 | 44.5±11.1 | 0.62 |
| Aortic pulse wave velocity (m/s) | 5.59±1.16 | 4.43±1.04 | **0.02** |
| Augmentation index (%) | 8.5±12.5 | 2.9±19.4 | 0.49 |
| Heart rate (b/min) | 76.02±10.54 | 72±9.52 | 0.06 |
| Carotid IMT (mm) | 0.59±0.15 | 0.51±0.09 | 0.17 |
| EDT (ms) | 213.8±44 | 206±31.2 | 0.68 |
| E/A ratio | 1.21±0.32 | 1.33±0.41 | **0.03** |
| IVRT (ms) | 82.6±14.4 | 80.8±7.2 | 0.77 |

Data are means ± standard deviation
*Abbreviations:* IMT=intima-media thickness, EDT= E-wave deceleration time; E/A ratio = transmitral E/A ratio; IVRT = isovolumetric relaxation time.

Table III. Correlations of vascular markers with clinical, biological and cardiac parameters in HIV infected patients.

| Parameters | Correlation coefficient | P |
|---|---|---|
| **Aortic pulse wave velocity (m/s)** | | |
| Age (years) | 0.67 | **<0.001** |
| Male gender | 0.23 | 0.45 |
| Smoking status | 0.18 | 0.73 |
| BMI (kg/m²) | 0.42 | **0.005** |
| Systolic blood pressure (mmHg) | 0.28 | 0.07 |
| Diastolic blood pressure (mmHg) | 0.16 | 0.32 |
| Mean blood pressure (mmHg) | 0.34 | **0.04** |
| Fasting plasma glucose (mg/dl) | 0.28 | 0.09 |
| Total cholesterol (mg/dl) | 0.31 | **0.04** |
| Triglycerides (mg/dl) | 0.30 | **0.05** |
| E/A ratio | -0.31 | **0.04** |
| Peak E (m/s) | -0.56 | **0.008** |
| Peak A (m/s) | -0.13 | 0.39 |
| EDT (ms) | 0.16 | 0.32 |
| IVRT (ms) | 0.32 | **0.001** |
| Left atrium (mm) | 0.58 | **<0.001** |
| CD4+ (cells/mm³) | -0.18 | 0.24 |
| Viral load (copies/ml) | -0.13 | 0.41 |
| Duration of HIV-infection (months) | 0.04 | 0.78 |
| ARV treatment exposure (months) | 0.08 | 0.61 |
| RTI exposure (months) | 0.05 | 0.74 |
| PI exposure (months) | -0.12 | 0.44 |
| **Carotid intima-media thickness (mm)** | | |
| Age (years) | 0.73 | **<0.001** |
| Male gender | 0.28 | 0.35 |
| Smoking status | 0.14 | 0.63 |
| BMI (kg/m²) | 0.53 | **<0.001** |
| Systolic blood pressure (mmHg) | 0.23 | 0.13 |
| Diastolic blood pressure (mmHg) | 0.15 | 0.32 |
| Mean blood pressure (mmHg) | 0.19 | 0.21 |
| Fasting plasma glucose (mg/dl) | 0.10 | 0.52 |
| Total cholesterol (mg/dl) | 0.31 | **0.04** |
| Triglycerides (mg/dl) | 0.30 | **0.05** |
| E/A ratio | -0.47 | **0.002** |
| Peak E (m/s) | -0.58 | **<0.001** |
| Peak A (m/s) | 0.05 | 0.75 |
| EDT (ms) | 0.06 | 0.68 |
| IVRT (ms) | 0.37 | **0.01** |
| Left atrium (mm) | 0.57 | **<0.001** |
| CD4+ (cells/mm³) | -0.19 | 0.21 |
| Viral load (copies/ml) | -0.05 | 0.77 |
| Duration of HIV-infection (months) | 0.13 | 0.39 |
| ARVT exposure (months) | -0.07 | 0.67 |
| RTI exposure (months) | -0.15 | 0.35 |
| PI exposure (months) | -0.09 | 0.56 |

Abbreviations: *BMI = body mass index; peak E = early trans-mi*tral flow velocity; Peak A = atrial flow velocity; E/A ratio= ratio of early trans-mitral flow velocity to atrial flow velocity; EDT= E-wave deceleration time; IVRT = isovolumic relaxation time; ARVT=antiretroviral treatment; RTI=reverse transcriptase inhibitors; PI=protease inhibitors.

Table IV. Clinical, biological and vascular parameters in HIV patients with and without diastolic dysfunction

| | Patients without DD N=27 | Patients with DD N=16 | P |
|---|---|---|---|
| Age (years) | 32.6±12 | 46.7±12.6 | **0.001** |
| Gender (Male/female) | 16 (59.3%)/11(40.7%) | 10 (62.5%)/6 (37.5%) | 0.83 |
| Current smokers (%) | 8 (30%) | 6 (37.5%) | 0.59 |
| BMI (kg/m²) | 23.3±3.8 | 23.9±3.4 | 0.59 |
| Viral load | 28 748±96 654.8 | 5386.9±18 419.3 | 0.91 |
| PWV (m/s) | 5.1±0.9 | 6.3±1.2 | **0.002** |
| AIx (%) | 6.94±12.8 | 11.1±11.9 | 0.29 |
| IMT (mm) | 0.54±0.10 | 0.67±0.19 | **0.02** |
| SBP (mmHg) | 120.1±13.2 | 125.3±15.4 | 0.25 |
| DBP(mmHg) | 71.2±10.9 | 75.1±10.9 | 0.19 |
| MAP(mmHg) | 87.2±10.8 | 91.2±10.2 | 0.14 |
| PP (mmHg) | 48±9.2 | 48.3±13.4 | 0.94 |
| TC (mm/dl) | 179.1±43.1 | 199.7±64.2 | 0.21 |
| TG (mm/dl) | 152.8±75.2 | 181±95 | 0.46 |
| FPG (mm/dl) | 86.8±7.4 | 91±11.4 | 0.21 |
| CD4+ (cells/mm³) | 422.4±250.9 | 369.3±202.5 | 0.53 |
| HIV specific treatment n (%) | 24 (88.9%) | 13 (81.2%) | 0.64 |
| Duration HIV infection (months) | 54.2±49 | 66±41.5 | 0.34 |
| ARV therapy exposure (months) | 57.4±50.5 | 51.7±37 | 0.84 |
| RTI exposure (months) | 53.3±49.7 | 58.6±38.2 | 0.55 |
| PI exposure (months) | 36.5±49.4 | 24.7±44.4 | 0.49 |
| Dyslipidemia (%) | 8 (30%) | 6 (37.5%) | 0.59 |

Data are means ± standard deviation
*Abbreviations:* BMI = body mass index; PWV = aortic pulse wave velocity; Aix = augmentation index; IMT = carotid intima-media thickness; SBP =systolic blood pressure; DBP = diastolic blood pressure; MBP = mean blood pressure; PP = pulse pressure; TC = total cholesterol; TG = triglycerides; FPG = fasting plasma glucose; ART = anti-retroviral treatment; RTI = reverse transcriptase inhibitors; PI = protease inhibitors; DD = diastolic dysfunction

## Discussion

In this study, patients with HIV infection had an increased aortic pulse wave velocity compared to controls. These results are concordant with previous studies that found increased arterial stiffness in patients with HIV infection compared with healthy controls [9,20-22].

The mechanism for this increase is not completely understood, but the implication of classical cardiovascular risk factors, of systemic chronic inflammation [8] and the adverse metabolic effects of antiretroviral therapy are discussed [8,21,22].

Patients with HIV infection are exposed, as in the general population, to the same classical cardiovascular risk factors that have been shown to be associated with increased arterial stiffness [4,5,23,24]. In this study we found direct correlations of aortic PWV with age, BMI, mean arterial pressure, total cholesterol and triglycerides. When compared to controls only triglycerides values were significantly increased in HIV infected patients. With the exception of dyslipidemia found in 14 patients (32.5%), our patients had no other important cardiovascular risk factors, such as diabetes mellitus, arterial hypertension, metabolic syndrome or obesity.

Concerning the role of viral infection and of the immune system, in this study aortic PWV was not correlated with viral load, duration of HIV infection and current CD+ level.

Many data sustain the role of a persistent low grade inflammation in the development of large arteries stiffness [25]. Higher rates of inflammation have been reported in HIV infected patients [8]. Kaplan et al, among a cohort of HIV-infected women, studied the association of carotid artery stiffness with expression of markers of T cell activation (CD38+HLA-DR+). They suggested that activation of CD4+ T cells is associated with increased vascular stiffness among HIV-infected women [26]. Another recent study showed that arterial stiffness was associated with a low nadir CD4+ count, in HIV-infected individuals concluding that an early ARV treatment may be of benefit in reducing arterial modifications [27]. In our study we did not find a correlation between CD4+ and arterial stiffness markers, but we measured only current and not nadir CD4+ levels.

Concerning the role of specific ARV therapy in the development of arterial stiffness in HIV infected patients, in the present study aortic PWV did not correlate with exposure to ARV therapy.

Literature data regarding the effect of ARV treatment on arterial stiffness are conflicting. Several studies have reported an association between antiretroviral treatment and increased arterial stiffness in HIV-infected patients [21,28,29]. Prolonged administration of ARV therapy, particularly PI, has been shown to induce insulin resistance and dyslipidemia [3,30,31]. Van Vonderen et al found that the effect of ARV therapy on the arterial wall stiffening in patients with HIV may occur preferentially in muscular femoral artery than in elastic carotid artery [8]. Other studies found no influence of HIV specific antiretroviral therapy on arterial stiffness [22] or a possible favorable interaction related to its anti-inflammatory effect and to the reduction of immunosupression [27].

**HIV infection and carotid IMT**

We found increased carotid IMT in patients compared with controls but the differences were not statistically significant. Carotid IMT in our study correlated with some classical risk factors such as age, BMI and lipid values. We did not find an association between IMT and parameters of HIV infection (viral load, duration of HIV infection, current CD4 count) or ARV treatment (duration of exposure, type of medication).

Data from studies that investigated the relationship between HIV infection and carotid IMT are conflicting. In a well-matched cohort of HIV infected and uninfected patients, Currier et al did not find significant differences for carotid IMT between patients and controls and between patients treated with PI and those without PI exposure [32]. Merci et al, in a multi-center prospective study of 423 HIV-infected subjects, concluded that only conventional cardiovascular risk factors are independently associated with increased IMT [33]. Two recent studies reported increased carotid IMT in HIV infected patients than in controls with similar age and sex distribution but significant differences in important cardiovascular risk factors [8,34]. Grunfeld et al, in a cross sectional study of HIV-infected and control subjects without pre-existing cardiovascular disease from the study of Fat Redistribution and Metabolic Change in HIV infection (FRAM) and the Multi-Ethnic study of Atheroslerosis (MESA), measured IMT at the level of common and internal carotid artery. They concluded that the stronger association of HIV infection with IMT in the internal/bulb region compared to the common carotid may explain previous discrepancies in the literature [35].

**HIV infection and left ventricular diastolic dysfunction**

The prevalence of LVDD in our study was 37%. Patients with LVDD had a significant increase in age, PWV and carotid IMT compared to controls. After adjusting for age in a multiple regression logistic analyze we found that only aortic PWV was independently associated with LVDD.

LVDD detected by echocardiography has been previously reported in HIV infected patients. The prevalence found in echocardiographic studies varies between 37 to 64%, in HIV-infected patients without known cardiovascular disease [36,37,38] and between 2% to 6%, in the general population younger than 55 years [39]. Reinsch et al, found that HIV-infected patients with diabetes mellitus or arterial hypertension were approximately four times more likely to develop LVDD than those without diabetes mellitus or hypertension. Those with hyperlipidemia were approximately one and a half times more likely to have diastolic dysfunction than those without hyperlipidemia (13). The prevalence of LVDD in our study was similar with the lowest prevalence reported in HIV infected patients. This reduced prevalence may be explained by the fact that patients included in our study were young and without important cardiovascular risk factors associated.

The pathogenesis of LVDD in HIV infected patients is not known but it is likely multifactorial. The implication of each potential mechanism, i.e. HIV infection itself, the side effects of ARV treatment or the metabolic abnormalities associated, is difficult to establish. An altered left ventricle diastolic function was found in naïve untreated patients, in the early stage of HIV infection [40]. The authors observed that indices of LVDD correlated with HIV-RNA copy number and with elevated plasma levels of TNF-α, suggesting that HIV may de-

termine diastolic dysfunction through inflammatory and immunological responses [40]. HIV may directly affect cardiomyocytes. Autopsy studies have found sequences of HIV-1 in myocardium of patients with HIV infection [41]. The alteration of the diastolic function of the left ventricle was also reported in treated patients and it was associated with lower CD4 count and longer duration of non nucleoside reverse transcriptase inhibitors therapy. The authors suggested that advanced immunodeficiency and/or side effects from medication may mediate the development of LVDD [12].

Increased PWV has been associated with ultrasonographically determined LVDD in patients with hypertension [14] and also, in the general population [15].

To our knowledge this is the first report regarding the association between increased aortic PWV and LVDD in HIV-infected patients. Therefore increased arterial stiffness in HIV population might be considered a risk factor for diastolic dysfunction.

We did not find an independent association between carotid IMT and LVDD. There are no data regarding this association in HIV – infected patients. Several studies in hypertensive patients have shown an association of carotid IMT with markers of LVDD [42-44]. However, in general this correlation has not been proved [15].

Our study has several limitations. Due to the cross-sectional analysis we can not firmly establish the cause-effect relationship between vascular and cardiac parameters. The sample size of our patient group was small and without important cardiovascular risk factors associated. Also, we did not make a separate analysis of comparison between patients treated and untreated. Finally we used only pulse wave parameters of mitral flow for the determination of LVDD.

## Conclusions

Patients with HIV infection have increased arterial stiffness and LVDD compared to controls. Our study suggested that aortic pulse wave velocity might be an independent predictor of LVDD in young HIV infected patients without overt cardiovascular and metabolic diseases.

**Conflict of interest**: none

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