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Arterial stiffness and carotid intima-media thickness in HIV infected patients

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Abstract

Background: Cardiovascular disease is an increasing cause of morbidity and mortality in HIV-infected patients. The increased cardiovascular risk is linked to traditional risk factors for atherosclerosis but also, to HIV infection itself which can damage the arterial wall and the antiretroviral therapy (ART) implicated in metabolic disturbances. The aim of our study was to identify the effects of HIV and ART on carotid artery intima-media thickness (C-IMT) and on arterial stiffness, parameters which are used for the evaluation of cardiovascular risk. **Patients and methods:** A cross-sectional case-control study of 63 HIV-infected patients (56 exposed to ART, 7 ART naive) and 36 controls matched for age and sex was performed. C-IMT, and arterial stiffness were measured ultrasonographically using an ALOKA ProSound α 10 echo-device. Parameters of arterial stiffness were measured at the common carotid and brachial arteries. **Results:** HIV-infected patients had a greater C-IMT than controls ($p<0.01$). There were significant differences regarding arterial stiffness parameters in HIV infected patients compared to controls, and between the groups of patients with different types of ART, especially at the level of carotid artery. Patients with HIV infection had reduced carotid compliance compared to controls ($p<0.01$). Patients exposed to reverse transcriptase inhibitort (RTI), had increased β stiffness index ($p=0.01$) and carotid PWV ($p=0.02$) and reduced carotid compliance ($p<0.01$) compared to controls. **Conclusions:** HIV infection and ARV treatment is associated with increased C-IMT, and an increase in the arterial stiffness of the large arteries. These vascular modifications are possible causes of increased cardiovascular risk observed in HIV infected patients.

Keywords: HIV infection, carotid intima-media thickness, arterial stiffness

Rezumat

Ipoteza de studiu: Afecțiunile cardiovasculare sunt o cauză tot mai frecventă de morbiditate şi mortalitate la pacienții infectați cu HIV. Riscul crescut cardiovascular este legat de factorii de risc tradiționali dar şi de infecția cu HIV per se care poate leza peretele arterial şi de terapia antiretrovirală, implicată în apariția perturbărilor metabolice. Scopul acestui studiu a fost de a determina efectele infecției cu HIV şi a terapiei antiretrovirale asupra grosimii intimă-medie carotidiene (GIM-C) şi a rigidității arteriale, parametrii utilizați pentru evaluarea riscului cardiovascular. **Pacienți şi metodă:** Am efectuat un studiu transversal, cazmartor, pe 63 pacienți infectați cu HIV (56 sub tratament antiretroviral, 7 fără tratament) şi 36 subiecți sănătoşi potriviți ca vârstă şi sex. GIM-C şi rigiditatea arterială au fost determinate ultrasonografic, folosind un aparat ALOKA ProSound α 10. Parametrii de rigidiate arterială au fost măsurați la nivelul arterelor carotide comune şi brahiale. **Rezultate:** Pacienții infectați cu HIV au avut GIM-C mai mare decât lotul martor ($p<0.01$). Am găsit diferențe semnificative în ceea ce priveşte parametrii de rigiditate arterială între lotul de bolnavi şi lotul martor şi între grupele de pacienți cu tipuri difetrite de tratament antiretroviral, în special la nivelul arterei carotide. Pacienții infectați cu HIV au avut complianța carotidiană ($p<0.01$) redusă comparativ cu lotul martor. **Concluzii:** Infecția cu HIV şi tratamentul antiretroviral determină creşterea GIM-C şi a rigidității arteriale. Aceaste modificări vasculare reprezintă cauze posibile ale riscului cardiovascular crescut la pacienții infectați cu HIV.

Cuvinte cheie: infecția cu HIV, gosimea intimă-medie carotidiană, rigiditatea arterială

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Cardiovascular diseases (CVD) are the first cause of mortality in the general population. In HIV infected patients, CVD, which includes coronary heart disease, stroke, congestive cardiac failure and hypertensive disease, is the leading cause of death in both the United States and Europe [1,2].

Mortality rates from HIV infection are in decline in

developed countries after the initiation of highly active antiretroviral therapy (HAART) [3]. After years of administration, these highly effective therapies have begun to show their side effects and toxicities as unexpected cardiovascular events in young patients with HIV, especially in those with protease inhibitors (PI) treatment [4].

Risk factors for cardiovascular diseases are the same in general populations as in HIV infected patients: smoking status, blood pressure, age, sex, race and menopausal status, but there are other specific factors: chronic inflammation due to HIV infection per se, metabolic changes associated with PI therapy and lipodystrophy [5, 6].

Retrospective studies addressing the risk of cardiovascular events in antiretroviral therapy (ART) – treated patients showed conflicting results [7-9]. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study, a large international observational study of more than 23,400 HIV-infected patients from 11 cohorts in Europe, Australia, and the United States, established that the cardiovascular risks may be related to ART. It was estimated as a double risk of myocardial infarction (MI) over five years [10].

Premature atherosclerosis has been reported in young adults with HIV infection in the pre-highly active antiretroviral therapy era [11]. SMART (Strategies for Management of Antiretroviral Therapy) study shows that in patient with episodic antiretroviral therapy, the risk of cardiovascular disease is higher compared to patients with continuous treatment [12]. These results suggest that viral infections itself may increase the cardiovascular risk. Hhypercholesterolemia and hypertriglyceridemia have been associated with the use of ART [13,14] but untreated HIV infection generate similar changes in lipids metabolism - increased LDL cholesterol and decreased HDL cholesterol, with high levels of triglycerides, in advanced stages of the disease [15].

Carotid artery intima-media thickness (C-IMT), however, is a valid measure of subclinical atherosclerosis, which has consistently been related to future cardiovascular events in population studies [16,17]. Arterial stiffness is also a marker of increased cardiovascular risk and an independent predictor of cardiovascular events and mortality in general populations [18,19].

The aim of the present study was to investigate C-IMT and carotid and brachial artery stiffness in patients with HIV infection with different ART and compare these data with uninfected controls. We hypothesized that patients with HIV infection have increased C-IMT and arterial stiffness and that ART especially PI treatment increases C-IMT and arterial stiffness.

Patients and methods

In this case-control study, between April 2008 and October 2010, 65 patient infected with HIV (from **anti-AIDS Regional Center)** and 36 healthy **controls matched for age and sex** were evaluated for C-IMT and arterial stiffness at the brachial and carotid artery. Exclusion criteria were: co-infection with hepatitis B and C virus, diabetes mellitus, endocarditis, history of heart failure, acute myocardial infarction, abnormal renal function, and age under 18. Patients and controls gave their informed consent and the study was approved by the University and Hospital Ethics Committee.

We recorded data on smoking, history of cardiovascular disease, hyperlipidemia, and family history of dia-

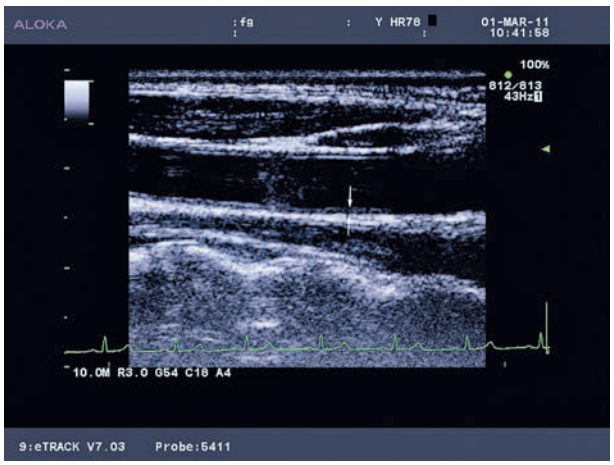

Fig 1. Measurement of the intima-media thickness in the common carotid artery.

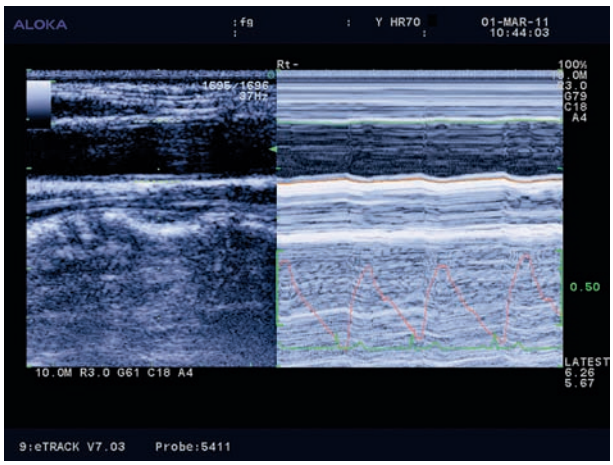

Fig 2. Examination of the common carotid artery with simultaneous presentation of carotid waveforms derived from cyclic changes in arterial diameter.

betes mellitus type 2 and cardiovascular disease (in first-degree relatives: male under age 55, female under age 65). Plasma glucose, cholesterol and triglycerides were determined in both groups. In HIV infected patients, mode of transmition, Centers for Disease Control stage, and complete history of prior and current ART use, were recorded. CD4 cells and viremia was determined. We excluded HIV infection in controls by anamnesis, clinical examination and serological tests.

Arterial parameters were determined ultrasonographically, using an ALOKA ProSound α 10 machine equipped with an e-Tracking programme and a 7.5-13 MHz linear array probe. Properties of the right common carotid and brachial arteries were obtained by a single investigator. The carotid artery parameters were measured 10 mm proximal to the beginning of the bulb, and the brachial artery 20 mm above the antecubital fossa.

Carotid arteries were scanned for the detection of plaques and stenosis. Carotid plaque was defined as a focal region with carotid intima-media thickening < 1.5 mm that protrudes in the lumen. We considered carotid stenosis a reduction of more than 50% of artery diameter (hemodinamically, peak systolic velocity >150 cm/s, peak end diastolic velocity > 50 cm/s). C-IMT was measured in a region free of plaque at the level of the posterior wall, 1 cm proximal to the bifurcation. Perpendicularity between the ultrasound beam and the far wall assured good visualization of the C-IMT as two parallel echoic lines (the lumen-intima interface and media-adventitia interface) (fig 1).

Arterial stiffness parameters were recorded 12 hours after the last administration of a vasoactive drug or alcohol consumption and after 3 hours of abstinence of caffeine and tobacco. Patients rested 10 minutes in a supine position in a quiet room at a temperature of 20-22 °C before measurements were done [20]. Measurements were done at the level of the common carotid artery, 1 cm proximal to the carotid bulb. Echo-tracking gates were manually set at a high echoic line just outside the intima-media complex, near the edge of the adventitia side. Changes in diameters were evaluated by measuring the tracking gates (fig 2). The echo-tracking system accurately measures arterial diameter changes with the precision of the ultrasound wavelength (0.013mm) and data are updated at a rate of 1 kHz [21].

The following parameters were calculated automatically: beta stiffness index, carotid pulse wave velocity (c-PWV), augmentations index (AIx), arterial compliance (AC), and C-IMT. Beta stiffness index was calculated as: β stiffness index= ln(SBP/DBP)/[(Ds-Dd)/Dd]. It is uninfluenced by the change in blood pressure. Carotid PWV is a measure of local pulse wave velocity, PWV (cm/s) = (dP/dU)/ρ, where dP is the change in pressure, dU is the change in velocity and ρ is the density of blood (1040 kg/m³). AC was calculated as an absolute change in lumen area for a given increase in pressure, $AC= \pi(2d\Delta d+\Delta d^2)/4PP$, where d is arterial end-diastolic adventitia-adventitia diameter, Δd is the change in diameter from diastole to systole, and PP is the pulse pressure. AIx represents a supplementary increase in blood pressure during systole due to the reflection of the forward travelling pressure waves from the peripheral circulation, AIx = (ΔP/PP) x 100, where ΔP is the pressure difference between the shoulder of the wave and peak systolic pressure and PP is the pulse pressure [20].

Blood pressure (SBP-systolic blood pressure and DBP-diasolic blood pressure) was determined at the level of the left brachial artery, at 5 min intervals, using an oscillometric sphygmomanometer (Model DS56, WelchAllyn, NY, USA) and the values obtained for each patient were included in the system.

According to NCEP ATP III from 2004 normal level for cholesterol <200mg/dl, and for triglycerides <150mg/dl [10] were considered for the diagnosis of dyslipidemia.

Repeatability was assessed in 5 healthy subjects who were examined by the same observer twice, 1 week apart, in the same conditions. The coefficients of variance were as follows: 3.6% for C-IMT, 7.7% for β stiffness index, 8.3% for PWV, 7.5% for AC and 8.8% for Aix.

Statistical analysis

Analyses were done using SPSS statistical software version 10. Differences between groups in clinical characteristics were evaluated using the Mann-Whitney U test for continuous variables and the χ^2 test for categorical variables. Comparisons of arterial properties were done using analysis of variance. P value <0.05 was considered statistically significant.

Results

Clinical characteristics of the study population

From 65 patients with HIV infection, two patients were excluded: one due to newly diagnosed diabetes mellitus and the other due to endocarditis diagnosis. Fifty-six of the 63 patients had been exposed to ART; all but 9 (15.78%) were currently using ART, 6 were ART naïve, and 1 had interrupted ART for 2 years. This one was included in the ART naïve group. Twenty-nine patients (46.03%) were only on reverstranscriptase inhibitors (RTI) and 27 (42.86%) were exposed to both RTI and PI.

Infection mode was nosocomial in 15 (23.8%) and sexual in 48 patients (76.2%) - homosexual transmis-

sion in 10 (15.9%) and heterosexual transmission in 38 (60.3%).

Most of the patients (42.86%) had CD4 cell <500/mm³ but there were 13 (20.63%) patients with CD4 cell<200/mm³, and 1 (1.58%) with CD4<50/mm³. Twenty-six patients (41.27%) were female, and the distribution on the CDC stage of disease showed a predominance of C3 stage (44.44%), and B2 stage (28.57%).

Characteristics of patients and controls are shown in table I. There were no differences between the two groups for BMI, SBP, DBP and smoking status. Patients had a significant higher heart rate (HR) compared to controls. HIV-patients had significantly elevated values for lipidic parameters (total cholesterol and triglycerides).

Vascular parameters in HIV infected patients and controls

We found that patients with HIV infection had statistically significant increased values of C-IMT ($p<0.01$), and also for carotid compliance, compared to controls ($p<0.01$).

Carotid β-stiffness index and PWV were increased compared to controls but the differences were not statistically significant. At the level of the brachial artery, values of arterial stiffness were elevated in patients compared to controls but without statistical significances (table II).

Examinations of carotid artery revealed carotid plaques in 4 patients (6.3%) and in 2 controls (5.5%).

Comparison between HIV infected patients with different types of treatment

We performed Paired-Samples T test to compare arterial stiffness parameters, C-IMT, and lipids in patients with HIV exposed to RTI or RTI and PI.

We found significant differences for triglycerides between RTI+PI patients compared to controls ($p<0.001$) and also for RTI patients compared to controls ($p<0.01$). Parameters of arterial stiffness β carotid stiffness index, carotid PWV were significantly increased in patients exposed to RTI treatment. Carotid artery compliance was significantly reduced in the RTI patients group. The group exposed to the combination RTI and PI had a trend of reduced arterial compliance that does not have, however, statistical power.

We do not find significant differences in arterial and metabolic parameters between the two groups of patients exposed to RTI and PI, respectively to PI. There were no differences in age, SBP, DBP, and smoking status between the two groups of treated patients and between these treated patients and controls (table III).

Table I. Characteristics of HIV patients and of controls

Arterial parameters	Patients with HIV (n=63)	Controls (n=36)	p
Age (years)	37.98±13.17	37.13±11.94	0.90
Gender	F-25 (39.68%) M-38 (60.32%)	F=14 (38.88%) M=22 (61.12)	0.94
BMI (kg/m²)	23.54±3.43	23.05±1.53	0.32
SBP (mmHg)	121.52±13.91	119.64±12.92	0.55
DBP (mmHg)	74.32±11.73	75.53±9.28	0.42
Heart rate (b/min)	76.79±11.71	68.44±9.92	<0.01
Current smokers	20 (31.75%)	10 (27.78%)	0.74
TC (mg/dl)	189.55±48.06	169.42±29.43	<0.01
Trygliceride (mg/dl)	171.85±87.56	94.11±30.05	<0.01
Fasting plasma glucose (mg/dl)	89.76±11.91	89.52±8.75	0.86

Data were expressed as mean ±SD
Definition of abbreviations: BMI-body mass index; SBP-systolic blood pressure; DBP- diastolic blood pressure. F-female, M male, TC-total cholesterol.
The $p<0.05$ between groups (Mann-Whitney U test for continuous variables)

Table II. Arterial stiffness in HIV patients and in controls

Arterial parameters	Patients with HIV (n=63)	Control group (n=36)	p
ß carotid stiffness index	6.95±2.97	5.67±2.08	0.04
Carotid artery compliance (mm²/kPa)	0.89±0.35	1.67±3.36	<0.01
Carotid AIx (%)	8.66±12.05	10.33±16.35	0.99
Carotid PWV (m/s)	5.60±1.21	5.12±0.98	0.06
ß brachial stiffness index	12.28±8.65	10.38±5.32	0.48
Brachial artery compliance (mm²/kPa)	0.20±0.13	0.27±0.24	0.12
Brachial AIx (%)	8.78±18.32	5.35±19.57	0.52
Brachial PWV (m/s)	7.18±2.31	6.83±1.82	0.70
C-IMT (mm)	0.60±0.15	0.51±0.08	<0.01

Data were expressed as mean ±SD
Definition of abbreviations: C-IMT-carotid intima-media thickness; carotid PWV- carotid pulse wave velocity.
The $p<0.05$ between groups (Mann-Whitney U test for continuous variables)

Table III. Arterial stiffness and metabolic parameters in HIV patients with RTI vs. PI

Arterial parameters	Patients with RTI (n=29)	Patients with PI and RTI (n=27)	Control group (n=36)	p	P*	P#
BMI (kg/m²)	23.34±3.27	23.98±3.69	23.05±1.53	0.63	0.09	0.58
SBP (mmHg)	121.63±12.6	122.62±14.8	119.64±12.92	0.69	0.34	0.74
DBP (mmHg)	74.19±11.27	74.41±12.76	75.53±9.28	0.98	0.56	0.44
ß carotid stiffness index	6.45±2.46	7.44±3.08	5.67±2.08	0.29	0.01	0.22
Carotid artery compliance (mm²/kPa)	0.93±0.36	0.83±0.34	1.67±3.36	0.28	<0.01	0.07
Carotid AIx (%)	10.44±13.67	8.35±10.93	10.33±16.35	0.90	0.85	0.93
Carotid PWV (m/s)	5.41±1.09	5.80±1.25	5.12±0.98	0.24	0.02	0.30
C-IMT (mm)	0.56±0.13	0.63±0.16	0.51±0.08	0.08	<0.01	0.19
ß brachial stiffness index	13.35±7.60	12.88±9.89	10.38±5.32	0.59	0.44	0.13
Arterial brachial compliance (mm²/kPa)	0.18±0.08	0.20±0.11	0.27±0.24	0.67	0.12	0.06
Brachial AIx (%)	6.11±17.18	11.46±18.03	5.35±19.57	0.28	0.24	0.99
Brachial PWV (m/s)	7.53±2.15	7.37±2.40	6.83±1.82	0.73	0.54	0.26
TC (mg/dl)	190.70±49.73	191.86±44.4	169.42±29.43	0.89	0,01	0,02
Trygliceride (mg/dl)	170.81±96.18	181.52±86.7	94.11±30.05	0.41	<0,01	<0,01
Fasting plasma glucose (mg/dl)	86.85±8.50	91.79±13.71	89.52±8.75	0.13	0.56	0.27

Data were expressed as mean ±SD
Definition of abbreviations: BMI-body mass index; SBP-systolic blood pressure; DBP- diastolic blood pressure; carotid AIx- carotid augmentation index; C-IMT-carotid intima-media thickness; carotid PWV- carotid pulse wave velocity; brachial AIx – brachial aurmentaion index; brachial PWV – brachial pulse wave velocity; TC-total cholesterol
The P<0,05 between HIV patients with RTI treatment and HIV patients with RTI and PI treatment
The p*<0,05 between HIV patients with RTI treatment and controls
The p#<0,05 between HIV patients with RTI and PI treatment, and controls

Discussion

The main findings of this study are that patients with HIV had increased C-IMT, and increased arterial stiffness of the carotid artery compared with healthy controls matched for age and sex.

C-IMT has been shown to be elevated in chronic inflammatory conditions and chronic infection [22]. Chronic HIV infection may lead to vascular endothelial damage and increase vessel wall thickness by interaction with endothelial cell, and by sustaining a low degree of inflammation [23]. This hypothesis is supported by large studies which reported a significantly higher C-IMT in 2 of the 3 carotid segments in HIV-infected subjects than in age- and sex-matched controls [24-27]. This effect was still visible in the ART-naive subcohort (28). There are also authors that do not find modifications at the carotid level in HIV infection [29].

In many of these studies, differences in exposure to ART in patients' groups make it difficult to distinguish between the effects of HIV and ART. Conflicting evidence exists also regarding the association between the use of ART in general and the cumulative exposure to different drug classes, especially PI, and C-IMT [24-26, 29-31]. We did not find significant differences in C-IMT between the group exposed to both RTI and PI and the group exposed only to RTI.

Parameters of arterial stiffness were modified in our patients with HIV infection. The most important changes involved carotid artery. Carotid artery compliance was reduced in patients compared to controls. In the group of patients exposed to combined RTI and PI treatment we found more important changes. Beta-stiffness index and carotid PWV were increased and arterial compliance reduced compared to controls. These patients had also elevated values of plasma lipids.

Arterial stiffening is a complex process involving structural and functional changes in the arterial wall, which occur as part of normal aging and are accelerated by a number of conditions including diabetes mellitus type 2, hypertension, and renal failure [32]. Evidence is accumulating that in addition to these traditional risk factors, acute and low-grade inflammation are also associated with large artery stiffness by promoting structural changes or by inducing endothelial dysfunction [33, 34]. Chronic inflammation resulting from HIV infection may therefore explain the association between HIV infection and increased arterial stiffness, as has been shown for chronic inflammatory diseases such as rheumatoid arthritis [22]. Our findings are in agreement with some other studies previously reported in children and adults with HIV measuring carotid arterial stiffness by the same techniques [24, 25, 27, 29, 35]. Brachial artery stiffness has been studied less extensively and results have been conflicting. In patients with diabetes and impaired glucose metabolism, brachial artery stiffness followed a pattern similar to that of the femoral artery [36]. Our findings suggest that the effect of HIV infection and ARV treatment on arterial wall stiffness is more important at the level of carotid artery than at the brachial site, indicating a predominant alteration of central elastic arteries. However, prospective studies will be necessary to clarify this issue. It also remains to be determined whether these modifications are due to direct effects of the antiretroviral drugs or caused indirectly, by their metabolic side effects.

Recent studies showed that cardiovascular risk actually improved after the introduction of ART, despite the rapid onset of dyslipidemia and that, interrupted treatment generates side effects which increase this risk [10,37,38].

The balance between the beneficial effects of diminishing active infection/inflammation and the negative effects of ART such as dyslipidemia may be essential to determine the net effect in an individual patient and in different arterial segments. The ART effect on lipids metabolism is well known and the hypertrigliceridemia that we found is concordant with the results of other studies which investigated the same parameters [39,40]. It is also known that HIV infection per se may change the lipid metabolism by decreasing HDL cholesterol, and at the same time, by increasing LDL cholesterol, and total cholesterol. These alterations were noted in HIV infected patients without ART and in an advanced stage of infection which is associated with increased levels of triglycerides [41].

Our study has several limitations. First, the cross-sectional design did not allow us to investigate progression of abnormalities in arterial properties; also, the sample size of patient subgroups, mainly ART-naive patients may have been insufficient to detect smaller differences in arterial properties. For the calculation of arterial parameters we used brachial arterial pressure that is different from central carotid pressure. Nevertheless, this method was also used in other clinical studies [42].

Conclusions

HIV infection and ARV treatment is associated with increased C-IMT and generally increased arterial stiffness, especially at the level of the carotid arteries. This suggests that patients with HIV infection may be at an increased cardiovascular disease risk, independent of the presence of classical cardiovascular risk factors.

Conflict of interest: None

Acknowledgments

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