



ARTERIAL STIFFNESS 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 in HIV infected patients is linked to traditional risk factors but also to HIV infection itself which can damage the arterial wall. The antiretroviral treatment (ART) is implicated in metabolic disturbances which can also affect the arterial wall. The aim of our study was to identify the effects of HIV and ART on the aortic artery and the cardiovascular risk by the evaluation of arterial stiffness parameters. **Material and methods:** A cross-sectional case-control study of 59 HIV-infected patients (55 exposed to ART, 5 ART-naïve) and 40 controls matched by age and sex was performed. Aortic stiffness parameters and brachial parameters were measured using a device called Arteriograf TensioMed attached to a laptop with a TensioMed special software which provided automatic calculations of these markers. **Results:** HIV-infected patients had a greater aortic pulse wave velocity than the control group ($p=0.02$) and an increased heart rate ($p=0.02$). HIV infection and ARV treatment are additional risk factors for rapid onset and progression of atherosclerosis. **Conclusions:** HIV infection and ARV treatment are associated with increased arterial stiffness and increased heart rate. These vascular alterations are possible causes of the increased cardiovascular risk observed in HIV infected patients.

Keywords: HIV infection, aortic stiffness, antiretroviral treatment, cardiovascular risk

Introduction

The mortality of patients infected with HIV has decreased since the introduction of ARV treatment, but despite this consideration, patients infected with HIV are dying at younger ages than the general population [1]. One of the reasons of the increased mortality in younger HIV infected patients may be the fact that they have developed atherosclerosis earlier, which increases the risk of cardiovascular disease [2]. The role of antiretroviral therapy and HIV infection itself in the development of atherosclerosis is not well known, however it is known that they induce changes in the lipid profile and insulin resistance. These are known as risk factors for cardiovascular disease and develop-

ment of atherosclerosis. Also HIV infection may lead to changes in the vascular endothelium by depressed immunity, sustained inflammation, and viral replication. These assumptions are supported by recent studies that have shown that interruption of antiretroviral treatment or its intermittent administration increases cardiovascular risk [3,4].

At the present we do not know if HIV infection itself is an independent risk factor for the onset and progression of atherosclerosis. But one study has shown an increased arterial stiffness in HIV infected patients who were not receiving ARV therapy [5].

Currently, the preferred methods for assessing cardiovascular risk are non-invasive. They are easy to apply and allow investigation of a large number of people. Many studies applied in the general population have shown that large artery stiffness is a marker of subclinical atherosclerosis and a predictor of increased cardiovascular mortality [6]. The evaluation is made by ultrasound methods determining intima-media thickness, pulse wave

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velocity, augmentation index and arterial compliance at carotid artery level. By this method we can also evaluate the flow mediated dilation at the brachial artery which is a marker for endothelial dysfunction. Other methods for arterial stiffness evaluation are tonometry and oscillometry.

In this study we used oscillometric methods to evaluate the aortic stiffness in HIV infected patients with or without ARV treatment. This is the first study of its kind performed in Romania on HIV-infected patients.

Materials and methods

We performed a cross sectional case-control study between 2009 and 2010. In this period we evaluated 59 patients (from The Centre for Monitoring and Surveillance of HIV/AIDS Infection Cluj) with known or newly diagnosed HIV infection and 40 healthy controls matched for age and sex.

Patients were randomly selected, but we excluded those who had a co-infection with hepatitis B or C virus, known history of heart diseases (endocarditis, myocardial infarction, angina pectoris), diabetes mellitus, impaired renal function and patients under 18 years.

Parameters of arterial stiffness were assessed using a device called Arteriograf TensioMed that is attached to a laptop with TensioMed software that automatically calculates the arterial parameters.

This device evaluated the brachial augmentation index (Aixbr), aortic augmentation index (Aixao), aortic systolic pressure (SBPao), aortic pulse pressure (PPao), aortic pulse wave velocity (PWVao) and peripheral systolic, diastolic blood pressure and mean blood pressure, pulse pressure and heart rate.

Arterial parameters were assessed according to guidelines for user procedures with valid methods and devices [7]

The measurements were performed by a single investigator in a quiet room, at 21°C. The patients rested for 15 minutes in supine position in this room. They also abstained from smoking for at least 3 hours and from alcohol consumption for 1 day before the examination. They were not under vasoactive medications. Between 10-12 afternoon, 2 measurements were performed for each patient.

The *augmentation index* (Aix) is calculated according to the formula $Aix (\%) = \Delta P / PP \times 100$ where ΔP is the pressure difference between the shoulder of the wave and peak systolic pressure and PP is the pulse pressure. Aix represents a supplementary increase in blood pressure during the systole due to the reflection of the forward travelling pressure waves from the peripheral circulation [8].

Aortic pulse pressure is a better prognostic index for the occurrence of cardiovascular events than the brachial artery pressure [9].

Central systolic pressure is the pressure exerted on the aortic wall by the volume of blood ejected from the left ventricle. According to the latest medical outcomes the traditional measurement of blood pressure is not accurately reflecting the changes in central systolic blood pressure. *Pulse wave velocity* (PWVao) is determined by measuring the difference in time required for the pulse wave determined by the blood volume ejected during the systole to cover a known distance. It is calculated using the formula: $v = s / t$ where

- • v is the pulse wave velocity
- • s is the distance between the aortic root and aortic bifurcation
- • t is the measured time [10]

Pulse pressure is determined as the difference between systolic blood pressure and diastolic blood pressure measured at the brachial artery.

Laboratory tests were performed to evaluate HIV infection (CD4 leucocytes and viral load). We also evaluated the level of total cholesterol, triglycerides and fasting plasma glucose. Hypercholesterolemia was considered at values of total cholesterol > 200mg/dl, and hypertriglyceridemia at triglyceride levels > 150mg/dl. These data are selected according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria from 2004. The clinical and immunological stage of HIV infection was determined according to Centers for Disease Control (CDC) from 1993.

We evaluated the presence of metabolic syndrome in patients, defined by: abdominal obesity (waist circumference > 94 cm for men and > 80 cm for women) as the main determinant, and at least two of the following criteria: levels of triglycerides > 150 mg /dL or specific treatment for this type of dyslipidemia, HDL-cholesterol lower than < 40 mg/dl in men and < 50 mg/dL in women or specific treatment for this type of dyslipidemia, increased systolic blood pressure > 130 mmHg or diastolic > 85 mmHg, or treatment for previously diagnosed hypertension, fasting plasma glucoses level higher than 100 mg/dL or previously diagnosed type 2 diabetes [11].

We also measured the body mass index calculated by the formula: $BMI = G / I^2$ (G-weight expressed in kilograms, I-height expressed in meters) and the smoking status.

Differences between groups were calculated using the Mann-Whitney U test for continuous variables and χ^2 tests for categorical variables. P was considered statistically significant at values < 0.05. The program used for statistical analyses was Statistica version 7.

We used multiple linear regressions to assess the correlation between the HIV infection and ARV treatment and vascular parameters. For multiple

linear regression models we used HIV infection, antiretroviral therapy, the CD4 leucocytes level, HDL cholesterol, triglycerides, total cholesterol, fasting plasma glucose, age, gender, BMI, presence or absence of metabolic syndrome, the smoking status as independent variables, and vascular parameters as dependent variables. P was considered statistically significant at values <0.05 .

Results

We evaluated 60 patients with known or newly diagnosed HIV infection. One patient was subsequently removed from the study because of being diagnosed with endocarditis.

The controls group was composed of 40 healthy people without HIV infection, no history of cardiovascular disease, hypertension, type 2 diabetes or renal failure. They were matched by age and sex with the patients group.

Distribution by gender was quite uniform: almost half of the patients were male 24 (40.68%).

The way the infection was transmitted was heterosexual in 38 (64.41%) patients, nosocomial in 14 (23.73%) patients (these patients were infected in childhood), and 7 (11.86%) patients with homosexual transmission.

At the time of evaluation the patients were grouped in different stages of disease according to the 1993 CDC criteria. There were 1 (1.69%) patients in A2 stage, 18 (30.52%) in B2 stage, 8 (13.56%) in B3 stage, 1 (1.69%) C1 stage, 5 (8.47%) in C2 stage and 26 (44.07%) in C3 stage. Five (8.47%) patients were without treatment, 29 (49.16%) patients were under reverse transcriptase inhibitors (RTI) and 25 (42.37%) patients were under RTI and protease inhibitors (PI). One patient without ARV treatment was in the A2 stage and one in the B2 stage which required no treatment. Another one was newly confirmed and in the B3 stage due to start treatment, and two were in the B3 and C3 stage and dropped the treatment.

More than half of the patients 36 (61.02%) had undetectable viral loads, 18 (30.51%) had detectable viral loads and in 5 (8.47%) patients the viral loads were not assessed. Among patients who had detectable viral loads only 4 were without ARV therapy at the time, the others being non-adherent to treatment or infected with a virus resistant to treatment.

One of the patients without assessed viral load was not undergoing ARV treatment because he dropped out, one was not enrolled in the Cluj Center, one rarely came to monitoring, and two were recently confirmed and due to begin treatment.

Twenty three (38.98%) patients had a medium immunological status with CD4 leucocytes levels between 200-499 cell/mm³, 22 (37.29%) patients

had a good immunological status with CD4 levels > 500 cell/mm³, 12 (20.35%) patients had a low immunological status, with values of CD4 leucocytes between 51-200/mm³ and one (1.69%) patient had a poor immunological status with a value of CD4 < 50 /mm³. One patient was not assessed because he was not registered in the Cluj Center.

Three (5.08%) patients were diagnosed with cachexia according to the BMI, 35 (59.33%) were normal, 20 (33.90%) were overweight and 1 (1.69%) patient was obese. Also 16 (27.12%) patients had metabolic syndrome and 43 (72.88%) did not. Eight (50%) of these patients were treated with RTI, 6 (37.5%) were receiving both PI and RTI, the difference between them not being statistically significant ($p = 0.66$). Two (12.5%) of the patients with metabolic syndrome were without ARV treatment.

Total cholesterol assessment has shown that 24 (40.68%) patients had hypercholesterolemia. Thirteen of these were treated with RTI, 9 were treated with combined PI and RTI, the difference between them not being statistically significant ($p = 0.48$). Two of them were without ARV treatment. Twenty three (38.98%) patients had hypertriglyceridemia. Thirteen of these were receiving RTI treatment, 9 were under combined PI and RTI. The difference between these two groups was not statistically significant ($p = 0.48$). One patient did not undergo ARV treatment.

The characteristics of patients and controls are shown in Table I. There were no differences between the two groups for age, sex, BMI, SBP, DBP and smoking status. Patients had a significant higher heart rate (HR) compared to controls.

Also the patients had a significant higher pulse wave velocity ($p = 0.02$). (Table II). The augmentation index in both the aortic and brachial arteries was lower in the group of HIV patients but the difference was not statistically significant. Pulse pressure at both levels was higher in the group of HIV patients but without any statistically significant differences. Aortic systolic blood pressure was lower in the group of patients.

We made a multiple linear regression model applied to the group of patients. (Table III)

The results highlight that blood pressure is not affected by HIV-specific parameters, systolic blood pressure (SBP) being significantly affected only by the metabolic syndrome and the sex of the patients. Diastolic blood pressure (DBP) is also affected by the presence of metabolic syndrome and by the age of the patients and median blood pressure (MBP) is affected by the age and the sex of the patients. Heart rate (HR) was not significantly influenced by any parameter. The aortic stiffness parameters were significantly influenced by the HIV specific parameters.

| Parameters | HIV infected patients (n=59) | Controls (n=40) | P |
|--------------------------|---------------------------------|--------------------------------|-------|
| Age (years) | 38.24±13.58 | 38.58±13.55 | 0.85 |
| Sex | F-25 (42.37%) M-34 (57.63%) | F=17 (42.50%) M=23 (57.50%) | 0.99 |
| Menopause | 5 (8.47%) | 4 (10%) | 0.81 |
| BMI (kg/m ²) | 23.50±3.52 | 22.98±2.02 | 0.41 |
| Smokers | 23 (38.98%) | 10 (25%) | 0.30 |
| SBP (mmHg) | 124.22±14.44 | 124.40±15.55 | 0.96 |
| DBP (mmHg) | 74.64±9.73 | 75.50±10.67 | 0.59 |
| MBP (mmHg) | 91.10±10.54 | 91.38±11.73 | 0.80 |
| HR (b/min) | 76.59±11.57 | 70.30±10.09 | 0.02 |
| TC (mg/dl) | 189.69±49.09 | 175.13±16.51 | 0.052 |
| CD4 leucocytes | 446.81±288.09 | | |
| Viral load | 17252.26±69687.26 | | |

Table I. Characteristics of HIV patients and of controls

Data are expressed as mean ±SD.

Definition of abbreviations: BMI- body mass index, SBP- systolic blood pressure, DBP- diastolic blood pressure, MBP- medium blood pressure, HR- heart rate, TC- total cholesterol

| Arterial parameters | HIV infected patients (n=59) | Controls (n=40) | P |
|---------------------|---------------------------------|--------------------|------|
| Aixao (%) | 18.37±15.36 | 18.54±12.35 | 0.67 |
| PWVao (m/s) | 8.76±2.55 | 7.60±1.48 | 0.02 |
| Aixbr (%) | -36.98±31.48 | -35.15±27.38 | 0.59 |
| PP (mmHg) | 49.63±10.06 | 48.60±11.10 | 0.60 |
| PPao (mmHg) | 41.21±10.29 | 38.93±10.85 | 0.70 |
| SBPao (mmHg) | 115.78±16.84 | 116.02±14.95 | 0.84 |

Table II. Arterial parameters in HIV patients and in controls

Data are expressed as mean ±SD

Definitions of abbreviations: Aixao- aortic augmentation index, PWVao- aortic pulse wave velocity, Aixbr- brachial augmentation index, PP- brachial pulse pressure, PPao- aortic pulse pressure, SBPao- aortic systolic blood pressure

This proves that the parameters of HIV infection are risk factors for occurrence of arterial stiffness. Aortic pulse wave velocity was influenced by the age and viral load; aortic augmentation index was influenced by the age, ARV treatment, disease stage and metabolic syndrome; the brachial augmentation index was influenced by the age, sex of the patients, ARV, presence of metabolic syndrome and total cholesterol. The brachial pulse pressure was influenced only by the age and the sex of patients, and aortic pulse pressure was influenced by the age and HDL cholesterol. Aortic systolic blood pressure was influenced by the disease stage and total cholesterol.

Discussion

Results from this study show that HIV infected patients, with or without antiretroviral therapy have an increased aortic stiffness. These results have practical significance, because these indices of arterial stiffness are already accepted as surrogate markers for increased cardiovascular risk in the general population. In fact, impaired arterial elasticity is known as the onset of hypertension and the presence of arterial stiffness is associated with increased risk of cardiovascular events and even death [6].

Antiretroviral treatment is known to be involved in the development of cardiovascular changes, but

| Dependent parameter | Independent parameter | Standardized beta | R | P |
|---------------------|-----------------------|-------------------|-------|--------|
| SBP | Sex | 0.394 | 0.514 | 0.003 |
| | Metabolic syndrome | -0.334 | | 0.013 |
| DBP | Age | 0.480 | 0.672 | 0.006 |
| | Metabolic syndrome | -0.313 | | 0.030 |
| MBP | Age | 0.340 | 0.629 | 0.021 |
| | Sex | 0.283 | | 0.030 |
| HR | Treatment | 0.215 | 0.275 | 0.115 |
| | Body mass index | -0.175 | | 0.199 |
| PWVao | Age | 0.660 | 0.736 | <0.001 |
| | Viral load | -0.219 | | 0.046 |
| Aixao | Age | 0.805 | 0.829 | <0.001 |
| | Treatment | -0.285 | | 0.015 |
| | Disease stage | 0.243 | | 0.032 |
| | Metabolic syndrome | -0.338 | | 0.003 |
| Aixbr | Age | 0.821 | 0.845 | <0.001 |
| | Sex | -0.232 | | 0.024 |
| | Treatment | -0.244 | | 0.024 |
| | Metabolic syndrome | -0.311 | | 0.006 |
| PP | Total cholesterol | -0.292 | 0.438 | 0.023 |
| | Sex | 0.337 | | 0.015 |
| | Age | -0.336 | | 0.039 |
| PPao | Age | 0.396 | 0.522 | 0.021 |
| | HDL cholesterol | 0.361 | | 0.019 |
| | Age | 0.631 | | <0.001 |
| SBPao | Metabolic syndrome | -0.316 | 0.722 | 0.018 |
| | Disease stage | 0.287 | | 0.039 |
| | Sex | 0.275 | | 0.031 |
| | Total cholesterol | -0.307 | | 0.045 |

Table III. Multiple linear regression for patients group

Definitions of abbreviations: SBP- systolic blood pressure, DBP- diastolic blood pressure, MBP- medium blood pressure, HR- heart rate, Aixao- aortic augmentation index, PWVao- aortic pulse wave velocity, Aixbr- brachial augmentation index, PP- brachial pulse pressure, PPao- aortic pulse pressure, SBPao- aortic systolic blood pressure

its benefits are far outweighed by the risks posed by this medication presence. [12]. Also ARV treatment interruption was shown to increase the risk of cardiovascular disease and the occurrence of asymptomatic myocardial infarction [3]. The same effect seems to appear in the delay of ARV therapy introduction, patients in this situation presenting an increased risk of cardiac ischemia [13].

In this study we tried to prove the involvement of HIV infection and ARV therapy in the development of arterial stiffness and a more rapid progression of atherosclerosis in these patients compared with the general population. We tried to avoid the factors which are already known as risk factors such as presence of heart disease history, type 2 diabetes, and renal failure. The differences in smokers ratio and, for women, the menopausal status had no statistical significance, and the controls were matched with patients regarding age and sex. (Table I)

Our study showed that the presence of ARV treatment, the viral load and stage of disease are risk factors for increased aortic stiffness. The degree of involvement of each of them remains to be established. This result has practical significance because there are new classes of antiretroviral drugs which can change that.

In our study hypercholesterolemia and hypertriglyceridemia were not influenced by the type of ARV treatment in our study. Also the metabolic syndrome was not influenced by the type of treatment, occurring in almost equal proportions in patients from both treatment groups, with and without PIs.

Another feature of our group of patients is a relatively young age because of a significant proportion of patients infected during childhood. Increased pulse wave velocity in this group showed an increased arterial stiffness in HIV infected patients.

Our results are similar with the results of other studies in the literature which shown that HIV is an independent risk factor for atherosclerosis [5].

Our study has several limitations. First, the cross-sectional design did not allow us to investigate progression of abnormalities in arterial properties. Also because of the small number of patients the statistical analysis in the ARV treatment specific group was not possible.

Conclusions

Our results show that HIV infection and ARV treatment increase arterial stiffness in the aortic artery. HIV infected patients present vascular disease at younger ages. The disease stage was identified as a risk factor for increased aortic stiffness. These findings show that HIV infected patients, with or without antiretroviral therapy, have increased arterial stiffness which is associated with an increased cardiovascular risk. In our study hypertriglyceridemia and hypercholesterolemia were not influenced by the type of treatment. Also the metabolic syndrome was not influenced by the type of treatment, possibly because of a small number of studied patients.

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