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Evaluation of endothelial function and arterial stiffness in HIV-infected patients: a pilot study

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Abstract

Background: In the era of combination antiretroviral therapy (cART), life expectancy of HIV-infected patients is the same as that of the general population, resulting in increasing prevalence of cardiovascular disease in this patient group.

Aim: To assess the prevalence of endothelial dysfunction in HIV-infected patients and to identify factors which affect endothelial function and arterial stiffness.

Methods: Thirty-seven adult HIV-infected patients, regardless of the fact and the type of cART, were enrolled into the study. In patient, reactive hyperaemia peripheral arterial tonometry assessment was performed using the Endo-PAT2000 device (ITAMAR®). This method allows evaluation of endothelial function ant arterial stiffness.

Results: Final analysis included 37 patients (median age 38 years, range 32–45 years), including 89.2% men. Endothelial dysfunction was found in 13 (35.1%) HIV-infected patients. We found no differences in demographic and clinical characteristics, laboratory data, and cardiovascular drug therapy between patients with or without endothelial dysfunction, except for platelet count which was higher in patients with endothelial dysfunction (174 [119–193] × 10^3/mm^3 vs. 222 [168–266] × 10^3/mm^3, p = 0.03). No demographic or clinical variables were identified as predictors of endothelial dysfunction in HIV-infected patients. In addition, no association was found between factors related to HIV infection, chronic drug therapy and the risk of endothelial dysfunction. Statistically significant correlations were found between arterial stiffness and age (ρ_s = 0.53, p < 0.001), red blood cell count (ρ_s = –0.39, p = 0.018), and platelet count (ρ_s = 0.42, p = 0.009). CD4+ and CD8+ lymphocyte count and viral load were similar in patients with or without endothelial dysfunction. Arterial stiffness was significantly higher in patients with higher viral load (ρ_s = –0.39, p = 0.0018) and in those with established AIDS (9.5 [1.0–16.0] vs. –5 [–10–5], p = 0.009). cART had no effect on endothelial dysfunction, while arterial stiffness was higher in patients treated with cART (10 [0–15] vs. –5 [–10–3], p = 0.014).

Conclusions: Endothelial dysfunction is common in HIV-infected patients. In general, none of the analysed factors had an effect on endothelial function but cART had a negative effect on arterial stiffness.

Key words: HIV, combined antiretroviral therapy, endothelial dysfunction, arterial stiffness

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INTRODUCTION

Human immunodeficiency virus (HIV) infection and subsequent acquired immune deficiency syndrome (AIDS) are a pandemic of the 21st century. The number of HIV-infected worldwide has been estimated at about 34 million. In Poland, about 27,000 people are infected with HIV [1]. With modern antiretroviral therapy, early diagnosis, and prompt treatment, life expectancy of HIV-infected subjects does not differ significantly from that of the general population [2]. As a result, concomitant, mostly age-related conditions become more common in these patients. Cardiovascular (CV) disease is the most common cause of death among HIV-infected subjects receiving antiretroviral therapy [3, 4]. For this reason, identification of subclinical changes in the CV system, including endothelial dysfunction and increased arterial stiffness, may be important for prevention and monitoring of CV disease.

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Endothelial dysfunction is an early marker of coronary artery disease and peripheral arterial disease [5]. As endothelial dysfunction is reversible, its early identification may be of major prognostic and therapeutic importance [6]. Endothelial dysfunction is not limited to coronary vessels, where it is technically difficult to assess, but may be also measured in a clinically useful way in peripheral vessels [7, 8]. Reactive hyperaemia peripheral arterial tonometry (RH-PAT) is a non-invasive technique allowing functional evaluation of peripheral microcirculation vessels by measuring changes in tissue tone during reactive hyperaemia [9, 10]. Patients with endothelial dysfunction in the coronary microcirculation were shown to be characterised by low peripheral hyperaemic response compared to subjects with normally functioning coronary endothelium [11].

In addition to functional changes, vascular remodelling may also be an indicator of preclinical changes in coronary and peripheral arteries. Previous studies showed that arterial stiffness is an independent risk factor for CV events and correlates with all-cause mortality [12]. Measurement of the augmentation index (AI) is an indirect method to evaluate arterial stiffness.

It was shown that HIV infection is associated with increased levels of inflammatory interleukins, which correlate with higher levels of von Willebrand factor and tissue plasminogen activator [13]. These are biochemical indicators of endothelial damage in this patient group. The role of nitric oxide (NO), a factor exerting a major effect on endothelial function, has been discussed in multiple papers [14]. HIV proteins reduce endothelial NO synthase level and decrease arterial elasticity, as shown in porcine models [15]. Viral gp120 glycoprotein induces endothelial damage by stimulating macrophages to produce NO [16].

The aim of this study was to evaluate the prevalence of endothelial dysfunction and arterial stiffness and the effect of antiretroviral therapy on endothelial function and arterial stiffness, and thus on CV risk in HIV-infected patients.

METHODS

Study group

We studied 37 adult patients with the diagnosis of HIV infection. Assessment of endothelial function and arterial stiffness was from January 2011 till November 2013. Exclusion criteria included pregnancy and lactation women, previous combination antiretroviral therapy (cART) interrupted less than 6 months prior to study inclusion, and neoplasms unrelated to HIV infection. All patients gave written informed consent for participation in the study. The study protocol was approved by the bioethics committee at the Medical University of Warsaw.

Clinical evaluation and laboratory testing

Each patient underwent history taking and physical examination within 7 days prior to evaluation of endothelial function and arterial stiffness. During physical examination, particular attention was paid to evaluation of CV risk factors, including body mass index and blood pressure. At the same time, blood samples were taken for laboratory testing. Laboratory tests included complete blood count with quantitative evaluation of CD4+ and CD8+ cells, number of viral copies, serum creatinine, bilirubin, alanine and aspartate aminotransferase, gammaglutamyltransferase, C-reactive protein, and D-dimer levels, and lipid profile.

Combined antiretroviral therapy and patient monitoring

Decisions to initiate or continue cART were made based on the Polish AIDS Society recommendations [17], taking into account history, physical examination, and laboratory test findings. Other factors taken into account when making decisions regarding the choice of therapy included family situation, occupation, planned pregnancy, bone disease, HIV-associated nephropathy, liver dysfunction associated with hepatitis B and/or C virus infection, and psychiatric disease.

Evaluation of endothelial function and arterial stiffness

In each patient, RH-PAT assessment was performed using the Endo-PAT2000 device (ITAMAR®). The device allows non-invasive evaluation of endothelial function and indirect assessment of vascular stiffness. Its mechanism of action is based on endothelium-dependent arterial response to 5-min brachial artery occlusion. Temporary upper limb ischaemia results in a subsequent increase in blood flow within the evaluated vascular bed. This response is based on endothelium-dependent vasodilatation in reaction to a local decrease in partial oxygen tension and increase in potassium ion concentration. In these circumstances, endothelium releases local factors that cause arterial smooth muscle relaxation. Peripheral Arterial Tonometry (PAT®) is a patented technology allowing non-invasive measurements of changes in the arterial tone within peripheral vascular beds. The non-invasive Endo-PAT2000 system includes a pair of plethysmographic sensors that impart a uniform pressure field to distal two thirds of the fingers including their tips. To standardise results, measurements in all patients were performed in a sitting position after at least 15 min of rest, allowing stabilisation of the CV system and adjustment to the ambient temperature. In all cases, patient's hand were supported at the heart level. After placing sensors connected to the Endo-PAT2000 device on index fingers of both hands and a sphygmomanometer cuff on one arm, a baseline measurement was performed. Brachial artery flow was then occluded for 5 min by inflating the cuff. Following this period, pressure was released and further PAT measurements were made. The duration of a single examination was about 15 min. The degree of arterial tone changes in response to ischaemia was expressed as the reactive hyper-

aemia index (RHI). Normal endothelial function was defined as RHI > 1.67. This cutoff value was suggested by the device manufacturer based on previous studies [9, 18]. Baseline pressure waveform obtained by PAT was used to calculate AI using the height of two systolic waveform peaks. Due to a significant effect of heart rate on AI, AI values were corrected for heart rate using an arbitrarily defined reference heart rate of 75 bpm, commonly used in other studies that evaluated arterial stiffness [12]. Endothelium-independent arterial response to transient ischaemia was not evaluated in the present study.

Statistical analysis

Qualitative variables were reported as percentages and in some cases also as absolute values. All quantitative variables were reported as medians and interquartile ranges. The exact Fisher test and the Mann-Whitney U test were used to evaluate between-group differences in qualitative and quantitative variables, respectively. Correlations between quantitative variables were evaluated using the Spearman correlation coefficient. Univariate logistic regression analysis was used to determine the odds ratio of endothelial dysfunction. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the SAS software, version 9.2.

RESULTS

Our final analysis included 37 patients. Median age was 38 years (range 32–45 years), and men comprised 89.2% of the study group. Endothelial dysfunction was found in 13 (35.1%) HIV-infected subjects. No significant differences were found between subjects with or without endothelial dysfunction in regard to demographic and clinical data, laboratory test results, and use of cardiac medication, except for platelet count that was significantly lower in subjects with endothelial dysfunction compared to those without endothelial dysfunction (174 [119–193] $\times 10^3/mm^3$ vs. 222 [168–266] $\times 10^3/mm^3$, $p = 0.03$). Among patients with endothelial dysfunction, platelet count $< 150 \times 10^3/mm^3$ was found in 31% of subjects, compared to 17% among patients without endothelial dysfunction. A trend for higher heart rate and higher triglyceride levels was also noted among patients with endothelial dysfunction. Detailed comparison of patients with and without endothelial dysfunction is shown in Table 1. None of the demographic and clinical parameters was an independent predictor of endothelial dysfunction among HIV-infected patients. Similarly, we did not find an association between factors related to HIV infection and chronic drug therapy and the risk of endothelial dysfunction. These data are shown in Table 2. Of all demographic, clinical, and laboratory data, a significant association was found between arterial stiffness and patient age ($\rho_s = 0.53$, $p < 0.001$), red blood cell count ($\rho_s = -0.39$, $p = 0.018$), and platelet count ($\rho_s = 0.42$, $p = 0.009$). In addition, a trend was noted between serum high density lipoprotein cholesterol level and arterial stiffness ($\rho_s = -0.36$, $p = 0.08$).

Number of CD4+ and CD8+ cells and the number of viral copies

Our findings indicate no significant association between the number and percentage proportions of CD4+ and CD8+ cells and endothelial dysfunction. Similarly, the number of viral copies did not differ between patients with and without endothelial dysfunction. Detailed data are shown in Table 3. Arterial stiffness was found to be inversely proportional to the number of viral copies in individual patients ($\rho_s = -0.39$, $p < 0.01$). No significant association was found between arterial stiffness and the number and percentage proportions of CD4+ and CD8+ cells.

Combination antiretroviral therapy

Antiretroviral therapy was used in 20 (54.1%) patients. The most commonly used drugs were nucleoside reverse transcriptase inhibitors. No significant association was found between cART and endothelial dysfunction. The rates of particular drug class use in patients with and without endothelial dysfunction are shown in Table 4. In contrast, we found an association between cART and arterial stiffness. Compared to patients not receiving cART, those on cART were characterised by higher arterial stiffness (10 [0–15] vs. –5 [–10–3], $p = 0.014$). Higher arterial stiffness was noted in patients treated with nucleoside reverse transcriptase inhibitors and protease inhibitors. Detailed data are shown in Table 5.

DISCUSSION

Our findings indicate that endothelial dysfunction is relatively common among HIV-infected patients. Although large studies evaluating endothelial dysfunction in healthy young adults are lacking, available data indicate that the prevalence of endothelial dysfunction in this population is less than 25% [19, 20]. We were unable to identify demographic, clinical, or laboratory factors that would clearly indicate an increased risk of endothelial dysfunction. In addition, no factors identified those HIV-infected patients in whom increased arterial stiffness would be more prevalent.

HIV infection and endothelial dysfunction

Previous studies showed that HIV infection is associated with endothelial dysfunction. Solages et al. [21] evaluated flow mediated dilatation (FMD) in the brachial artery and found a higher degree of endothelial dysfunction among HIV-infected patients compared to the control group. Defining normal FMD as 7%, that study showed that the prevalence of endothelial dysfunction among HIV-infected patients was nearly 50%, higher than in our study. However, our patients were younger and had less concomitant conditions that adversely affect the endothelium. A high degree of endothelial

Table 1. Baseline patient characteristics and assessment of endothelial function

	Overall (n = 37)	Endothelial dysfunction (n = 13)	No endothelial dysfunction (n = 24)	P
Endothelial function and arterial stiffness				
Reactive hyperaemia index	1.90 (1.57–2.50)	1.47 (1.34–1.57)	2.22 (1.93–2.80)	< 0.0001
AI@75	2 (–5–11)	1 (–5–4)	6 (–5–15)	0.40
Demographic data				
Men	89.2%	84.6%	917%	0.60
Age [years]	38 (32–45)	36 (32–43)	39 (31–46)	0.58
Clinical data				
Body mass index [kg/m^2]	22.8 (21.0–26.0)	23.0 (22.0–26.0)	22.8 (20.6–25.9)	0.47
SBP [mm Hg]	125 (110–140)	134 (110–140)	120 (115–135)	0.58
DBP [mm Hg]	80 (70–80)	80 (70–90)	80 (70–80)	0.53
Heart rate [bpm]	75 (70–90)	80 (73–94)	74 (68–82)	0.09
Smoking	56.8%	61.5%	54.2%	1.0
Atrial fibrillation	0.0%	0.0%	0.0%	1.0
Hypertension	5.4%	7.7%	4.2%	1.0
Diabetes	0.0%	0.0%	0.0%	1.0
History of MI	0.0%	0.0%	0.0%	1.0
History of stroke	0.0%	0.0%	0.0%	1.0
HBV infection	8.1%	15.4%	4.2%	0.27
Previous HBV infection	18.9%	15.4%	20.8%	1.00
HCV infection	21.6%	30.8%	16.7%	0.41
Laboratory tests				
RBC [10^6/mm^3]	4.46 (3.79–5.03)	4.46 (3.94–5.15)	4.50 (3.77–5.02)	0.75
Haemoglobin [g/dL]	14.3 (13.2–15.3)	14.0 (12.6–15.3)	14.3 (13.3–15.3)	0.80
Platelets [10^3/mm^3]	194 (160–231)	174 (119–193)	222 (168–266)	0.03
WBC [10^3/mm^3]	5.5 (4.9–7.4)	5.8 (4.8–7.7)	5.5 (5.0–7.2)	0.82
Serum creatinine [mg/dL]	0.82 (0.72–0.94)	0.77 (0.68–0.92)	0.82 (0.76–0.96)	0.34
Serum bilirubin [mg/dL]	0.69 (0.57–1.18)	0.78 (0.61–1.91)	0.66 (0.55–1.18)	0.56
AlAT [U/L]	34 (25–51)	39 (24–68)	31 (25–40)	0.35
AspAT [U/L]	27 (23–52)	52 (23–81)	26 (23–36)	0.20
GGTP [U/L]	34 (25–59)	59 (25–70)	29 (22–44)	0.13
C-reactive protein [mg/L]	4.5 (< 1–10)	5 (4–8)	4 (< 1–14)	0.98
D-dimer [μg/L]	405 (193–821)	592 (352–1022)	396 (153–726)	0.49
Total cholesterol [mg/dL]	172.5 (149.0–206.0)	177.9 (157.5–205.4)	168.2 (146.3–206.0)	0.37
Triglycerides [mg/dL]	121.2 (89.4–212.4)	164.6 (102.2–288.1)	120.4 (82.3–176.1)	0.09
HDL cholesterol [mg/dL]	44.7 (32.7–53.5)	48.3 (28.9–55.4)	43.7 (36.0–49.9)	0.93
LDL cholesterol [mg/dL]	103.2 (72.8–125.9)	91.0 (68.9–127.1)	105.3 (74.7–125.7)	0.92
Chronic drug therapy				
Beta-blocker	8.1%	7.7%	8.3%	1.0
ACE inhibitor	5.4%	7.7%	4.2%	1.0
Angiotensin receptor antagonist	2.7%	0.0%	4.2%	1.0
Statin	8.1%	0.0%	12.5%	0.53
Diuretic	2.7%	7.7%	0.0%	0.35
Acetyl salicylic acid	2.7%	0.0%	4.2%	1.0
P2Y12 inhibitor	0.0%	0.0%	0.0%	1.0
Calcium antagonist	0.0%	0.0%	0.0%	1.0

AI@75— augmentation index standardised for a heart rate of 75 bpm; SBP — systolic blood pressure; DBP — diastolic blood pressure; MI — myocardial infarction; HBV — hepatitis B virus; HCV — hepatitis C virus; RBC — red blood cells; WBC — white blood cells; AlAT — alanine aminotransferase; AspAT — aspartate aminotransferase; GGTP — gammaglutamyltransferase; HDL — high density lipoprotein; LDL — low density lipoprotein; ACE — angiotensin-converting enzyme

Table 2. Univariate analysis

Parameters	Odds ratio for endothelial dysfunction	P
Male gender	0.50 (0.06–4.04)	0.52
Age [years]	0.97 (0.91–1.04)	0.36
Body max index [kg/m^2]	1.01 (0.85–1.20)	0.91
Systolic blood pressure [mm Hg]	1.01 (0.97–1.05)	0.56
Diastolic blood pressure [mm Hg]	1.03 (0.97–1.09)	0.40
Heart rate [bpm]	1.06 (0.99–1.12)	0.08
Smoking	1.35 (0.34–5.36)	0.67
Hypertension	1.92 (0.11–33.41)	0.66
HBV infection	4.18 (0.34–51.24)	0.26
Previous HBV infection	0.69 (0.68–4.18)	0.69
HCV infection	2.22 (0.45–10.94)	0.32
AI@75	0.96 (0.91–1.02)	0.20
CD4+ cells [1/mm^3]	1.00 (0.99–1.01)	0.96
Percentage of CD4+ cells [%]	1.00 (0.96–1.03)	0.80
CD8+ cells [1/mm^3]	1.00 (0.99–1.01)	0.70
Percentage of CD8+ cells [%]	1.01 (0.97–1.05)	0.80
Number of viral copies [1/mm^3]	1.00 (1.00–1.00)	0.53
Total cholesterol [mg/dL]	1.01 (0.99–1.03)	0.25
Triglycerides [mg/dL]	1.01 (1.00–1.02)	0.06
HDL cholesterol [mg/dL]	1.00 (0.94–1.06)	0.99
LDL cholesterol [mg/dL]	1.00 (0.97–1.03)	0.99
Antiretroviral therapy	0.61 (0.16–2.38)	0.48
Nucleoside reverse transcriptase inhibitors	0.53 (0.13–2.09)	0.36
Non-nucleoside reverse transcriptase inhibitors	0.90 (0.18–4.40)	0.90
Protease inhibitors	0.42 (0.09–1.93)	0.26
Integrase inhibitors	1.92 (0.11–33.41)	0.66
Beta-blockers	0.92 (0.08–11.18)	0.95
Angiotensin-converting enzyme inhibitors	1.92 (0.11–33.41)	0.66

HBV — hepatitis B virus; HCV — hepatitis C virus; AI@75 — augmentation index standardised for a heart rate of 75 bpm; HDL — high density lipoprotein; LDL — low density lipoprotein

dysfunction is also seen in patients on chronic cART [22]. It was shown that among patients receiving cART for at least 2 years, abnormal FMD indicating endothelial dysfunction may be present in more than 50% of subjects. Of note, the method to evaluate endothelial dysfunction in the above mentioned studies differed from the currently used approach. FMD measurements are a subjective method that mostly evaluates endothelial function in the macrocirculation. The objective RH-PAT approach used in our study mostly evaluates small vessel endothelial function. As this method has been relatively recently introduced into the clinical practice, no studies are available that would use it to evaluate endothelial function in HIV-infected patients. A significant effect of low platelet count on endothelial function is also of interest. Low platelet count is a typical feature of HIV infection. As indicated by Torre and Pugliese [23], similar pathogenetic mechanisms may be responsible for both low platelet count and endothelial dysfunction in HIV-infected patients.

Severity of HIV infection and disturbances of endothelial function and arterial structure

Our study did not show a significant association between the number and percentage of CD4+ and CD8+ cells and the number of viral copies (i.e., viral load) and endothelial dysfunction. An earlier study showed that the number of viral copies may have a negative effect on endothelial function [24]. That study was, however, performed in patients who at least 30 viral copies per mL, while in our study, had 15 patients had viral load below the limit of detection, i.e. 40 copies per mL. This might have affected the observed lack of association between the number of viral copies and endothelial function in the present study. On the other hand, Dube et al. [25] found no significant association between the number of viral copies and endothelial function and also obtained similar results in regard to the number of CD4+ cells. These data are consistent with our findings, indicating that neither the number of viral copies nor the number of CD4+ cells were predictors of endothelial dysfunction. Both these parameters also had no effect on arterial stiffness, as shown in a study in 261 HIV-infected patients [26]. Of note, despite no effect of the number of CD4+ cells determined at the time of arterial stiffness testing, the lowest number of CD4+ cells found during the patient's lifetime was indeed identified as a predictor of increased arterial stiffness. However, we did not analyse such data in our study, and thus we are unable to provide any further interpretation of that particular finding.

Combination antiretroviral therapy and endothelial dysfunction and arterial stiffness

Our analysis showed no significant association between cART and endothelial dysfunction. Both the use of any cART and the use of specific drug classes had no effect on endothelial function. These findings are partially consistent with the results of previous studies. Some of them showed no association between either the fact or duration of cART, while others indicated a negative effect of cART, particularly using protease inhibitors, on endothelial function [25, 27]. It is also of interest that levels of circulating biomarkers of endothelial injury decrease following initiation of cART, which may indicate its beneficial role in preventing endothelial dysfunction [28]. Previous studies showed a significant negative association between the degree of arterial stiffness and the use of cART, particularly with nucleoside and non-nucleoside reverse tran-

Table 3. Number and percentage of CD4+ and CD8+ cells and the number of viral copies in patients with or without endothelial dysfunction

	Overall (n = 37)	Endothelial dysfunction (n = 13)	No endothelial dysfunction (n = 24)	P
CD4+ cells [1/mm^3]	366 (135–546)	366 (168–509)	372 (123–561)	0.91
Percentage of CD4+ cells [%]	30 (30–44)	27.0 (20.0–44.0)	32.0 (18.0–42.5)	0.89
CD8+ cells [1/mm^3]	692 (522–1024)	733 (525–1024)	659 (449–978)	0.68
Percentage of CD8+ cells [%]	66 (58–76)	66.0 (55.0–76.0)	67.5 (58.5–77.0)	1.0
Number of viral copies [1/mm^3]	758 (< 40–35997)	7601 (154–94328)	377 (< 40–24739)	0.11

Table 4. Effect of combination antiretroviral therapy on endothelial function

	Overall (n = 37)	Endothelial dysfunction (n = 13)	No endothelial dysfunction (n = 24)	P
Antiretroviral therapy	54.1%	46.2%	58.3%	0.51
Nucleoside reverse transcriptase inhibitors	48.6%	38.5%	54.2%	0.49
Non-nucleoside reverse transcriptase inhibitors	24.3%	23.1%	25.0%	1.00
Protease inhibitors	35.1%	23.1%	41.7%	0.31
Integrase inhibitors	5.4%	7.7%	4.2%	1.00

Table 5. Effect of combination antiretroviral therapy on arterial stiffness as evaluated based on augmentation index standardised to a heart rate of 75 bpm (AI@75)

	AI@75 in patients receiving a given drug	AI@75 in patients not receiving a given drug	P
Antiretroviral therapy	10 (0–15); n = 20	–5 (–10–3); n = 17	0.014
Nucleoside reverse transcriptase inhibitors	11 (1–16); n = 18	–5 (–10–4); n = 19	0.006
Non-nucleoside reverse transcriptase inhibitors	1 (–5–11); n = 9	3 (–6–12); n = 28	0.77
Protease inhibitors	11 (4–16); n = 13	–3 (–8–6); n = 24	0.017
Integrase inhibitors	1 (–9–11); n = 2	2 (–5–13); n = 35	0.82

scriptase inhibitors, while no such association could be clearly shown for protease inhibitors [25, 29]. Our conclusions are only partially consistent with previously reported results. The observed association between higher viral load and reduced arterial stiffness should be likely interpreted in the context of the use of cART, as it seems that not the low number of viral copies but the use of cART itself has a negative effect on arterial stiffness.

Limitations of the study

One limitation of the present study is a small number of participants. Assessment of endothelial function was offered to all patients presenting about every 6 months for follow-up appointments at the Department of Hepatology and Acquired Immune Deficits, Medical University of Warsaw. The studied group was heterogeneous in regard to the types and duration of antiretroviral therapy, which certainly rendered our findings more difficult to interpret, particularly in regard to the effect of cART on endothelial function and arterial stiffness. In our study, we used an indirect method to evaluate arterial stiffness based on AI measurements. It is considered less precise than the current reference method of pulse wave velocity measurements.

CONCLUSIONS

Our study showed that endothelial dysfunction is common among HIV-infected patients. However, we were unable to identify factors directly affecting endothelial dysfunction in this patient group. Of the evaluated factors, cART was found to have a possible effect resulting in increased arterial stiffness. In view of a pilot nature of the present study, we will continue to follow up the included patients and recruit new ones. This may help in identification of parameters that might indicate an increased CV risk in these patients.

Conflict of interest: *none declared*

References

1. UNAIDS. Joint united nations program on HIV/AIDS and world health organization: UNAIDS Report On The Global Aids Epidemic, 2009.
2. Lewden C, Chene G, Morlat P et al. HIV-infected adults with a cd4 cell count greater than 500 cells/mm3 on long-term combination antiretroviral therapy reach same mortality rates as the general population. J Acquir Immune Defic Syndr, 2007; 46: 72–77.
3. Sackoff JE, Hanna DB, Pfeiffer MR, Torian LV. Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York city. Ann Int Med, 2006; 145: 397–406.
4. Rawdanowicz J, Pikto-Pietkiewicz W, Marczynska M. Cardiovascular diseases associated with HIV infection and their management. Kardiol Pol, 2013; 71: 1183–1187.
5. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature, 1993; 362: 801–809.
6. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol, 2003; 23: 169–175.
7. Anderson TJ, Gerhard MD, Meredith IT et al. Systemic nature of endothelial dysfunction in atherosclerosis. Am J Cardiol, 1995; 75: 71B–74B.
8. Anderson TJ. Assessment and treatment of endothelial dysfunction in humans. J Am Coll Cardiol, 1999; 34: 631–638.
9. Bonetti PO, Barsness GW, Keelan PC et al. Enhanced external counterpulsation improves endothelial function in patients with symptomatic coronary artery disease. J Am Coll Cardiol, 2003; 41: 1761–1768.
10. Gerhard-Herman M, Creager MA, Hurley S, et al. Assessment of endothelial function (nitric oxide) at the tip of a finger. Circulation, 2002; 102 (suppl. II): 851.
11. Bonetti PO, Pumper GM, Higano ST et al. Noninvasive identification of patients with early coronary atherosclerosis by assessment of digital reactive hyperemia. J Am Coll Cardiol, 2004; 44: 2137–2141.
12. VlachopoulosC, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cuse mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol, 2010; 55: 1318–1327.
13. deLarranaga GF, Petroni A, Deluchi G et al. Viral load and disease progression as responsible for endothelial activation and/or injury in human immunodeficiency virus-1-infected patients. Blood Coagual Fibrynolysis, 2003; 14: 15–18.
14. Torre D. Nitric oxide and endothelial dysfunction in HIV type 1 infection. Clin Infect Dis, 2006; 43: 1086–1087.
15. Paladugu R, Fu W, Conklin BS. Hiv tat protein causes endothelial dysfunction in porcine coronary arteries. J Vasc Surg, 2003; 38: 549–555.
16. Chi D, Henry J, Kelley J et al. The effects of HIV infection on endothelial function. Endothelium, 2000; 7: 223–242.
17. Horban A, Podlasin R, Cholewinska G et al. Zasady opieki nad osobami zakażonymi HIV. Zalecenia PTN AIDS, 2011–2013.
18. Bonetti PO, Pumper GM, Higano ST et al. Research highlights — editorial review of a noninvasive test for endothelial dysfunction. Nature Clin Practice Cardiovasc Med, 2005; 2: 64–65.
19. Chatterjee Adhikari M, Guin A, Chakraborty S et al. Subclinical atherosclerosis and endothelial dysfunction in patients with early rheumatoid arthritis as evidenced by measurement of carotid intima-media thickness and flow-mediated vasodilatation: an observational study. Semin Arthritis Rheum, 2012; 41: 669–675.
20. Celermajer DS, Sorensen KE, Georgakopoulos D et al. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. Circulation, 1993; 88: 2149–2155.
21. Solages A, Vita JA, Thornton DJ et al. Endothelial Function in HIV-infected persons. Clin Infect Dis, 2006; 42: 1325–1332.
22. Masiá M, Padilla S, García N et al. Endothelial function is impaired in HIV-infected patients with lipodystrophy. Antivir Ther, 2010; 15: 101–110.
23. Torre D, Pugliese A. Platelets and HIV-1 infection: old and new aspects. Curr HIV Res, 2008; 6: 411–418.
24. Blum A, Hadas V, Burke M et al. Viral load of the human immunodeficiency virus could be an independent risk factor for endothelial dysfunction. Clin Cardiol, 2005; 28: 149–153.
25. Dubé MP, Shen C, Mather KJ et al. Relationship of body composition, metabolic status, antiretroviral use, and HIV disease factors to endothelial dysfunction in HIV-infected subjects. AIDS Res Hum Retroviruses, 2010; 26: 847–854.
26. Monteiro P, Miranda-Filho DB, Bandeira F et al. Is arterial stiffness in HIV-infected individuals associated with HIV-related factors? Braz J Med Biol Res, 2012; 45: 818–826.
27. Shankar SS, Dubé MP, Gorski JC et al. Indinavir impairs endothelial function in healthy HIV-negative men. Am Heart J, 2005; 150: 933.
28. Kristoffersen US, Kofoed K, Kronborg G et al. Reduction in circulating markers of endothelial dysfunction in HIV-infected patients during antiretroviral therapy. HIV Med, 2009; 10: 79–87.
29. Sevastianova K, Sutinen J, Westerbacka J et al. Arterial stiffness in HIV-infected patients receiving highly active antiretroviral therapy. Antivir Ther, 2005; 10: 925–935.

Ocena funkcji śródbłonka i sztywności naczyń u pacjentów zakażonych HIV: badanie pilotażowe

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Streszczenie

Wstęp: Dzięki stosowaniu kompleksowej terapii antyretrowirusowej (cART, *combined antiretroviral therapy*) długość życia pacjentów zakażonych HIV nie różni się istotnie od populacji ogólnej. Oznacza to, że wśród tych osób wzrasta częstość występowania chorób towarzyszących. W prewencji oraz monitorowaniu chorób układu sercowo-naczyniowego istotne może się okazać wykrywanie subklinicznych zmian w układzie krążenia, w tym dysfunkcji śródbłonka i nadmiernej sztywności tętnic.

Cel: Celem badania była ocena częstości występowania dysfunkcji śródbłonka wśród pacjentów zakażonych HIV oraz znalezienie czynników wpływających na pojawienie się dysfunkcji śródbłonka i wpływających na sztywność tętnic.

Metody: Do badania włączono 37 dorosłych chorych z rozpoznanym zakażeniem HIV, bez względu na fakt i rodzaj prowadzonej cART. Kryteria wyłączenia obejmowały: kobiety w ciąży lub karmiące piersią, cART przerwaną krócej niż 6 miesięcy przed włączeniem do badania oraz pacjentów z nowotworami niezwiązanymi z zakażeniem HIV. U każdego chorego wykonano badanie oceniające obwodową tonometrię tętniczą reaktywnej hiperemii przy użyciu urządzenia Endo-PAT2000 firmy ITAMAR®. Metoda ta pozwalała na czynnościową ocenę funkcji śródbłonka i sztywności tętnic.

Wyniki: Do końcowej analizy włączono 37 osób. Mediana wieku chorych wynosiła 38 lat (32–45 lat), 89,2% całej badanej grupy stanowili mężczyźni. Dysfunkcję śródbłonka stwierdzono u 13 (35,1%) osób zakażonych HIV. Uwzględniając dane demograficzne, kliniczne, wyniki badań laboratoryjnych oraz terapię lekami kardiologicznymi, nie wykazano istotnych różnic między osobami z dysfunkcją śródbłonka i bez niej. Wyjątek stanowiła jedynie liczba płytek krwi, która była istotnie statystycznie niższa u pacjentów z dysfunkcją śródbłonka w porównaniu z pozostałymi chorymi (174 [119–193] *vs.* 222 [168–266]; p = 0,03). Żaden z parametrów demograficznych i klinicznych nie okazał się niezależnym predyktorem wystąpienia dysfunkcji śródbłonka w grupie chorych zakażonych HIV. Podobnie nie wykazano korelacji między czynnikami związanymi z zakażeniem HIV oraz stosowaną przewlekle farmakoterapią a ryzykiem wystąpienia dysfunkcji śródbłonka. Zaobserwowano istotny statystycznie związek między sztywnością tętnic a wiekiem pacjenta (ρ_s = 0,53; p < 0,001), liczbą czerwonych krwinek (ρ_s = –0,39; p = 0,018) i liczbą płytek krwi (ρ_s = 0,42; p = 0,009). Biorąc pod uwagę sztywność tętnic, wykazano, że jest ona odwrotnie proporcjonalna do liczby kopii wirusa identyfikowanej u poszczególnych chorych (ρ_s = –0,39; p = 0,0018). W porównaniu z chorymi bez cART, chorzy poddani cART charakteryzowali się wyższą sztywnością naczyń (10 [0–15] *vs.* –5 [–10–3]; p = 0,014).

Wnioski: Niniejsze badanie pokazało, że dysfunkcja śródbłonka jest częstym zjawiskiem występującym wśród chorych zakażonych HIV. Brakuje czynników wpływających bezpośrednio na zaburzenie funkcji śródbłonka w tej grupie osób. Kompleksowa terapia antyretrowirusowa może mieć działanie negatywne, zwiększające sztywność tętnic. W związku z pilotażowym charakterem badania, będzie prowadzona dalsza obserwacja już włączonych pacjentów i rekrutacja nowych. Może to pomóc w ustalenia parametrów, które mogą wskazać osoby o podwyższonym ryzyku sercowo-naczyniowym.

Słowa kluczowe: HIV, kompleksowa terapia antyretrowirusowa, dysfunkcja śródbłonka, sztywność tętnic

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