Organ Damage in HIV-Positive Patients with High Blood Pressure

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Abstract

Our objective has been the investigation of possible cardiovascular or renal organ damage in HIV patients with confirmed high blood pressure by means of instrumental cardiovascular investigation and renal function evaluation. A total of 265 consecutive patients accessing our outpatient facility were enrolled in the study. Patients with confirmed pathological pressure values or high normal values were submitted to clinical and instrumental monitoring by 24-hour ambulatory blood pressure monitoring (ABPM), to derivation of 12-lead ECG registration, to echocardiography and to epi-aortic vessel echo-color-Doppler. The ECG and echocardiographic data were compared to a control group of 40 hypertensive HIV-negative subjects. Renal damage was evaluated by means of the microalbuminuria/creatininuria ratio on a spot urine sample, plus 24-hour albuminuria and proteinuria measurements. 61 (23.0%) of the subjects examined were hypertensive: 24 (39.3%) had a previous hypertensive diagnosis but had never been treated for this condition, and 37 (60.7%) had a new diagnosis; in 100% of cases, 24-hour ABPM confirmed the hypertension and 27.8% of the patients resulted non-dippers. The ECG showed left ventricle overload, V4-V6 strain, or left ventricular hypertrophy in 64.3% of cases compared to 35.7% in the control group. Echocardiography demonstrated increasing in left ventricle parietal thickness with concentric remodeling and hypertrophy in 85.2% of patients. HIV-positive patients showed a statistically significant tendency to concentric remodeling and concentric hypertrophy, even in presence of mild hypertension. Echocolor-Doppler examination detected intima-media thickness > and/or carotid plaques in 72.1% of patients. Renal function seems spared in these subjects. Our data highlights the importance of investigating arterial hypertension among our patients as it is a frequently undiagnosed condition, and illustrates the utility of 24-hour ABPM to confirm hypertension and to identify the non-dipper subject. Moreover, the ECG, echocardiography and echocolor-Doppler examinations evidenced a premature tendency to organ damage in these patients that showed altered cardiac remodeling compared to those without HIV. This stresses the need for an early diagnosis, including a complete instrumental evaluation to properly identify organ damage even at a subclinical level.

Keywords: Antiretroviral therapy; High blood pressure; Cardiovascular damage; Renal organ damage

Background

The introduction of highly active antiretroviral therapy (HAART) has resulted in a completely new approach to HIV-infection and has determined a lower association of morbidity and mortality, thus initiating a profound transformation of the disease which is progressively becoming a chronic condition. Nevertheless, the long-term toxicity provoked by HAART might present an obstacle to the hope of a life expectancy similar to that of the general population.

In particular, a disputed problem is that of high blood pressure in HIV-infected patients and its consequences in terms of organ damage. In fact, hypertension is a common condition in HIV-infected people, although the real prevalence is still unclear, ranging from 13 to 34% [1-3].

Hypertension is treatable disease, although, if neglected, it is considered a established risk factor for cardiovascular and kidney diseases. Nevertheless, few studies have reported the prevalence of important abnormalities in cardiac structure and function, blood vessels and kidneys among HIV-positive persons. 12-lead ECG registration, 24-hour ambulatory blood pressure monitoring (ABPM), echocardiography, epi-aortic vessel echo-color-Doppler, microalbuminuria/creatininuria ratio on a spot urine sample, plus 24-hour albuminuria and proteinuria measurements together with glomerular filtration rate (GFR) assessment, are simple, repeatable, inexpensive and well validated tools for the diagnosis of premature cardiovascular and kidney changes due to hypertension.

The objective of this study was to investigate possible cardiovascular or renal organ damage in HIV patients with confirmed high blood pressure by means of instrumental cardiovascular and renal function evaluation.

Patients and Methods

A total of 265 consecutive patients accessing our outpatient facility from September 2010 to September 2011 were enrolled in the study. Patients in treatment with antihypertensive agents and patients with acute pathologies were excluded.

Data collection (except imaging) occurred at the clinic site and coincided with subjects’ schedule of routine blood collection. Imaging studies coincided with schedule of routine physical examination, generally no more than a fortnight later.

The blood pressure of each patient was measured after at least 5-10 minutes of rest, and each final value was based on the mean of three different measurements. The degree of hypertension was classified according to the European Society of Hypertension and European Society of Cardiology guidelines for the management of arterial hypertension [4]. Patients showing pathological pressure values with

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alterations of either systolic or diastolic pressure > 140/90 mmHg for hypertension or > 130/85 mmHg for High Normal blood pressure confirmed in two different sessions within 6 months were submitted to clinical and instrumental monitoring by ABPM. Measurements were performed on a weekday with a validated oscillometric automatic device (Spacelabs 90207, SpaceLabs, Redmond Wash.) which recorded BP and heart rate at 20-minute intervals during the day (07:00–22:00) and 30-minute intervals during the night (22:00–07:00). Cuff size was selected according to measured arm circumference and the non-dominant arm was used. Patients were instructed to keep their arm still during BP measurements to ensure good-quality recordings. Hypertension diagnosis was confirmed if day-time readings were ≥135/85 mmHg [4].

A nocturnal non-dipping blood pressure profile was defined as 10% or lesser magnitude reduction in average systolic and/or diastolic blood pressure at night time compared to daytime systolic blood pressure average values. The remainder defined as dipping blood pressure [5,6].

Patients were then submitted to derivation of 12-lead ECG registration, to echocardiography and to epi-aortic vessel echo-color-Doppler.

Left ventricular hypertrophy on ECG was defined as RaV1 + SV3 > 24 mm for males and 20 mm for females (Cornell modified). V4-V6 strain pattern on ECG was defined as ST-T segment vector shifted in > 24 mm for males and 20 mm for females (Cornell modified). V4-V6 strain pattern on ECG was defined as ST-T segment vector shifted in direction opposite to mean QRS vector in V4-V6 leads.

Echocardiograms were performed according to standardized procedures described elsewhere [7-11]. Studies were recorded on videotape and digitized offline on a commercially available workstation. They were interpreted by a single experienced reader (GA) blinded to the study [7]. Left Ventricular Mass Index was calculated as follows: m-mode 2D driven from left ventricle, immediately under blinded to the study [7]. Left Ventricular Mass Index was calculated procedures described elsewhere [7-11]. Studies were recorded in a comfortable room. Patients were informed that the investigation was non-invasive. The common, internal, and external carotid vessels were subjected to the investigation using a last generation power color-Doppler. The speed measurements were performed based backbone, and 3 (4%) with a zidovudine-based backbone, while 39 (63.9%) with a tenofovir-based backbone, 31 (50.8%) had a protease inhibitor as a third drug, and 29 (47.5%) a non-nucleoside reverse transcriptase inhibitor. One patient (1.6%) was treated with a abacavir-based backbone, 39 (63.9%) with a tenofovir-based backbone, and 3 (4%) with a zidovudine-based backbone, while 31 (50.8%) had a protease inhibitor as a third drug, and 29 (47.5%) a non-nucleoside reverse transcriptase inhibitor. One patient (1.6%) was not subjected to antiretroviral treatment.

The ECG and echocardiographic data were compared to a control group of 40 hypertensive HIV-negative subjects with normal renal function, consecutively accessed during the same period at the outpatient facility of the Department of Cardiology and matched for median age, gender, and blood pressure. The control group was composed of 1/3 of the patients attending the out-patient clinic who were hypertensive but HIV negative, a samples size according with a right statistical analysis. Both patients with a previous hypertensive diagnosis but not in treatment (17 pts: 42.5%) and patients of new diagnosis (23 pts: 57.5%) were included in control group. Renal damage was evaluated by means of the microalbuminuria/creatininuria ratio on a spot urine sample, plus 24-hour albuminuria and proteinuria measurements (values respectively >30 mg/g and >3 g/24h were considered pathological) and by means of GRF assessment calculated both with Cockcroft-Gault and CKD-EPI. Values of <60 ml/min for one or both formulas were considered pathological. We did not use MDRD formula because it tends to overestimate if GFR <60 ml/min.


**Statistical analysis**

Data were expressed as mean +/- SD or median. Statistical comparison between mean values of each parameter was performed by the Mann-Withney U-test for non paired samples. Variation of each parameter of each groups of patients was performed by the non-parametric multiple pared sample test, according to the Friedman’s test, which restitutes a Chi-square value.

**Results**

Of the 265 subjects examined, 61 (23.0%) were hypertensive: 24 (39.3%) had a previous hypertensive diagnosis but had never been treated for this condition, and 37 (60.7%) had a new diagnosis; all had Grade 1 hypertension (<160/100 mmHg). Mean age was 46.7 (range: 37-59) and 42 were males. In 100% of cases, 24-hour ABPM confirmed the hypertension diagnosed at screening and 17 (27.8%) patients resulted non-dippers. Regarding antiretroviral therapy, 19 patients (31.1%) were treated with a abacavir-based backbone, 39 (63.9%) with a tenofovir-based backbone, and 3 (4%) with a zidovudine-based backbone, while 31 (50.8%) had a protease inhibitor as a third drug, and 29 (47.5%) a non-nucleoside reverse transcriptase inhibitor. One patient (1.6%) was not subjected to antiretroviral treatment.

The ECG showed pathological patterns in 64.3% of cases compared to 35.7% in the control group. The documented alterations were: left ventricle overload, V4-V6 strain, and signs of left ventricular hypertrophy.

Echocardiography demonstrated pathological results in 52 patients (85.2%). 38 of them were dippers, 14 non-dippers. In patients with echocardiographic alterations, left ventricle parietal thickness was increased with concentric remodeling and hypertrophy. Diastolic filling and isovolumetric relaxation time were often modified. A similar pattern was present both in non-dipper and in dipper patients. When compared to the control group, HIV-positive patients showed a statistically significant tendency to concentric remodeling and concentric hypertrophy, even in presence of mild hypertension. Data
regarding 24-hr ABPM, ECG and echocardiographic evaluations are summarized in Table 1.

Echocolor-Doppler examination detected intima-media thickness (IMT) of >1 mm and/or atherosclerotic plaques in 72.1% of patients.

Evaluation of GFR with Cockroft-Gault and CKD-EPI, microalbuminuria/creatininuria ratio on spot urine sample, 24-hour albuminuria and proteinuria measurements demonstrated normal values in all subjects except one who was affected with a polycystic kidney disease.

**Discussion**

High blood pressure was found in 23% of our patients. Interestingly, in 60.7% of patients hypertension was diagnosed for the first time. This suggests that the proportion of undiagnosed hypertension among HIV patients is still relevant. The majority of these hypertensive patients are relatively young (mean age 46.7). The 24-hr ABPM confirmed the hypertension diagnosed at screening in 100% of the cases and indicates the importance of this diagnostic tool in confirming a suspect of hypertension. The 24-hr ABPM demonstrates a higher sensitivity for detection of the individual pressure load in addition to a better reproducibility and better predictor of clinical outcome with respect to the standard outpatient measures [12,22,23]. Moreover, 24-hr ABPM provides indications regarding the circadian pressure rhythm. In fact, under physiological conditions, blood pressure is reduced about 10-20% during sleep (dipping) [24]. Non-dipper patients are at a higher

<table>
<thead>
<tr>
<th></th>
<th>HIV-1 patients</th>
<th>Control group</th>
<th>p (significance level 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>24-hours Ambulatory Blood Pressure (BP) Monitoring</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mean day systolic BP (mmHg)</td>
<td>148.15</td>
<td>149.04</td>
<td>0.8574</td>
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<tr>
<td>Mean day diastolic BP (mmHg)</td>
<td>97.01</td>
<td>89.92</td>
<td>0.5962</td>
</tr>
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<td>Mean day frequency beats per minute (bpm)</td>
<td>79.57</td>
<td>78.44</td>
<td>0.5624</td>
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<td>Mean night systolic BP (mmHg)</td>
<td>129.54</td>
<td>128.88</td>
<td>0.5123</td>
</tr>
<tr>
<td>Mean night diastolic (mmHg)</td>
<td>78.70</td>
<td>79.82</td>
<td>0.7895</td>
</tr>
<tr>
<td>Mean night frequency (bpm)</td>
<td>90.58</td>
<td>71.72</td>
<td>0.7374</td>
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<tr>
<td><strong>Dipper</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>71.42%</td>
<td>78.58%</td>
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<tr>
<td>no</td>
<td>28.58%</td>
<td>21.42%</td>
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<tr>
<td><strong>ECG^</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S V3</td>
<td>11.29</td>
<td>10.93</td>
<td>0.8276</td>
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<tr>
<td>R aVL</td>
<td>6.70</td>
<td>7.00</td>
<td>0.7963</td>
</tr>
<tr>
<td>QT</td>
<td>0.39</td>
<td>0.40</td>
<td>0.4970</td>
</tr>
<tr>
<td>FC</td>
<td>68.50</td>
<td>70.86</td>
<td>0.6044</td>
</tr>
<tr>
<td><strong>left ventricular overload</strong></td>
<td></td>
<td></td>
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<tr>
<td>yes</td>
<td>57.2%</td>
<td>35.7%</td>
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<tr>
<td>no</td>
<td>42.8%</td>
<td>64.3%</td>
<td></td>
</tr>
<tr>
<td><strong>Left ventricular hyper trophy</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>64.3%</td>
<td>35.7%</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>35.7%</td>
<td>64.3%</td>
<td></td>
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<tr>
<td>Left Ventricular Internal Dimension diastole (mm)</td>
<td>46.88</td>
<td>48.90</td>
<td>0.3127</td>
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<td>Left Ventricular Internal Dimension systole (mm)</td>
<td>27.15</td>
<td>30.23</td>
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<td>Interventricular septum (mm)</td>
<td>11.58</td>
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<td>Posterior wall (mm)</td>
<td>10.49</td>
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<td>Left ventricular Ejection fraction (%)</td>
<td>74.29</td>
<td>72.86</td>
<td>0.4816</td>
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<tr>
<td>E wave velocity</td>
<td>58.84</td>
<td>73.94</td>
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<td>A wave velocity</td>
<td>72.75</td>
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<td>Isovolumic relaxation time (msec)</td>
<td>117</td>
<td>96</td>
<td>0.0057</td>
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<td>Left atrium (mm)</td>
<td>29.27</td>
<td>29.39</td>
<td>0.6589</td>
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<tr>
<td>Aortic root (mm)</td>
<td>33.46</td>
<td>30.70</td>
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<tr>
<td>Relative wall thickness</td>
<td>0.50</td>
<td>0.40</td>
<td>0.5620</td>
</tr>
<tr>
<td>Left ventricular mass (LVM) (g)</td>
<td>231.92</td>
<td>196.94</td>
<td>0.1767</td>
</tr>
<tr>
<td>LVM indexed to body surface area (g/m2)</td>
<td>117.86</td>
<td>101.93</td>
<td>0.2016</td>
</tr>
</tbody>
</table>

* p-value = 1
** p-value = 0.4495
*** p-value = 0.2568

^ ECG parameters were expressed in mV (1 mV = 10 mm).

**Table 1:** Results of 24-hr ABPM, ECG and echocardiographic evaluations and comparison with the control group.
risk of organ damage [25-28] and cardiovascular complications [29-31]. In our study, 27.8% of patients resulted non-dipper, thus confirming the results of a previous study indicating that 35% of non-dippers were found among antiretroviral naive HIV-positive patients compared to 15% in HIV-negative subjects [32].

ECG frequently demonstrated pathologic patterns with typical signs of high blood pressure in HIV-positive patients with respect to HIV negatives (64.3 vs 35.7%); even if not statistically significant, studies on a greater sample size are warranted. The most relevant finding of our study was the presence of left ventricle overload and V4-V6 strain (changes of ventricular repolarization in these derivatives: flat-negative T waves with under leveling descending ST), symptomatic of a left ventricular hypertrophy. A pathologic ECG is generally typical of a long standing hypertension: this is in contrast with the young mean age of the patients.

Regarding the echocardiographic examination, the comparison of HIV patients with the control group indicates a statistically significant concentric remodeling and hypertrophy, apparently not justified by the degree of hypertension. Also among the patients with dipper behavior (generally considered a mild form of hypertension), we observed a significant tendency to echoic changes (38 out of 44 patients = 86.3%).

At present, few studies have reported the prevalence of important abnormalities in cardiac structure and function among HAART subjects [33,34]. Hakim et al. in the Proceedings of the International AIDS Conference of 1996, presented an abstract regarding of echocardiographic findings in hospitalized HIV patients demonstrating that 50% of the patients had echocardiographic abnormalities [35]. A more recent study shows that ecocardiographic abnormalities are frequent among HIV patients, ranging from 18% to 40% [36]. These percentages are, however, lower with respect to those emerged in our study.

Moreover, a significant percentage of hypertensive patients (72.1%) showed an intima-media damage at echocolor-Doppler evaluation. This percentage was markedly higher when compared to the 52.4% found in an our previous study on HIV-positive patients with respect to vascular and cardiac damage.

In conclusion, our data highlights the importance of investigating arterial hypertension among our patients as it is a frequently undiagnosed condition, and illustrates the utility of 24-h ABPM to confirm hypertension and to identify the non-dipper subject. Moreover, in our experience, the ECG, echocardiography and echocolor-Doppler examinations evidenced a premature tendency to organ damage in these patients; in particular, a statistically significant altered cardiac remodeling, when compared to those without HIV.

This stresses the need for an early diagnosis, including a complete instrumental evaluation to properly identify organ damage even at a subclinical level.

Acknowledgements

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