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Original article

Left ventricular hypertrophy detected by echocardiography in HIV-infected patients

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ABSTRACT

Background: Left ventricular hypertrophy (LVH) is a predictor of overall mortality in the general population. The most sensitive diagnostic method is transthoracic echocardiography (TTE). In this study, we describe the prevalence of LVH, and the factors associated with it, in a group of patients with HIV infection.
Methods: TTE was offered to all patients attending the outpatient clinic of the Hospital Costa del Sol (Marbella, Spain) between 1 December 2009 and 28 February 2011. The corresponding demographic and clinical data were obtained. The left ventricular mass (LVM) was calculated and indexed by height$^{2.7}$. LVH was defined as LVM >48 g/m$^{2.7}$ in men or >44 g/m$^{2.7}$ in women.
Results: We examined 388 individuals (75.5% male, mean age 45.38 years). Of these, 76.1% were receiving HAART; 11.9% had hypertension, 6.2% had diabetes mellitus, 23.2% had dyslipidaemia and 53.6% were tobacco users. The risk of cardiovascular disease at 10 years (RV10) was 12.15% (95%CI: 10.99–13.31%). 19.1% of these patients had a high RV10. A total of 69 patients (19.8%) presented high LVM. Age, hypertension, dyslipidaemia, RV10 and the use of nevirapine were associated with a greater presence of LVH in the univariate analysis. In the logistic regression analysis performed, the factors retained in the model were the presence of high RV10 (OR: 2.92, 95%CI: 1.39–6.15) and the use of nevirapine (OR 2.20, 95%CI: 1.18–4.14).
Conclusions: In this group of patients, the use of nevirapine and the presence of high RV10 were associated with LVH. The use of nevirapine might be related to its prescription for patients with higher RV10.

1. Introduction

Following the introduction of highly active antiretroviral therapy (HAART) against human immunodeficiency virus (HIV), AIDS-associated morbidity and mortality have declined continuously [1]. However, cardiovascular morbidity and mortality have presented less improvement during this period, compared with the results achieved for AIDS and liver diseases [2]. It has been reported that both HIV infection and HAART may be involved in the occurrence of events such as acute myocardial infarction [3–5], the progression of carotid atherosclerotic disease [6,7] or heart disease [8,9], and that they also influence other parameters of subclinical involvement such as the ankle-brachial index [10]. This has led to the development of various observational, cross-sectional studies focusing on the safety and security of the different components of HAART.

One phenomenon implicated in the pathogenesis of heart disease and the occurrence of cardiovascular events is that of left ventricular hypertrophy (LVH). Increased left ventricular mass (LVM) is a prognostic factor for overall and cardiovascular mortality [11,12], and is the most sensitive method available to diagnose transthoracic echocardiography (TTE). In particular, the presence of LVH, confirmed by TTE, is associated with a relative risk of death from any cause of 1.5–2 compared to patients with normal LVM, and the corresponding value for vascular events is around 2. Increased LVM has been related with gender (higher in women) [13], obesity [14], age [11], hypertension [15] and diabetes mellitus [16], among others.

In recent years, some studies have shown that the prevalence of LVH is higher among HIV-infected patients [17,18], regardless of the associated factors in the non-infected population. Also implicated as factors associated with LVH in patients with HIV infection are the use of inhibitors of nucleoside reverse transcriptase [19] and that of protease inhibitors [20].

In this study we investigate the prevalence of LVH diagnosed by TTE in a cohort of patients with chronic HIV infection and presenting the risk factors associated with its occurrence.

2. Material and methods

2.1. Study design

Descriptive, cross-sectional study performed in patients who regularly attended the HIV clinic at the Costa del Sol Hospital in Marbella (Spain) between 1 December 2009 and 28 February 2011. TTE was offered in all cases. When consent was given, data were obtained

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regarding epidemiological and clinical parameters, as well as for traditional cardiovascular risk factors and variables associated with their HIV infection status. Patients were classed as hypertensive when this was stated in their clinical background, or when their systolic blood pressure exceeded 140 mm Hg or when their diastolic blood pressure was greater than 90 mm Hg, measured on two separate occasions at least three months apart, or when they were receiving antihypertensive treatment. Patients were considered diabetic when this was stated in their clinical background, when they had fasting plasma glucose levels above 126 mg/dl measured on two separate occasions at least three months apart, or when they were receiving treatment with antidiabetic oral agents or insulin. Patients were considered dyslipidaemic when this was stated in their clinical background, when they had LDL cholesterol levels above 160 mg/dl or triglycerides equal to or greater than 150 mg/dl, or when they were receiving treatment with hypolipidaemic drugs. Patients were considered HBV co-infected if they had antibodies to HBV core antigen (AntiHbcAc), and HCV co-infected if they presented positive ELISA for HCV. We calculated the duration of HIV infection assuming its onset to be the first serology (Western blot analysis) positively reflected in the patient's medical history. Ten years cardiovascular risk was estimated by the Framingham equation, which is shown in the European AIDS Clinical Society web site, available in: http://www.cphiv.dk/TOOLS/Framingham/tabid/302/Default.aspx. Risk was classified as follows: <10% low risk, 10–20% intermediate risk and >20% high risk. Medical histories in our hospital are computerized, so every patient's report was reviewed considering medication prescribed in each visit. For this purpose, a team of antiretroviral therapy experienced doctors was designed, with extensive knowledge of available drug combinations.

TTE was performed by a single expert echocardiographer, using a Siemens Acuson Sequoia C256 with 3.5 MHz transducer. Measurements were performed on the parasternal long axis, using the 2D-guided M mode, and recording the following parameters: LV diastolic and systolic diameter (LVDD and LVSD, respectively), interventricular septal thickness (IVS) and posterior wall (PW) thickness, ejection fraction and left atrial volume, following the guidelines of the American Society of Echocardiography (ASE) [21].

LVM was measured by the following formula: LVM (ASE) = $0.8 \times \{1.04\ [(\mathrm{LVDD} + \mathrm{IVS} + \mathrm{PW})^3 - (\mathrm{LVDD})^3]\} + 0.6$ g, adjusting for height$^{2.7}$ to avoid underestimating the prevalence of LVH in obese or overweight patients. The normal range bounds specified by the ASE were used to establish the presence or otherwise of LVH in men and women (>48 g/m$^{2.7}$ and >44 g/m$^{2.7}$ respectively).

2.2. Statistical analysis

Data were compiled directly into SPSS 15.0 (Statistical Package for Social Sciences, Inc. Chicago, Illinois, USA). The quantitative variables were described using the mean, with a 95% confidence interval (95%CI), and the qualitative variables are given as percentages. The quantitative variables were compared using Student's t test, after verifying the normality of the samples; when this condition was not met, the Mann–Whitney test was used. The qualitative variables were compared using the χ^2 test. In the initial analysis, the dependent variable was taken as the presence of LVH, according to the criteria stipulated above. The variables that presented a statistical association with LVH ($p < 0.05$) were included in the logistic regression analysis, using a forward stepwise method. The odds ratio (OR) was calculated at 95%CI and statistical significance was set at $p < 0.05$. At the decision of the investigator, the antiretrovirals (ARVs) that were not given to at least five patients in each group (normal and elevated LVM) were omitted from the logistic regression analysis.

3. Results

TTE was performed on a total of 388 patients (Table 1) of whom the majority were male (75.5%). The average age of the study participants was 45.38 years (95%CI: 44.4-46.3). The main route of virus acquisition was via heterosexual transmission (38.4%). The average duration of HIV infection was 9.13 years (95%CI: 8.5–9.8). Only 13.9% of patients were naive to antiretroviral therapy (ART); of those who received ART, the average exposure was 6.20 years (95%CI: 5.7–6.7). 25.3% presented AIDS-associated parameters. The mean count of CD4 lymphocytes was 650/μl (95%CI: 616–685), with a mean nadir of 286 cells/μl (95%CI: 263–309). Viral load values were obtained for 98.2% of the participants, and remained below 50 copies/mL in 65.5% of the patients. 32.2% of the patients were co-infected with HCV. The average body mass index (BMI) was 24.9 kg/m^2 (95%CI: 24.4–27.3).

Regarding the classical cardiovascular risk factors, 11.9% of the patients were hypertensive, 6.2% had diabetes mellitus, 23.2% dyslipidaemia and 53.6% consumed tobacco. The 10-year risk of cardiovascular disease (RV10) was 12.15% (95%CI: 11–13.3). 19.1% of the patients had a high RV10.

Nineteen patients were under antithrombotic therapy (4.8%), 23 (5.8%) received betablocker, 16 (4%) ACE inhibitors, 12 (3%) Angiotensin II receptor blocker, 5 (1.3%) dihydropyridines, 2 (0.5%) doxazosin, 8 (2%) diuretics, 45 (11.3%) statins, 20 (5%) fibrates, 1 (0.3%) ezetimibe, 4 (1%) fatty acids, 16 (4.1%) oral antidiabetic and 4 (1%) insulin.

3.1. Prevalence of high LVM

A total of 69 patients (19.8%) presented LVH. The average LVM value was 39.6 g/m$^{2.7}$ (95%CI 38.3–40.7).

3.2. Use of ART

The antiretroviral (ARV) most frequently used, according to the patients' clinical histories, was tenofovir (61.1%). Among nonnucleoside reverse transcriptase inhibitors (NNRTI), efavirenz was the most used (55.2%), and among protease inhibitors (PI) lopinavir–ritonavir was the most widely used (18.6%).

With respect to the accumulated use of ARV, lamivudine had been used for longest (62.2 months, 95%CI: 56.4–68.07). Among nucleoside reverse transcriptase inhibitors, zidovudine had the longest accumulated use (50.3 months, CI95%: 44.2–56.5); nevirapine had the longest accumulated use among NNRTI (51 months, CI95%: 41.4-60.8) and fosamprenavir–ritonavir among PI (28 months, CI95%: 19.2–36.9). At the time of data compilation, again tenofovir was the most commonly used (54.1%), followed by efavirenz (52.3%).

3.3. Factors associated with LVH

The patients with high LVH presented a higher average age (49 vs. 44.6 years, $p = 0.001$). There were no significant differences in immunovirological status. The proportion of patients with HCV co-infection was lower among the patients with high LVH (22.4% vs. 34.3%) without reaching statistical significance ($p = 0.058$). The latter also had a higher BMI (27.4 vs. 24.4 kg/m^2).

LVH was more frequent among hypertensive patients (19.1 vs. 10.4%, $p = 0.04$) and those with dyslipidaemia (34.8% vs. 20.7%, $p = 0.012$). RV10 was greater among patients with LVH (16.7% vs. 11.1%, $p = 0.001$), and moreover there was a higher proportion of patients with high RV among those with LVH (32.4% vs. 16.2%, $p = 0.001$).

With respect to the use of ARVs, a history of nevirapine use was more frequent among patients with LVH (17.6% vs. 33.3%, $p = 0.003$), as was also the case with maraviroc, although in this case, there were only six patients. We also observed an association between the current use of maraviroc and a lower cumulative exposure to enfuvirtide.

We performed a logistic regression analysis (Table 2), which included the duration of ART (assessed by the researcher), hypertension, dyslipidaemia, RV10 (categorised as low, medium or high) and the use of nevirapine in the patient's clinical history. The factors retained in the model were the presence of high RV10 (OR 2.92,