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Doppler tissue imaging unmasks right ventricular function abnormalities in HIV-infected patients

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Abstract

Background: *We sought to investigate right ventricular (RV) function with Doppler tissue imaging (DTI) in human immunodeficiency virus (HIV)-infected patients receiving highly-active antiretroviral treatment, without any heart-related symptoms.*

Methods: *We studied 38 asymptomatic HIV patients (aged 44.5 ± 9.2 years, 22 of them men) and 25 age-matched and sex-matched controls. All subjects underwent conventional and DTI estimation of left ventricular (LV) systolic and diastolic function, measuring peak systolic and diastolic myocardial velocities at the mitral annulus (Sm, Em, Am). Two-dimensional (2-D) echocardiographic study of the right ventricle (RV) was performed from the four-chamber view, and RV end-diastolic dimensions were measured. DTI recordings from the RV free wall at the tricuspid annulus were used to determine systolic (Sm_{RV}) and diastolic function (Em_{RV} and Am_{RV}).*

Results: *HIV-infected patients compared to controls exhibited significantly lower peak systolic velocities at the septal-Sm_{IVS} (7.9 ± 1.3 vs 9.1 ± 1.4 cm/s, p = 0.002) and lateral mitral annulus — Sm_{LAT} (9.8 ± 1.7 vs 11.2 ± 1.3 cm/s, p = 0.025); no difference was observed regarding conventional 2-D examination of LV systolic and diastolic function and DTI-derived Em and Am. No significant difference occurred between HIV patients and controls regarding RV end-diastolic dimensions and pulmonary artery systolic pressure. However, Sm_{RV} (13.8 ± 1.6 vs 14.9 ± 2.2 cm/s, p = 0.040), Em_{RV} (11.6 ± 3 vs 13.5 ± 2.6 cm/s, p = 0.028) and Am_{RV} (10.9 ± 2.5 vs 13.8 ± 4 cm/s, p = 0.003) were significantly reduced in HIV patients as compared to controls.*

Conclusions: *DTI unmasks subtle and otherwise undetectable abnormalities of the longitudinal LV systolic function and both RV systolic and diastolic function, in asymptomatic HIV patients receiving highly-active antiretroviral treatment.* (Cardiol J 2010; 17, 6: 587–593)

Key words: HIV, right ventricular function, Doppler tissue imaging

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Introduction

Cardiac abnormalities have been reported in a substantial proportion of patients infected with the human immunodeficiency virus (HIV) and are associated with increased morbidity and mortality [1–3]. Among them, left ventricular (LV) dysfunction seems to be caused by a self-limiting myocarditis that rarely progresses to overt LV failure, while isolated right ventricular (RV) dysfunction may be either transient, as in cases of acute respiratory infection and parenteral drug use, or permanent, in the late disease complicated with pulmonary hypertension [4–7].

However, most studies have been undertaken before the era of highly-active antiretroviral treatment (HAART), which has significantly reduced HIV-associated morbidity and mortality rates [8]. Accordingly, few studies have screened for sub-clinical cardiac abnormalities in HIV-infected patients with well-controlled viral and immune status, providing contradictory data. Assessment of cardiac function through radionuclide ventriculography has exhibited rare left-sided impairment but a significant reduction in RV ejection fraction [9]. In contrast, evaluation of cardiac function using conventional echocardiography and novel techniques, including Doppler tissue imaging (DTI), revealed subtle systolic and consistent diastolic impairment regarding LV, whereas RV parameters, except for the arterial pulmonary pressure, were not affected [10–12]. Taking into account that DTI estimates contractility in the longitudinal axis and reveals abnormalities earlier when compared to conventional echocardiography, we assessed RV function with DTI in HIV-infected patients receiving HAART without any heart-related symptoms.

Methods

Study design

Our study population consisted of 38 patients (aged 44.5 ± 9.2 years, range 23–57, 30 of them men) with positive HIV serology and absence of any heart-related symptoms. The mean time from the diagnosis of HIV infection was 54 ± 30 months. Among them, 12 were in clinical stage A, 14 in clinical stage B and 12 in clinical stage C, according to the CDC criteria [13]. All patients included were receiving HAART, including two nucleoside analogues as backbone plus either a non-nucleoside analogue and/or a protease inhibitor. Antibody levels against HIV were measured by an enzyme linked immunosorbent assay and confirmed by western blot analysis. HIV-RNA was fully suppressed in 30 patients. CD4+ cell counts were determined within three days of the echocardiographic study (Facscan flow cytometer, Becton Dickinson, San Jose, California, USA). Furthermore, 25 apparently healthy, age-matched and sex-matched individuals (aged 43 ± 9.7 years, range 22–56, 19 of them men) with negative HIV serology were enrolled as control subjects.

Patients with ischemic, hypertrophic, congenital or rheumatic cardiomyopathy, ethanol abuse (> 90 g/day), diabetes mellitus, significant valvular disease, and those with grade 2 and 3 hypertension according to the European Society of Hypertension/ /European Society of Cardiology guidelines were excluded from the study [14]. Moreover, HIV patients requiring antihypertensive and/or lipid lowering medications were also excluded. The ethics committee of our institution approved the study and all patients gave written informed consent.

Echocardiographic methods

Standard transthoracic examination. Conventional echocardiographic examination was performed with a commercially available imaging system (SSA-380A Toshiba Powervision, Japan) using a 2.5-MHz phased array transducer employing second harmonic imaging by a single experienced operator, who was unaware of the subjects' subgroup. Two-dimensional (2-D) guided M-mode measurements of LV and left atrial dimensions were obtained in the parasternal long-axis view according to current guidelines [15]. LV mass was calculated according to Devereux et al. [16] and normalized for body surface area to obtain LV mass index [17]. Relative wall thickness was calculated at end diastole according to the following equation: (interventricular septum thickness + posterior wall thickness)/(LV end-diastolic diameter). LV ejection fraction was assessed using the biplane Simpson's method using conventional apical four- and two--chamber views. LV diastolic function was determined using conventional Doppler parameters (peak velocities of E and A waves of the transmitral flow, E/A ratio, isovolumic relaxation time and the deceleration time of the E wave).

Pulsed-wave Doppler tissue imaging. After establishing the resting baseline measurements, a pulse wave DTI study was carried out, as previously described [11, 18]. From the apical four-chamber view, a 5 mm pulsed Doppler sample volume for DTI was positioned just apical to the septal and lateral mitral annulus. Every effort was made to obtain a Doppler angle of incidence close to zero

Table 1. Clinical characteristics of the study population.

	HIV (n = 38)	Controls (n = 25)	p
Age (years)	44.5 ± 9.2	43.3 ± 9.7	0.78
Males (%)	78	76	0.82
Body mass index [kg/m^2]	25.0 ± 4.0	26.8 ± 3.7	0.11
Systolic blood pressure [mm Hg]	125.5 ± 12.0	124.3 ± 13.0	0.62
Diastolic blood pressure [mm Hg]	73.8 ± 9.0	72.0 ± 10.5	0.51
Heart rate [bpm]	80.1 ± 14.0	76.0 ± 13.0	0.25
CD4 count [cells/mL]	663 ± 236		
Viral load [copies/mL]	66.7 ± 30		
Nucleoside reverse transcriptase inhibitors (%)	100		
Non-nucleoside reverse transcriptase inhibitors (%)	47.4		
Protease inhibitors (%)	65.8		

CD4 count — viral load levels and medication data are available only for HIV patients

degrees between the interrogating Doppler beam and the longitudinal motion of the LV, to adjust the sample volume size proportionally to annular motion and to obtain recordings at end-expiratory apnea. The peak systolic myocardial velocities at the septal (Sm_{IVS}) and lateral (Sm_{LAT}) mitral annulus, as well as the peak early and late diastolic velocities (Em_{IVS}-Em_{LAT} and Am_{IVS}-Am_{LAT} respectively), and the ratios Emax/Em_{IVS} and Emax/Em_{LAT} were calculated. The value assigned to each parameter was the average of five cycles.

Right ventricular examination. The 2-D echocardiographic study of the RV was performed from the four-chamber view, and the following parameters were measured at end-diastole: tricuspid annular diameter was measured between the hinge points of the leaflets with the lateral wall and the septum. Longitudinal RV diameter was measured from the midpoint of tricuspid annular diameter to RV apex. Mid-cavity diameter was also measured at the four-chamber view [15, 19]. DTI recordings from the RV free wall at the tricuspid level were used to determine local systolic (Sm_{RV}) and diastolic function (Em_{RV} and Am_{RV}). Tricuspid regurgitation velocity was measured using continuous-wave Doppler. Pulmonary artery systolic pressure was determined using the modified Bernoulli equation ($P = 4 \times V^2$ + right atrial pressure). The use of the inferior vena cava size and dynamics was applied for estimation of the right atrial pressure [15].

Statistical analysis

SPSS statistical package, release 15.0 (SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses. Normality was tested using the Kolmogorov-Smirnov criterion. Logarithmic transformation was performed for skewed distributions before any parametric analysis. Significant differences between the study sub-groups were determined using the Student independent-samples test or the χ^2 test, where appropriate. Analysis of covariance (ANCOVA) was performed in order to eliminate any influence of age and body mass index on detected differences between HIV-infected subjects and controls. Correlation analyses were performed using the Pearson's correlation coefficient. Descriptive statistics were arithmetic means ± standard deviation or medians (interquartile range) for skewed data. Statistical significance was set at $p < 0.05$.

Results

The clinical characteristics of our study population are summarized in Table 1 and the results of the echocardiographic indices are presented in Tables 2–4 and Figures 1 and 2.

Left ventricular function

As regards LV function, conventional 2-D echocardiographic examination did not show any difference for all the variables studied between groups (Table 2). Indeed, no difference was found between HIV-infected patients and control individuals concerning the systolic performance ($p = 0.49$), the LV end-systolic ($p = 0.31$) and end-diastolic ($p = 0.82$) dimensions, as well as LV mass index ($p = 0.50$) and relative wall thickness ($p = 0.14$). Similarly, conventional Doppler study did not reveal any differences in the diastolic function of HIV-infected patients and controls, including LV relaxation (i.e. isovolumic relaxation time, $p = 0.82$), and LV filling (deceleration time, Emax, Amax, and Emax/Amax ratio).

Table 2. Comparison of left ventricular conventional echocardiographic variables between HIV patients and controls.

	HIV (n = 38)	Controls (n = 25)	p
Fractional shortening (%)	37.0 ± 5.5	37.0 ± 4.5	0.56
Ejection fraction (%)	66 ± 5	65 ± 7	0.49
LV end diastolic diameter [mm]	48.8 ± 4.6	47.5 ± 4.9	0.31
LV end systolic diameter [mm]	30.0 ± 3.9	29.8 ± 4.2	0.82
IVS [mm]	8.6 ± 1.7	9.1 ± 1.4	0.22
Posterior wall [mm]	8.8 ± 1.4	8.8 ± 1.0	0.99
Relative wall thickness	0.35 ± 0.05	0.38 ± 0.05	0.14
LV mass [g]	157.0 ± 46.0	154.5 ± 36.0	0.82
LV mass index [g/m^2]	82.9 ± 19.0	79.6 ± 16.6	0.50
Left atrial diameter [mm]	37.7 ± 4.4	35.9 ± 5.4	0.19

LV — left ventricular; IVS — interventricular septum thickness

Table 3. Comparison of left ventricular transmitral and Doppler tissue imaging variables between HIV patients and controls.

	HIV (n = 38)	Controls (n = 25)	p
Emax [cm/s]	75.5 ± 14.0	72.7 ± 17.0	0.52
Amax [cm/s]	63.7 ± 13.0	61.0 ± 15.0	0.49
Emax/Amax	1.23 ± 0.34	1.27 ± 0.48	0.74
IVRT [ms]	87.7 ± 12.6	84.5 ± 14.2	0.82
DT [ms]	210 ± 44	195 ± 37	0.19
Sm_{LAT} [cm/s]	9.8 ± 1.7	11.2 ± 1.3	**0.025**
Em_{LAT} [cm/s]	12.8 ± 4.0	13.0 ± 4.7	0.87
Am_{LAT} [cm/s]	9.7 ± 2.8	9.4 ± 2.8	0.66
Em_{LAT}/Am_{LAT}	1.46 ± 0.75	1.55 ± 0.90	0.69
$Emax/Em_{LAT}$	6.3 ± 1.7	5.9 ± 1.5	0.48
Sm_{IVS} [cm/s]	7.9 ± 1.3	9.1 ± 1.4	**0.002**
Em_{IVS} [cm/s]	9.8 ± 2.3	9.7 ± 3.8	0.94
Em_{IVS} [cm/s]	8.4 ± 2.0	9.3 ± 2.0	0.10
Em_{IVS}/Am_{IVS}	1.22 ± 0.40	1.11 ± 0.55	0.37
$Emax/Em_{IVS}$	8.0 ± 1.9	8.0 ± 2.2	0.99

Emax and Amax — peak velocity of transmitral E and A waves; IVRT — isovolumic relaxation time; DT — deceleration time; Sm_{LAT}/Sm_{IVS} — peak systolic myocardial velocities at the left ventricular (LV) lateral and septal wall, respectively; Em_{LAT}/Em_{IVS} and Am_{LAT}/Am_{IVS} — peak early diastolic and atrial systolic velocity at the lateral and septal LV wall

Table 4: Comparison of right ventricular conventional and Doppler tissue imaging echocardiographic variables between the groups studied.

	HIV (n = 38)	Controls (n = 25)	p
TAD [mm]	27.3 ± 4	27.2 ± 4	0.94
RVd 1 [mm]	29.5 ± 4.5	27.8 ± 4.2	0.15
RVd 2 [mm]	65.3 ± 8	68.8 ± 5.4	0.07
PASP [mm Hg]	26.1 ± 3.8	24.3 ± 3.2	0.09
Sm_{RV} [cm/s]	13.8 ± 1.6	14.9 ± 2.2	**0.040**
Em_{RV} [cm/s]	11.6 ± 3	13.5 ± 2.6	**0.028**
Am_{RV} [cm/s]	10.9 ± 2.5	13.8 ± 4	**0.003**
Em_{RV}/Am_{RV}	1.1 ± 0.32	1.1 ± 0.68	0.90

TAD — tricuspid annular diameter; RVd 1 — mid-cavity diameter; RVd 2 — longitudinal diameter; PASP — pulmonary artery systolic pressure; Sm — peak systolic myocardial velocity at the free right ventricular (RV) wall; Em_{RV} and Am_{RV} — peak early diastolic and atrial systolic velocity at the free RV wall as measured with Doppler tissue imaging

DTI study of the LV showed a significantly lower Sm_{IVS} ($p = 0.002$) and Sm_{LAT} ($p = 0.025$) at the mitral annulus in HIV-infected patients compared to controls, even after adjustment for age and body mass index (Table 3). As far as diastolic function was concerned, no differences were found between HIV patients and controls in both lateral and septal walls regarding peak Em ($p = 0.87$ and 0.94, respectively) and Am velocities ($p = 0.66$ for the lateral and 0.1 for the septal wall), as well as their ratios. Moreover, both the $Emax/Em_{LAT}$ and the $Emax/Em_{IVS}$ ratios did not differ significantly between the two study groups.

Right ventricular function

As far as RV was concerned, there was no difference between HIV patients and controls in RV end-diastolic dimensions (Table 4). Notably, a trend for higher pulmonary artery systolic pressure, even though in the normal range, was observed in the HIV subgroup 26.1 ± 3.8 *vs* 24.3 ± 3.2 mm Hg, $p = 0.09$. Moreover, in HIV patients, peak systolic Sm_{RV} at the RV free wall ($p = 0.040$) and both peak diastolic Em_{RV} ($p = 0.028$) and Am_{RV} ($p = 0.003$) were significantly reduced, even after adjustment for age and body mass index. In addition, Sm_{RV} was posi-

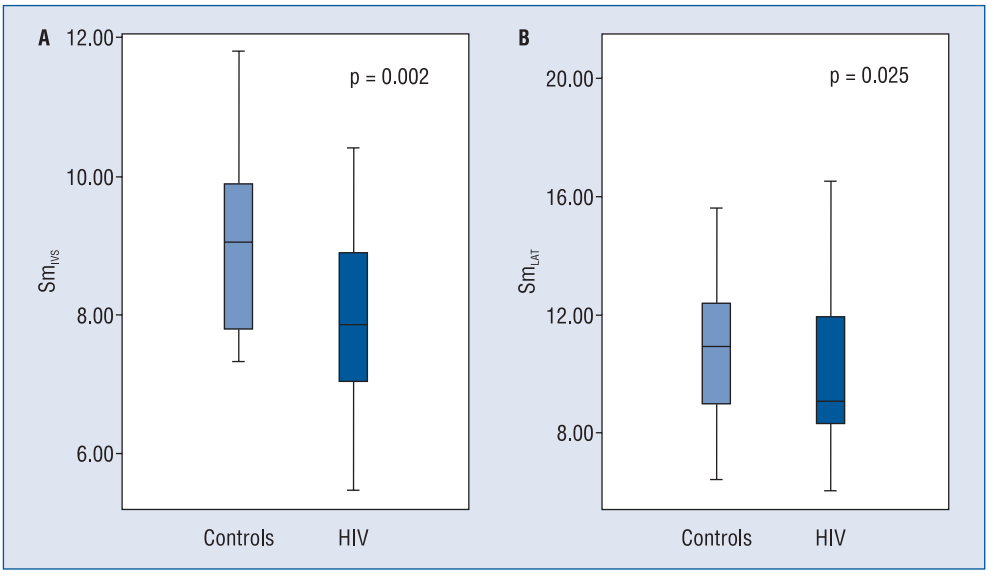

Figure 1. Box plot of peak systolic myocardial velocity at the left ventricular septal (Sm_{IVS}) (**A**) and lateral (Sm_{LAT}) (**B**) wall.

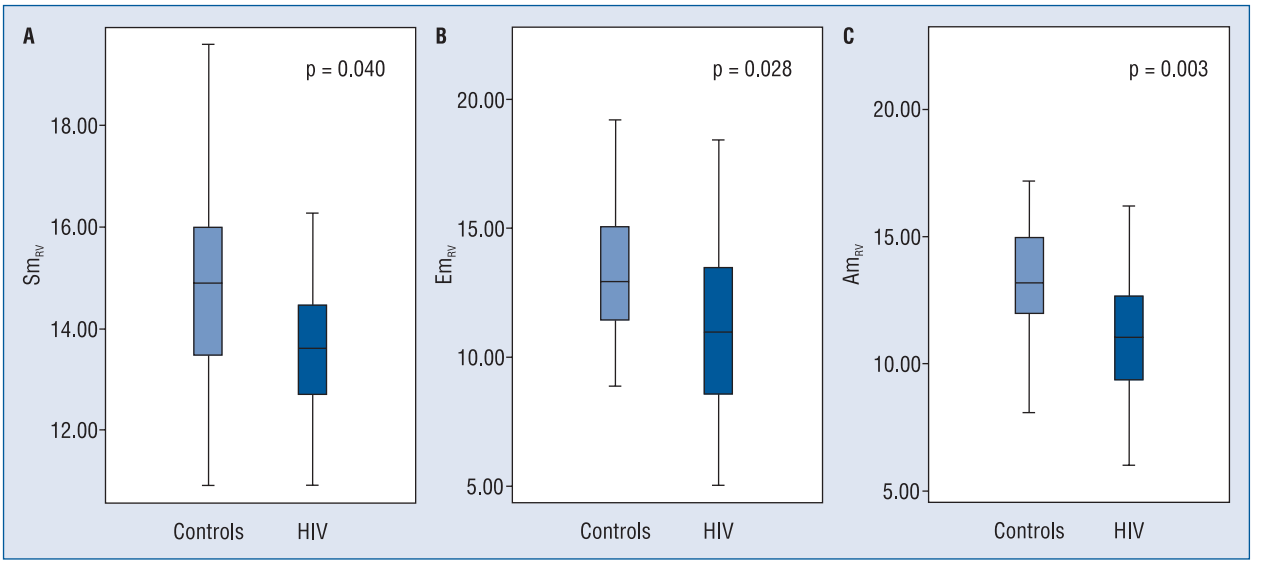

Figure 2. Box plot of peak systolic myocardial velocity (Sm_{RV}) (**A**), peak early diastolic (Em_{RV}) (**B**) and atrial systolic (Am_{RV}) (**C**) velocity at the free right ventricular wall.

tively correlated with Sm_{IVS} ($r = 0.496$, $p < 0.001$) and negatively with age ($r = –0.294$, $p = 0.033$).

Discussion

The main finding of the present study was that in asymptomatic HIV patients receiving HAART, compared with age- and sex-matched control subjects, DTI unmasked subtle (and undetectable by conventional echocardiography) abnormalities of the longitudinal LV systolic function and both RV systolic and diastolic function.

Evidence for the effects of HIV on the heart and vasculature has come most often from studies performed before the current era of HAART, in which viremia was less adequately suppressed. The incidence of LV systolic function in the pre-HAART era varied from 10% to 40% due to the diverse definitions used, as well as to the differences in the disease stages of the patients studied [1, 11, 20].

Shortly after the introduction of HAART, a decrease in HIV-related heart disease was reported, suggesting the beneficial effects of treatments on immunologic status and the subsequent decrease in opportunistic infections and myocarditis [21]. In the present study, we confirmed our previous findings of subtle systolic function abnormalities in patients on HAART, based on DTI measurements rather than conventional echocardiography [11]. The absence of diastolic function abnormalities, either with conventional echocardiography or DTI, in spite of previous reports, may be attributed to differences in the stage of the disease, patients' age, sample size, prevalence of arterial hypertension and metabolic disorders in the populations studied [10, 12, 22]. In addition, as we have previously shown, it seems likely that in asymptomatic HIV-infected patients, longitudinal LV and RV contractile function abnormalities, not otherwise detectable with conventional echo, precede diastolic dysfunction [11].

As far as RV function is concerned, echocardiographic studies conducted before HAART demonstrated the presence of either transient isolated RV dilatation associated with acute respiratory infection and parenteral drug use or pulmonary hypertension in late disease stages [4, 7, 23]. Moreover, in a small study using magnetic resonance imaging, RV ejection fraction impairment was found in one third of the patients when using standard cut-off values [6]. Interestingly, when HIV patients with suppressed viral status were examined using radionuclide ventriculography, a significant proportion (7%) of right-sided cardiac dysfunction, as measured by RV ejection fraction, was observed in the absence of LV dysfunction [9]. However, when cine magnetic resonance imaging was performed in treated HIV patients with radionuclide ventriculography-estimated RV systolic dysfunction, only a minority of them turned out to have a marginally reduced RV ejection fraction, in the setting of normal RV dimensions and mass [24].

In our investigation, DTI-derived peak systolic and diastolic velocities at the RV free wall were significantly reduced in HIV patients under HAART compared to controls, indicating abnormal RV function, at least in the long-axis. DTI study has been shown to be able to unmask subtle and otherwise undetectable cardiac damage because it estimates contractility in the longitudinal axis in contrast to conventional echocardiographic study [25]. Notably, systolic RV abnormalities were closely related with LV ones, suggesting a common underlying pathology. It is of interest that decreased RV diastolic velocities were found in HIV-infected patients in the context of unaffected LV diastolic velocities and in the absence of overt pulmonary hypertension. A possible explanation for the latter finding is that, even in the context of normal range, a trend for higher systolic pulmonary artery pressure was found in HIV-infected patients ($p = 0.09$) compared to healthy subjects. Thus, differences in the pulmonary artery systolic pressures may have altered RV diastolic function.

Cardiac pathological abnormalities in HIV disease are complex, and most probably multifactorial, and have been attributed to a direct myocardial effect of the virus (HIV infection of myocytes or dendritic cells), opportunistic infections, neoplasms, long-term cardiotoxic adverse effects of therapies, autoimmunity and abnormalities in nutritional status [3, 10, 26]. Mitochondrial toxicity of nucleoside reverse-transcriptase inhibitors, largely described in various tissues, including cardiomyocytes, is a possibility, while use of protease inhibitors has been associated with diastolic abnormalities based exclusively on transmitral flow parameters [27, 28]. However, frequent alterations in antiretroviral drug regimens as well as the limited sample size did not allow the correlation of observed cardiac abnormalities to different antiretroviral agents.

As cardiac involvement in HIV-infected patients affects negatively their prognosis (in terms of both morbidity and mortality), an early recognition of either LV or RV dysfunction is crucial. Indeed, even sub-clinical echocardiographic abnormalities independently predict adverse outcomes and identify high-risk groups to target for early intervention and therapy [2]. Under this point of view, DTI may constitute a useful diagnostic tool for asymptomatic HIV-infected patients, aimed at identifying precocious cardiac involvement and beginning appropriate treatment. Particularly, in patients revealing early cardiac function abnormalities with DTI, treatment shifting towards less cardiotoxic antiretroviral therapy should probably be considered. Moreover, early administration of therapy targeting to reduce progression (or cause regression) of early cardiac dysfunction in HIV-infected patients (and whether this approach translates into improved survival) remains to be established from prospective studies.

Limitations of the study

It is unclear whether cardiac abnormalities detected with DTI are more a result of the infection itself or the consequence of the aggressive treatment. Towards this direction assessment of HIV treatment-naive patients would help us dis-

criminate, at least partially, the pathogenic role of HIV infection and treatment separately. Moreover, the time from the diagnosis of HIV infection was different for each patient. As a result, the time period under therapy (or the period without therapy) differs between them. It would be of interest to study prospectively (with serial DTI studies) individuals with a recent exposure to HIV and assess the parameters (and the relative depth of time) which contribute to the longitudinal chambers function impairment. This is a limited size study and, as a result, large scale investigations are required to confirm our findings. However, even this sample size did not prevent us from identifying significant differences between patients and controls, at least for some of the parameters assessed. Furthermore, we have no data on acceleration time of pulmonary flow waves which would significantly improve assessment of pulmonary circulation.

Conclusions

DTI, but not conventional echocardiography, reveals cardiac function abnormalities in asymptomatic HIV patients, with well controlled viral and immune status compared to age- and sex-matched controls. Longitudinal RV systolic and diastolic dysfunction, although less frequently studied, seems to be more prominent in this setting.

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