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ORIGINAL RESEARCH

Inotropic Contractile Reserve Can Risk-Stratify Patients With HIV Cardiomyopathy

A Dobutamine Stress Echocardiography Study

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OBJECTIVES The purpose of this study was to assess whether inotropic contractile reserve (ICR) during dobutamine stress echocardiography (DSE) could risk-stratify patients with human immunodeficiency virus (HIV) cardiomyopathy and predict improvement of left ventricular ejection fraction (LVEF).

BACKGROUND HIV cardiomyopathy is an important cause of heart failure and death. ICR is associated with better survival and improvement of LVEF in patients with ischemic and nonischemic cardiomyopathies. However, the prognostic value of ICR in patients with HIV cardiomyopathy is unknown.

METHODS Patients with HIV cardiomyopathy and a LVEF <45% who were referred for DSE were enrolled. ICR was evaluated by the delta wall motion score index (ΔWMSI), calculated as the difference between rest and peak WMSI. Patients were followed for cardiac death and change in LVEF on follow-up.

RESULTS Sixty patients (75% men; age, 54 ± 9 years) with HIV cardiomyopathy (mean LVEF, 28 ± 11%) formed the study group. After 2.4 ± 2.1 years, 11 cardiac deaths occurred (event rate of 7.6%/year). A receiver-operating characteristic curve identified a ΔWMSI of 0.38 as an optimal cut point for the presence of ICR, with a specificity of 88% and a sensitivity of 73% for the prediction of cardiac death. On univariable analysis, the absence of ICR (hazard ratio: 6.6; 95% confidence interval: 1.93 to 22.62; $p = 0.003$) and New York Heart Association functional class IV (hazard ratio: 7.2; 95% confidence interval: 2.20 to 23.65; $p = 0.001$) were the only predictors of cardiac death. After 2.1 ± 1.8 years, 41 patients had a follow-up echocardiogram. LVEF improvement from baseline occurred in 23 patients (56%), more so in patients with ICR than without ICR. A ΔWMSI of 0.59 predicted improvement in the LVEF with a specificity of 78% and a sensitivity of 74%.

CONCLUSIONS The presence of ICR during DSE can risk-stratify and predict subsequent improvement in LVEF in patients with HIV cardiomyopathy. (J Am Coll Cardiol Img 2011;4:1231–8)

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Human immunodeficiency virus (HIV) cardiomyopathy is an important cause of heart failure and death. The incidence of HIV cardiomyopathy before the introduction of highly active antiretroviral therapy (HAART) was estimated at 15.9 per 1,000 annually (1). After the introduction of HAART, the prevalence of HIV cardiomyopathy decreased about 30% in developed countries (2,3). However, the access to HAART is limited, and the prognosis of those patients in whom HIV cardiomyopathy develops remains poor, with a median survival in acquired immunodeficiency syndrome (AIDS)–related death of 101 days in patients with left ventricular (LV) dysfunction and 472 days in patients with normal LV function at similar infection stage (4). Furthermore, patients with HIV cardiomyopathy had worse survival when compared with all other causes of dilated cardiomyopathy (ischemic and nonischemic) (adjusted hazard ratio [HR]: 5.86; 95% confidence interval [CI]: 3.92 to 8.77) (5).

ABBREVIATIONS AND ACRONYMS

AIDS = acquired immunodeficiency syndrome
CI = confidence interval
DSE = dobutamine stress echocardiography
HAART = highly active antiretroviral therapy
HIV = human immunodeficiency virus
HR = hazard ratio
ICR = inotropic contractile reserve
LV = left ventricular
LVEF = left ventricular ejection fraction
RV = right ventricular
WMSI = wall motion score index

Recent data suggest that the use of aggressive interventions such as ventricular assist devices and heart transplantation in patients with HIV may have a good outcome in selected patients (6,7). Hence, the ability to identify patients with HIV cardiomyopathy at high risk of cardiac death and who may benefit from early aggressive therapy and referral for specialized care would have important prognostic implications.

Dobutamine stress echocardiography (DSE) is clinically useful for distinguishing viable myocardium from scar in both ischemic and nonischemic cardiomyopathy. The presence of inotropic contractile reserve (ICR) is associated with better survival, improvement in regional and global LV function on follow-up, and better response to therapy (8–10). However, whether ICR can risk-stratify and predict left ventricular ejection fraction (LVEF) improvement in patients with HIV cardiomyopathy is not known.

METHODS

Study population. We identified 76 consecutive patients with a known diagnosis of HIV/AIDS and a LVEF <45%, referred to our laboratory for clinically indicated DSE from April 2004 through January 2009. Prospective follow-up was performed in all patients. Patients with a history of hemodynamically significant valvular abnormalities, long-standing or uncontrolled hypertension, known etiology of cardiomyopathy other than HIV, hemodynamic instability, poor acoustic windows (<13 of 16 segments visualized by echocardiography), inability to give informed consent, myocardial infarction, revascularization or hemodynamically significant coronary artery disease as defined by ≥50% stenosis of the left main coronary artery, ≥70% stenosis of the proximal left anterior descending artery, or ≥70% stenosis of 2 or more epicardial vessels were excluded from the study (n = 16). Hemodynamically significant coronary artery disease was excluded in all patients by means of coronary angiography performed any time within 5 years before study enrollment. Informed written consent was obtained from all patients, and the study was approved by St. Luke's-Roosevelt Hospital Center institutional review board. Clinical characteristics, medication regimen, and indications for testing were recorded at the time of DSE.

DSE protocol. Dobutamine was administered intravenously beginning at a dose of 5 to 10 μg/kg/min and increased by 5 to 10 μg/kg every 3 min up to a maximum of 50 μg/kg/min or until a study endpoint was achieved. The endpoints for termination of the dobutamine infusion included development of new segmental wall-motion abnormalities, attainment of 85% maximum predicted heart rate, and the development of significant adverse effects related to the dobutamine infusion. Atropine was administered intravenously in 0.25-mg increments every 3 min up to a maximum of 2.0 mg if a study endpoint was not achieved at the maximum dobutamine dose (11).

Beta-blockers were held on the morning of the DSE study. Using commercially available ultrasound equipment, 7 standard echocardiographic views were obtained with each acquisition: apical 4-chamber, apical 3-chamber, apical 2-chamber, parasternal long-axis, parasternal short-axis, subcostal short-axis, and subcostal 4-chamber views. All images were acquired within 60 s, and the entire sequence was repeated again to acquire a second run of images. Echocardiographic images were acquired at baseline, with each increment of dobutamine infusion, and during the recovery phase. Cardiac rhythm, 12-lead electrocardiograms, and blood pressure were monitored throughout the study.

Echocardiographic image analysis. Regional wall motion analysis was performed by an experienced echocardiographer blinded to the patient's demographic, clinical, and echocardiography outcomes. The left ventricle was divided into 16 segments and

a score assigned to each segment at baseline, at each stage of stress, and during the recovery phase (12). Each segment was scored as follows: 1 = normal; 2 = mild to moderate hypokinesis (reduced wall thickening and excursion); 3 = severe hypokinesis (marked reduced wall thickening and excursion); 4 = akinesis (no wall thickening and excursion); 5 = dyskinesis (paradoxical wall motion away from the center of the left ventricle during systole) (8). A LV wall motion score index (WMSI) during each stage was derived from the cumulative sum score of 16 LV wall segments divided by the number of visualized segments. The right ventricle was divided into 3 segments: apical, mid, and basal. Each segment was scored on a 1- to 5-point scale similar to the LV wall motion scale. A resting right ventricular (RV) WMSI was calculated as the cumulative sum score of the 3 segments divided by the number of visualized RV segments (11).

LV volume and ejection fraction assessment. Assessment of LV volumes and LVEF was performed using the apical 4- and 2-chamber views. The endocardial border at both end-systole and end-diastole was manually traced; and LV end-systolic volume, end-diastolic volume, and LVEF were determined using the biplane modified Simpson formula (13).

Inotropic contractile reserve. An LV segment was considered to have contractile reserve when it improved by at least 1 grade at peak stress (e.g., a hypokinetic segment becoming normal or an akinetic segment becoming hypokinetic). To quantify the amount of myocardium showing contractile reserve elicited by dobutamine, ICR was assessed according to a continuous parameter defined as ΔWMSI, which expresses the difference between rest and peak dose WMSI. This parameter provides information on the presence and extent of contractile reserve of dysfunctional myocardium. The presence of ICR was defined by cut point values of ΔWMSI that predicted with the highest accuracy cardiac death and subsequent LVEF improvement. The optimal ΔWMSI cut point values were determined using receiver-operating characteristic curves.

Patient follow-up. Serial prospective follow-up (mean 2.4 ± 2.1 years) was performed in all patients by means of a physician-directed telephone interview using a standardized questionnaire. The physicians involved in the patient's follow-up were blinded to the patient's clinical and echocardiography data. If the patient died during follow-up, the closest surviving relative and the patient's physician were interviewed to determine the cause of death. The primary outcome of the study was cardiac death. The definition of cardiac death required the following: documentation of significant arrhythmias or cardiac arrest or both, or death attributable to congestive heart failure or myocardial infarction in the absence of any other precipitating factors. Cardiac death was confirmed by review of the hospital medical record and/or death certificate. In case of death out of hospital, sudden unexpected death was attributed to a cardiac cause. Adjudication of cardiac death was done by physicians who were blinded to the clinical and stress echocardiographic data. Subjects who died of noncardiac causes were censored at date of death. A secondary outcome was to determine the change in LVEF on subsequent echocardiograms and correlate LVEF improvement (>5% increase) with the presence of ICR.

Statistical analysis. All analyses were carried out using a standard statistical software package (SPSS for Windows, Version 16.0, SPSS Inc., Chicago, Illinois). Data were summarized using standard statistical descriptors such as means, medians, SDs, percentiles, frequencies, and percentages. Patient groups were compared using the 2-sample Student *t* test for normally distributed continuous variables and Wilcoxon rank sum test for others. The Fisher exact test was used to compare categorical variables. Receiver-operator characteristic curves were constructed to assess the accuracy of ΔWMSI to predict cardiac death and subsequent LVEF improvement. The optimal cut point values from the receiver-operator characteristic curves were chosen by use of the Youden index. A univariable Cox proportional hazard model was used to identify predictors of cardiac death. Nonparametrically distributed variables were examined after logarithmic transformation was performed. Cumulative survival rates as a function of time after DSE were generated using Kaplan-Meier survival analysis and compared using log rank analysis. A p value <0.05 was considered to be significant. Because of the risk of mortality due to noncardiac causes as a competing outcome with cardiac death, a competing-risks survival regression analysis and an all-cause mortality analysis were performed.

RESULTS

Patient characteristics. A total of 60 consecutive patients (75% men; age 54 ± 9 years) with HIV and LV dysfunction (mean LVEF 28 ± 11%) met the inclusion criteria. Indications for DSE were chest pain (45%), dyspnea/heart failure (37%), pre-

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operative evaluation (8%), and other (10%). No significant adverse events occurred during the stress studies. Only 1 patient had a biphasic response during DSE, and no other patient had ischemia on DSE. A subsequent coronary angiogram revealed no evidence of coronary artery disease in this patient. The patient's demographic data are shown in Table 1. Among clinical characteristics, there was a high prevalence of cardiovascular risk factors, and most patients were at New York Heart Association functional class II and III at the time of testing. Patients carried a diagnosis of HIV infection for more than a decade, and more than half of the study group had received a diagnosis of AIDS. Accordingly, the mean CD4 count was low, and the majority of patients had increased viral loads. Among echocardiographic variables, the left atrium and left ventricle were enlarged, the LV systolic function was severely impaired, and the RV function was impaired as evidenced by an increased RV WMSI. With regard to medication use at the time of testing, more than two-thirds of the patients were taking beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. Nearly one-half of the study group was taking diuretics, and the majority of patients were receiving antiretroviral therapy.

Table 1. Baseline Characteristics of Patients With HIV Cardiomyopathy

Age, yrs	54 ± 9
Male	45 (75)
Hypertension	36 (60)
Diabetes mellitus	11 (18)
Dyslipidemia	21 (35)
NYHA functional class	
I	5 (8)
II	25 (42)
III	22 (37)
IV	8 (13)
Hemodynamic variables	
Resting SBP, mm Hg	128 ± 16
Resting DBP, mm Hg	80 ± 12
Resting heart rate, beats/min	81 ± 12
Echocardiographic variables	
Left atrial dimension index, cm/m^2	2.40 ± 0.43
LVEDVI, ml/m^2	82 ± 17
LVESVI, ml/m^2	60 ± 20
LVEF, %	28 ± 11
Resting LV WMSI	2.59 ± 0.57
Resting RV WMSI	1.58 ± 0.80
ΔWMSI	0.79 ± 0.53
Medications	
Beta-blocker	44 (73)
ACE-I or ARB	40 (67)
Diuretics	27 (45)
HIV-associated factors	
CD4 count, cell/mm^3	243 (86/348)
Viral load copies/ml	1,240 (<50/36,109)
AIDS diagnosis	35 (58)
Duration of HIV infection, yrs	11 ± 6
Antiretroviral therapy	46 (77)

Values are mean ± SD, n (%), or median (25th/75th percentile).
ACE-I = angiotensin-converting enzyme inhibitor; AIDS = acquired immunodeficiency syndrome; ARB = angiotensin II receptor blocker; DBP = diastolic blood pressure; HIV = human immunodeficiency virus; LV = left ventricular; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; NYHA = New York Heart Association; RV = right ventricular; SBP = systolic blood pressure; WMSI = wall motion score index.

Observed events. After 2.4 ± 2.1 years, there were 11 cardiac deaths (event rate 7.6%/year). The causes of death were worsening congestive heart failure and arrhythmia. Fatal or nonfatal myocardial infarctions were not observed. Twelve patients died of noncardiac causes (8 due to infections) and were censored at the time of death. The overall survival rate at the end of the study period was 62%. Receiver-operating characteristic curve analysis demonstrated a significant association between ΔWMSI and cardiac death. A cut point value for ΔWMSI of 0.38 predicted cardiac death with a specificity of 88% and a sensitivity of 73% (area under the curve = 0.75, 95% CI: 0.54 to 0.97; p = 0.01). Using this cut point value of ΔWMSI, we stratified the study group into patients with ICR and patients without ICR. There were no significant differences between the groups in the presence of cardiovascular risk factors or the use of antiremodeling medications. The group without ICR was more frequently taking diuretics (75% vs. 38%, p = 0.02), was less frequently receiving antiretroviral therapy (50% vs. 83%, p = 0.01), and had a tendency toward more immunosuppression. Patients without ICR had greater LV end-systolic volume index (74 ± 19 ml/m^2 vs. 57 ± 18 ml/m^2, p = 0.008) and LV end-diastolic volume index (92 ± 17 ml/m^2 vs. 80 ± 16 ml/m^2, p = 0.02), lower regional and global LV function (resting LV WMSI 2.9 ± 0.5 vs. 2.5 ± 0.5; LVEF 20 ± 11% vs. 30 ± 11%; p = 0.01), and worse RV function (resting RV WMSI 2.2 ± 0.9 vs. 1.4 ± 0.6, p = 0.001) compared with those patients with ICR. Patients without ICR had a 7 times higher event rate compared with patients who had ICR during DSE (event rate of 24%/year vs. 3.4%/year, p < 0.0001). A Cox proportional hazard model showed that the absence of ICR (HR: 6.6; 95% CI: 1.93 to 22.62; p = 0.003) and New York Heart Association functional class IV (HR: 7.2; 95% CI: 2.20 to 23.65;

p = 0.001) were predictors of cardiac death (Table 2). The presence of ICR effectively risk-stratified patients into high-risk and low-risk groups (Fig. 1). In a competing-risks survival regression analysis, including mortality from cardiac and noncardiac causes, there was consistency in both the magnitude and direction of the effect size such that the presence of ICR effectively risk-stratified patients into high-risk and low-risk groups (HR: 7.6; 95% CI: 2.4 to 24.2; p = 0.001). Survival analysis for the outcome of all-cause mortality followed a direction similar to that of cardiovascular mortality (HR: 2.1; 95% CI: 0.9 to 5.1; p = 0.08), although statistically nonsignificant.

LVEF improvement. After 2.1 ± 1.8 years, 41 patients had a follow-up echocardiogram. Six of the remaining 19 patients without a follow-up echocardiogram died during follow-up. Significant LVEF improvement from baseline occurred in 23 patients (56%) (LVEF change 29 ± 12% to 48 ± 9%, p < 0.0001) compared with the remaining 18 patients (44%) (LVEF change 26 ± 12% to 24 ± 11%, p = 0.15). The characteristics of patients with and without LVEF improvement are shown in Table 3. In the receiver-operator characteristic curve analysis, ΔWMSI was strongly related to LVEF improvement (area under the curve = 0.78; 95% CI: 0.64 to 0.93; p = 0.002). The value of ΔWMSI with the best sensitivity (74%) and specificity (78%) was 0.59. With this cut point value, patients were stratified into those with ICR and those without ICR. Sixteen patients (80%) in the group with ICR had LVEF improvement compared with 7 patients (33%) in the group without ICR (p = 0.003). In patients with ICR, there was a significant improvement in LVEF, from 30 ± 11% to 44 ± 11% (p < 0.0001) compared with patients without ICR (change in LVEF 24 ± 11% to 30 ± 17%, p = 0.06).

Table 2. Predictors of Cardiac Death in Patients With HIV Cardiomyopathy

Variable	HR	95% CI	p Value
Clinical variables			
Age, per yr	0.99	0.93–1.06	0.79
Hypertension, yes vs. no	0.68	0.20–2.22	0.52
Diabetes mellitus, yes vs. no	0.83	0.18–3.85	0.81
Dyslipidemia, yes vs. no	0.64	0.17–2.41	0.51
NYHA functional class IV vs. classes I to III	7.20	2.20–23.65	**0.007**
Hemodynamic variables			
Resting SBP, per mm Hg	1.01	0.97–1.06	0.56
Resting DBP, per mm Hg	1.01	0.95–1.07	0.76
Echocardiographic variables			
LADI, per cm/m^2	2.63	0.56–12.27	0.22
LVESVI, per ml/m^2	1.02	0.99–1.05	0.16
LVEDVI, per ml/m^2	1.02	0.99–1.06	0.15
LVEF, per percentage	0.96	0.91–1.01	0.17
Rest LV WMSI, per U	1.46	0.53–4.06	0.46
Rest RV WMSI, per U	1.35	0.68–2.66	0.39
ICR, absent vs. present	6.60	1.93–22.62	**0.003**
HIV-associated factors			
CD4 count, per cell/mm^3	1.00	0.99–1.00	0.90
Viral load, per copy/ml	1.00	1.00–1.00	0.87
Duration of HIV infection, per year	0.99	0.89–1.11	0.90

Values were generated using a univariable Cox proportional hazard analysis. Values in **bold** indicate statistical significance. A p value <0.05 is considered significant.
CI = confidence interval; HR = hazard ratio; ICR = inotropic contractile reserve; LADI = left atrial dimension index; other abbreviations as in Table 1.

DISCUSSION

To our knowledge, this is the first study evaluating the role of ICR in the risk stratification and prognostication of patients with HIV cardiomyopathy. The results of the present study show that even though the overall survival in patients with HIV cardiomyopathy has markedly improved in the contemporary era of HAART compared with previous studies (4,5), cardiac death remains an important cause of mortality in this group. Furthermore, the presence of ICR risk-stratified these patients into high-risk (ICR absent) and low-risk (ICR present) groups. Although patients with ICR had better survival and higher probability of subsequent LVEF improvement, patients without ICR had poor outcomes.

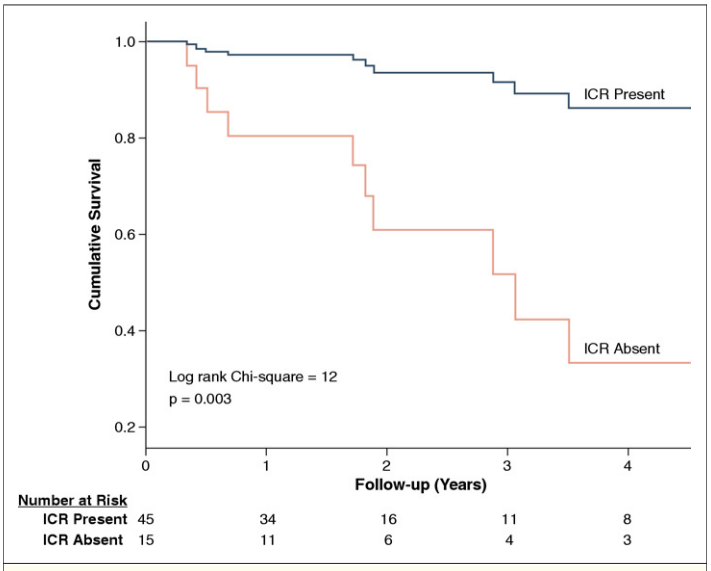

Figure 1. Cumulative Survival as a Function of the Presence of ICR

Inotropic contractile reserve (ICR) risk-stratified patients with human immunodeficiency virus cardiomyopathy into high-risk and low-risk groups. The number of patients at risk for each follow-up period is given **below the graph**.

Table 3. Characteristics of Patients With and Without LVEF Improvement

LVEF Improvement	Present (n = 23)	Absent (n = 18)	p Value
Clinical variables			
Age, yrs	51 ± 7.5	57 ± 11	0.06
Men	18 (78)	11 (61)	0.31
Hypertension	14 (60)	12 (66)	0.99
Diabetes mellitus	4 (17)	5 (27)	0.70
Dyslipidemia	5 (21)	8 (44)	0.18
NYHA functional class			
I	4 (17)	0	0.11
II	7 (30)	7 (39)	0.57
III	10 (43)	8 (44)	0.95
IV	2 (9)	3 (17)	0.64
Hemodynamic variables			
Resting SBP, mm Hg	125 ± 14	128 ± 18	0.61
Resting DBP, mm Hg	83 ± 9	77 ± 11	0.09
Resting heart rate, beats/min	78 ± 12	86 ± 11	**0.04**
Echocardiographic variables			
Left atrial dimension index, cm/m^2	2.34 ± 0.45	2.46 ± 0.44	0.41
LVEDVI, ml/m^2	81 ± 18	88 ± 18	0.23
LVESVI, ml/m^2	59.6 ± 21	66 ± 20	0.33
LVEF, %	29 ± 12	26 ± 12	0.45
Resting LV WMSI	2.63 ± 0.54	2.77 ± 0.60	0.44
Resting RV WMSI	1.51 ± 0.77	1.70 ± 0.86	0.45
ICR present	16 (70)	4 (22)	**0.003**
Medications			
Beta-blocker	15 (65)	16 (89)	0.14
ACE-I or ARB	14 (60)	11 (61)	1.00
Diuretics	10 (43)	10 (55)	0.54
HIV-associated factors			
CD4 count, cell/mm^3	257 (116/394)	211 (62/329)	0.50
Viral load copies/ml	159 (<50/6,365)	1874 (<50/36,100)	0.52
Duration of HIV infection, yrs	9 ± 5.9	11 ± 7.2	0.29
Antiretroviral therapy	18 (78)	13 (72)	0.72

Values are mean ± SD, n (%) or median (25th/75th percentile). Values in **bold** indicate statistical significance. A p value <0.05 is considered significant.
Abbreviations as in Tables 1 and 2.

HIV infection and cardiomyopathy. Since it was first described in 1986 (14), dilated cardiomyopathy has been recognized as a late manifestation of HIV infection. The cause of HIV cardiomyopathy is complex and includes myocarditis due to HIV itself or opportunistic pathogens, autoimmune processes, nutritional deficiencies (i.e., selenium) and cardiotoxicity due to antiretroviral agents (15). The development of dilated cardiomyopathy in patients with HIV is strongly associated with advanced stages of the disease (e.g., low CD4 count) (4,16). The introduction of HAART has significantly reduced the prevalence of HIV cardiomyopathy in developed countries. However, low socioeconomic status, noncompliance with HAART, and underdiagnosis of HIV infection are factors that contribute to a sustained high prevalence of dilated cardiomyopathy in this group. Studies performed in the contemporary era of antiretroviral therapy found a prevalence of dilated cardiomyopathy of 17.7% (16). In our study, 58% of the patients carried a diagnosis of AIDS. Although 77% of the patients were receiving antiretroviral therapy, the remaining 23% were not receiving antiretroviral therapy due to either noncompliance (n = 6) or lack of criteria to start therapy. Patients with ICR (ΔWMSI ≥0.38) had a tendency toward less immunosuppression and lower viral load and were more frequently receiving antiretroviral therapy.

Dobutamine stress echocardiography. In heart failure, the sympathetic nervous system is chronically activated, causing a maladaptive down-regulation and decrease in β_1-receptor density, ultimately determining the myocardial response to dobutamine. This response is inversely related to the degree of heart failure and remodeling of the left ventricle (17). Our findings are consistent with these observations, suggesting a worse degree of heart failure in patients without ICR, as evidenced by greater LV volumes, worse regional and global LV and RV function, and more frequent use of diuretics.

Prognostic value of ICR. The findings of the present study are in accordance with a large body of evidence supporting the value of ICR in the risk stratification and prognostication of patients with ischemic and nonischemic cardiomyopathy (8–10). Similarly, the presence of ICR further risk-stratified patients with HIV cardiomyopathy into high-risk (ICR absent) and low-risk (ICR present) groups. Patients without ICR had a yearly event rate that was 7 times higher than that in those with ICR. Using a Cox proportional hazard model, the absence of ICR and a New York Heart Association functional class IV were significant predictors of future cardiac death. Other clinical and traditional echocardiographic parameters evaluated in our study were not found to be predictors of cardiac death, although diastolic parameters other than left atrial size were not evaluated. Resting LVEF, a powerful predictor of future cardiovascular events in patients with and without HIV (4,18), showed a trend toward prediction of cardiac death; however, it did not reach statistical significance. This lack of effect of resting LVEF on outcomes could be related to the limited number of events in our cohort. The absence of ICR predicted future cardiac death with a specificity of 88% and a sensitivity of 73%.

Prediction of LVEF improvement. To our knowledge, this is the first study demonstrating reversibility of LV dysfunction in patients with HIV cardiomyopathy. A

prospective echocardiographic study conducted before the introduction of HAART did not show LVEF improvement in adults with HIV/AIDS and LV dysfunction after 1 year of follow-up (19). Reversibility of LV dysfunction in an adult with HIV and acute myocarditis has been previously reported (20), but not in patients with chronic LV dysfunction. Our study shows that 56% of the patients had improvement in LVEF on follow-up, although 6 of the remaining 19 patients without a follow-up echocardiogram died, which could potentially result in over- or underestimation of the number of patients with improvement in LVEF. The most significant difference between both groups was the presence ICR. The exact mechanism of this recovery is unclear. There were no differences between both groups in the use of antiremodeling medications. Patients without LVEF improvement had a tendency toward greater left atrial and LV size, worse LV and RV function, lower CD4 count, and longer duration of HIV infection. A possible explanation for this functional recovery is that patients with LVEF improvement had a less advanced stage of the diseases (HIV and cardiomyopathy), as evidenced by a trend toward less remodeling and immunosuppression, with a lesser degree of down-regulation of β_1-receptors, thus allowing a greater response to medical therapy. Interestingly, patients without LVEF improvement had higher resting heart rates, which may be related to a higher adrenergic drive and thus a worse degree of cardiomyopathy.

The presence of ICR predicted subsequent LVEF improvement with a specificity of 78% and sensitivity of 74%.

Clinical implications. The present study is the first to report LVEF improvement in patients with HIV cardiomyopathy. Although the development of dilated cardiomyopathy in patients with HIV is associated with poor outcomes, our results showed that the assessment and detection of ICR by DSE in this group identified a subset of patients with a higher probability of subsequent LVEF improvement and better outcomes. On the other hand, the absence of ICR was associated with a very poor prognosis. Therefore, patients with HIV cardiomyopathy without ICR may benefit from aggressive management of their antiretroviral regimen, early referral to a center experienced in the management of patients with end-stage HIV cardiomyopathy for intensification of medical therapy, or referral for device-based therapies (e.g., cardiac resynchronization therapy), and in very carefully selected patients (normal CD4 count, undetectable viremia, good compliance, and psychosocial support), advanced heart failure therapies might be a reasonable alternative.

Study limitations. Analysis of segmental wall motion is subjective. Nevertheless, this is routinely used in clinical practice for the detection of myocardial viability and is widely accepted. Medication regimens were only recorded at the time of testing; therefore, no information about duration of exposure or changes in regimen is available. Another limitation is that indexes of diastolic dysfunction, other than left atrial size, were not recorded. The number of events in our study group was limited, which did not allow us to adjust our variables in a multivariable analysis. Even though the patients in this cohort were carefully selected, causes of LV dysfunction other than HIV cannot be entirely excluded.

CONCLUSIONS

Our results show that the presence of ICR by DSE risk-stratifies and predicts outcomes in patients with HIV cardiomyopathy. Furthermore, the presence of ICR identifies patients with HIV cardiomyopathy who's LVEF will improve.

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Key Words: cardiomyopathy ■ dobutamine stress echo ■ human immunodeficiency virus ■ inotropic contractile reserve.