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Effect of Left Ventricular Dysfunction and Viral Load on Risk of Sudden Cardiac Death In Patients with Human Immunodeficiency Virus

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Abstract

Human Immunodeficiency Virus-infected patients are disproportionately affected by cardiovascular disease and sudden cardiac death (SCD). Whether left ventricular (LV) dysfunction predicts SCD in those with human immunodeficiency virus (HIV) is unknown. We sought to determine the impact of LV on SCD in patients with HIV. We previously characterized all SCDs and AIDS deaths in 2860 consecutive patients in a public HIV clinic between 2000 and 2009. Transthoracic echocardiograms (TTEs) performed during the study period were identified. The effect of ejection fraction (EF), diastolic dysfunction, pulmonary artery pressure, and LV mass on SCD and acquired immune deficiency syndrome (AIDS) death were evaluated: 423 patients had at least one TTE; 13 SCDs and 55 AIDS deaths had at least one TTE. In the propensity-adjusted analysis, EF 30–39% and EF <30% predicted SCD (HR 9.5, 95% CI 1.7–53.3, p=0.01 and HR 38.5, 95% CI 7.6–195.0, p<0.001, respectively) but not AIDS death. Diastolic dysfunction also predicted SCD (HR 14.8, 95% CI 4.0–55.4, p<0.001) but not AIDS death, even after adjusting for EF. The association between EF<40% and SCD was greater in subjects with detectable vs. undetectable HIV-RNA (adjusted HR 11.7, 95% CI 2.9–47.2, p=0.001 vs. HR 2.7, 95% CI 0.3–27.6, p=0.41; p=0.07 for interaction). In conclusion, LV systolic and diastolic dysfunction predict SCD but not AIDS death in a large HIV cohort, with greater effect in those with detectable HIV RNA. Further investigation is needed to thoroughly evaluate the effect of low EF and HIV factors

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on SCD incidence and the potential benefit of implantable cardioverter-defibrillator therapy in this high-risk population.

Keywords

AIDS; death; sudden; cardiomyopathy; diastolic dysfunction

Introduction

We recently determined that sudden cardiac death (SCD) comprised the majority of cardiac deaths over a 10-year period in a large, urban HIV-positive cohort, at an adjusted rate 4.5-fold higher than expected. (1)In the general population, left ventricular (LV) systolic dysfunction is strongly associated with an increased risk of SCD,(2–4)but this association has not been evaluated in the setting of Human Immunodeficiency Virus (HIV) infection. Because the majority of deaths in large HIV cohorts are still AIDS-related,(5,6) whether LV dysfunction carries the same prognostic importance for HIV-infected individuals is unknown. In addition, HIV-infected individuals may be at risk for ventricular arrhythmias by mechanisms independent of LV systolic dysfunction, including QT interval prolongation, (7–9)inflammation,(10) and direct viral effects on cardiomyocyte depolarization and repolarization.(11,12)We therefore sought to evaluate any potential association between pre-mortem LV dysfunction and SCD and Acquired Immunodeficiency Syndrome (AIDS)-related death in a large urban cohort of HIV-infected patients.

Methods

We previously identified records of 2,860 consecutive patients followed at a public HIV clinic at San Francisco General Hospital (SFGH) between April 1, 2000 and August 31, 2009.(1)This clinic serves approximately 20% of HIV infected patients in San Francisco. For this analysis, we included all patients ≥18 years old with documented HIV infection who had at least one transthoracic echocardiogram (TTE) during this period. The study was approved by the Institutional Review Board of the University of California, San Francisco.

We previously identified and classified all deaths in this cohort.(1) Briefly, SCDs were defined as meeting two published criteria: 1) primary ICD-10 code for all cardiac causes (13, 14) and 2) circumstances of death meeting World Health Organization (WHO) criteria for SCD (death within 1 hour of symptom onset if witnessed or within 24 hours of being observed alive and symptom-free if unwitnessed) (15) or unexpected out-of-hospital death. (16) Hospice, overdose, violence, suicide, cancer, or opportunistic infection deaths excluded. All unexpected deaths classified as SCD were confirmed as not meeting criteria for AIDS death. AIDS death required 2 of 3 published criteria: 1) primary ICD-10 code for HIV-disease related illness; 2) circumstances of death involving HIV-related infection or illness; or 3) most recent CD4 <50 cells/mm^3. (6)

Baseline characteristics were abstracted from the clinic's electronic medical record. We recorded the following variables: age, gender, race, CD4 cell count, HIV viral load, antiretroviral medication use, cardiac medication use, CAD, hypertension (HTN), diabetes mellitus (DM), smoking, disorders of lipid metabolism, chronic kidney disease (CKD), and illicit drug use.

We searched all cohort patients for any transthoracic echocardiogram (TTE) evaluation at SFGH during the study period. On TTE, LV systolic function, diastolic function, pulmonary artery systolic pressure, and LV mass were analyzed. LV function was independently assessed by 2 study authors and categorized as normal (EF >50%), mildly reduced (EF 40–

50%), moderately reduced (EF 30–39%), or severely reduced (EF <30%) by visual inspection. LV diastolic function was classified as normal, impaired relaxation (stage I), pseudonormal (stage II), or restrictive (stage III) using American Society of Echocardiography criteria. (17) Significant diastolic dysfunction was classified as stage II or III. Pulmonary artery systolic pressure (PASP, mmHg) was measured using tricuspid regurgitation jet velocity plus the estimated right atrial pressure by inferior vena cava diameter and response to inspiration. (18) Pulmonary hypertension was defined as PASP greater than 30 mmHg.(19) Left ventricular hypertrophy (LVH) was classified as none, mild, moderate, or severe by standard criteria. (20)

Baseline characteristics were compared using T or Chi^2 tests as appropriate. We used Cox proportional hazards models to estimate the association of TTE parameters with SCD and AIDS-related death, on the scale of time since the first TTE. To account for multiple TTE's, each parameter was treated as a time-dependent covariate, updated at the time of each later TTE. Because the SCD outcome was uncommon, we used propensity scores rather than conventional multivariate adjustment to control for potential confounding variables. Covariates in the logistic model used to estimate the scores were specified *a priori*. We also assessed modification of the TTE effects by two factors specified *a priori*: HIV-RNA treated as either a continuous or dichotomous variable (detectable vs. undetectable), and nadir and most recent CD4 count (<200 vs. >200 cells/mm^3) using interaction terms. Because several baseline characteristics differed between those who did and did not receive a TTE, we assessed for potential selection bias, first fitting a logistic model for the probability of inclusion in the subsample with at least one TTE as a function of baseline characteristics, then refitting the Cox models for SCD and AIDS-related death, weighted by the inverse of these probabilities. In additional sensitivity analyses, we used Fine-Gray models (21) to estimate TTE effects on SCD, treating other deaths as competing risks.

Results

The baseline characteristics of this cohort have been previously described.(9) 423 of the total 2860 cohort patients (15%) had echocardiographic evaluation. 136 patients had more than one echocardiogram (range 2–5)and 654 total studies were evaluated. Of the 423 patients with at least one TTE, 13 had SCD and 55 died of AIDS-related causes. The median time from most recent TTE to death was 566 days for SCDs and 366 days for AIDS deaths. Compared to individuals who did not have TTEs, subjects with TTEs were slightly older and more likely to be female and African American. In addition, they had higher rates of traditional risk factors including HTN, DM, CKD, and more advanced HIV disease, including lower CD4 counts and higher HIV-RNA levels.

Overall demographics between SCDs and AIDS deaths were similar, with AIDS deaths having higher HIV RNA levels and lower CD4 counts. Prevalence of HTN, CAD, and antiretroviral therapy use was not significantly different between SCDs and AIDS deaths (Table 1). A measurable tricuspid regurgitation jet permitted the measurement of pulmonary artery systolic pressure in 314 patients (74%) while diastolic dysfunction was assessed in 299 (not assessable in 124 due to atrial fibrillation/flutter or mitral stenosis). Compared to AIDS deaths, SCDs were more likely to have systolic dysfunction and diastolic dysfunction but had similar levels of pulmonary hypertension and LVH (Table 2).

LV dysfunction predicted SCD but not AIDS death. In the Cox model for SCD, employing a propensity score adjusting for age, race, gender, DM, CAD, most recent CD4 count, most recent HIV viral load, cardiac medication use by class, and antiretroviral medication use by class, the hazard ratio for EF <40% was 13.7 (95% CI 4.1–46.3, p<0.001). Lower EF was associated with progressively greater SCD risk, with hazard ratios of 9.5 (95% CI 1.7–53.3,

p=0.01)for EF 30–39% and 38.5 (95% CI 7.6–195.0, p<0.001) for EF<30%(Figure 1). Diastolic dysfunction was also associated with SCD (HR 14.8, CI 4.0–55.4, p<0.001), even after adjusting for the effect of LV systolic dysfunction (HR 8.0, 95% CI 2.5–25.8, p<0.001).

In the sensitivity analyses to assess for potential selection bias, the association of EF<30% with SCD was unchanged from the baseline model (HR 35.1, 95% CI 8.0–153.6, p<0.001). In the model treating AIDS death as a competing risk, the association of EF<30% with SCD was also unchanged (HR 37.5, 95% CI 8.4–168.3, p<0.001).

The association between EF<40% and SCD was greater in subjects with detectable vs. undetectable HIV-RNA (HR 11.7, 95% CI 2.9–47.2, p=0.001 vs. HR 2.7, 95% CI 0.3–27.6, p=0.41; p=0.07 for interaction). In contrast, we found no evidence for modification of the effect of EF<40% by most recent CD4 count (p=0.52). Neither pulmonary hypertensionnor left ventricular hypertrophy was associated with either SCD or AIDS death.

Discussion

In this large HIV-infected cohort, the presence of LV dysfunction strongly predicted SCD but not AIDS-related death. Specifically, we observed increasing risk of SCD in patients with moderate (EF 30–39%) and severe (EF<30%) systolic dysfunction. We also found substantially increased risk of SCD with stage II–III LV diastolic dysfunction, even after controlling for the effect of LV systolic dysfunction. Finally, higher HIV RNA levels increased the SCD risk for those with LV systolic dysfunction

For individuals without HIV, LV systolic dysfunction has consistently been shown to be the most powerful risk factor for lethal ventricular arrhythmias and largely informs the decision to place an implantable cardioverter defibrillator (ICD) for primary prevention of SCD.(2–4) LV dysfunction has also been long recognized in HIV patients, (22) either as a direct consequence of HIV infection or as sequelae of coronary atherosclerosis and myocardial infarction (MI), which occur at much higher rates in HIV-infected persons. (23) The prognostic importance of this finding has been less clear, because AIDS-related illnesses, presumably unrelated to LV dysfunction, have been the leading cause of mortality in contemporary practice.(5,6) However, we have recently shown that HIV-infected persons suffer SCD at a much higher adjusted rate than the background population.(1) Although AIDS remains the leading cause of mortality in our cohort (57%), SCD comprised 13% of all deaths and 86% of cardiac deaths in this group, thus highlighting the need to define risk factors for SCD in patients with HIV.

Similar to the general population, we found that a lower EF carried a stepwise and increased hazard of incident SCD. The magnitude of LV systolic dysfunction in this cohort is comparable to other high-risk HIV negative populations. In a contemporary study of 4,122 MI survivors, a EF of <30% was associated with a HR of SCD at 5 years of 5.99 (95% CI 2.73–13.14) as compared to those with EF>40%.(24) Our study also showed a much greater hazard of SCD for EF<30% as compared to EF>40% (HR of 22.0, 95% CI 6.0–80.9, p<0.001), suggesting that severe LV dysfunction in the setting of HIV infection carries at least as much prognostic importance as in patients with prior MI, traditionally considered to be the highest risk group for SCD. In a study of patients with non-ischemic cardiomyopathy, Grimm and colleagues demonstrated that each 10% decrement in EF was associated with a relative risk of 2.8 of major arrhythmia or SCD at a mean follow up of 52 months.(25) When accounting for AIDS death as a competing risk and adjusting for presence of CAD/MI, our findings point to a similarly high risk of incident SCD with progressively worsening LV systolic dysfunction in the HIV-infected.

The effect of LV systolic dysfunction on SCD was greater in patients with higher HIV-RNA levels. This suggests a synergistic relationship between active HIV-infection and structural heart disease in the genesis of ventricular arrhythmias. Although the mechanism has not yet been explored, chronic inflammation and/or a direct viral effect on ventricular myocardial cells may also play a role. In a transgenic murine model of HIV infection,(11,12) viral infection was found to directly affect ventricular myocardial depolarization and repolarization properties. In the setting of structural heart disease, such changes in conduction properties may further predispose individuals to ventricular arrhythmias.

LV diastolic dysfunction was also found to be a substantial independent predictor of SCD in this cohort, though the overall numbers of SCD with measured diastology were low. Diastolic dysfunction, either isolated or in the presence of systolic dysfunction, has not reliably been found to be a significant predictor of SCD or ventricular arrhythmias in prior studies.(26) The prognostic importance of at least moderate diastolic dysfunction in this population was noteworthy and warrants further exploration as a possible modifier of SCD risk, especially given the low sensitivity and specificity of EF alone in risk stratification.

Much of the study period predated contemporary primary prevention ICD implantation practices; indeed, none of the 30 identified SCDs had an ICD, although 10% of these patients (n=3) had EF meeting criteria for primary prevention, and possibly more had stricter surveillance of LV function been performed. Current guidelines do not address the issue of HIV infection directly, though they do specify that implantation of a device in those with an estimated survival less than one year is contraindicated.(27) In this cohort, most SCDs had CD4 counts above the threshold for classification of AIDS and had low overall rates of other chronic diseases including substance abuse. Thus, we anticipate that most patients would have had a life expectancy much greater than one year and therefore some SCDs may have been prevented by appropriate prophylactic implantation of an ICD. In addition, because we observed that viremia augmented SCD risk in the setting of LV dysfunction, optimal management of SCD risk may require both virologic control and appropriate maximal medical therapy before consideration of ICDs.

While prior studies by our group and others have shown an overall prevalence of systolic dysfunction of <10% in contemporary cohorts of largely treated and suppressed asymptomatic HIV-infected individuals,(28,29) we found a 20% prevalence of LV systolic dysfunction (EF<50%) in subjects receiving a TTE for clinical indications. Moreover, 50% of SCDs had LV systolic dysfunction and 33% of SCDs had reported cardiac complaints,(1) highlighting the importance of referral for further cardiac testing and care in symptomatic individuals.

This study has several important limitations. As this is a retrospective study, only a fraction of overall subjects had a TTE (15%) and it is possible that some patients with significant LV dysfunction did not receive a TTE. Because patients were presumably referred for TTE if they had cardiac symptoms, the baseline characteristics between those with and without a TTE were different. However, we found no evidence for selection bias for those subjects in the cohort receiving a TTE, as the weighted analysis to account for these differences did not affect the overall findings. The overall numbers of SCDs with antemortem TTE were low, thus we employed the propensity score method to account for potential confounders including CAD/MI, rather than a traditional multivariate analysis, thus highlighting the need to replicate these findings in an independent cohort. Finally, the association between LV systolic dysfunction and SCD is consistent with well-established findings in other populations, but modification of this effect with viral load and the association between diastolic dysfunction and SCD are novel findings requiring replication.

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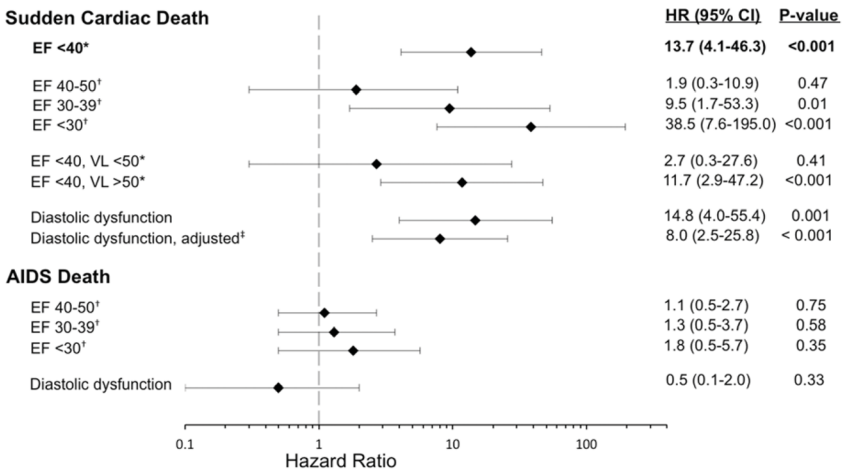

Figure 1.

Propensity Score-Adjusted Left Ventricular Dysfunction and Relative Hazard of Sudden Cardiac Death or AIDS Death

*= Compared to reference of EF>40; †= Compared to reference of EF>50; ‡= Adjusted for left ventricular systolic dysfunction

HR = Hazard Ratio, EF = Left ventricular ejection fraction, VL = HIV viral load (copies/mL)

Table 1

Comparison of Baseline Characteristics

Characteristic	All Subjects with TTE N=423	SCD N=13	AIDS Death N=55	P Value*
Mean age (years)	42.3 ± 9.4	43.6 ± 10.8	41.2 ± 8.6	0.39
Female	80 (19%)	1 (8%)	10 (18%)	0.36
Body mass index (kg/m^2)	25.0 ± 5.2	27.0 ± 6.9	24.4 ± 5.3	0.52
Race/Ethnicity:				0.38
African American	147 (35%)	8 (62%)	23 (42%)	
Asian American	14 (3%)	0	1 (2%)	
European American	174 (41%)	5 (38%)	21 (38%)	
Hispanic American	83 (20%)	0	10 (18%)	
Other	5 (1%)	0	1 (2%)	
Coronary artery disease	24 (6%)	1 (8%)	1 (2%)	0.26
Myocardial infarction	13 (3%)	0	1 (2%)	0.62
Hypertension	101 (24%)	4 (31%)	9 (16%)	0.21
Smoking	113 (27%)	2 (15%)	11 (20%)	0.52
Diabetes mellitus	38 (9%)	1 (8%)	5 (9%)	0.67
Chronic kidney disease	46 (11%)	2 (15%)	8 (15%)	0.62
Illicit drug use	128 (30%)	2 (15%)	14 (25%)	0.44
Medications:				
ACE inhibitor	66 (16%)	1 (8%)	11 (20%)	0.30
Beta blocker	64 (15%)	1 (8%)	7 (13%)	0.61
Statin	51 (12%)	1 (8%)	2 (4%)	0.52
NRTI	260 (61%)	6 (46%)	39 (71%)	0.09
NNRTI	138 (32%)	3 (23%)	17 (31%)	0.58
PI	229 (54%)	5 (38%)	32 (58%)	0.20
CD4 count, median (cells/mm^3) †	274 (89–458)	310 (268–534)	111 (35–278)	0.003
HIV RNA, median (log copies/mL) †	3.7 (1.9–4.8)	3.6 (2.3–4.0)	4.5 (1.9–5.3)	0.09

Values are mean ± SD, n (%), or median (interquartile range).

* P value for comparison between SCD and AIDS Deaths;

† Most recent measurement.

NNRTI = Non-nucleoside reverse transcriptase inhibitor, NRTI = Nucleoside reverse transcriptase inhibitor, PI = Protease inhibitor, SCD = Sudden cardiac death

Table 2

Transthoracic Echocardiogram Characteristics

Characteristic	All Subjects N=423	SCD N=13	AIDS Death N=55	P Value*
Left ventricular ejection fraction; n/total assessed				
>50	339/423 (80%)	3/13 (23%)	45/55 (82%)	<0.0001
40–50	39/423 (9%)	4/13 (31%)	5/55 (9%)	0.04
30–39	29/423 (7%)	3/13 (23%)	4/55 (7%)	0.09
<30	16/423 (4%)	3/13 (23%)	1/55 (2%)	0.003
Diastolic dysfunction†; n/total assessed	29/299 (10%)	5/8 (63%)	1/38 (3%)	<0.0001
Pulmonary artery systolic pressure, median (mmHg)	27.0 (21–33)	29.5 (22–42)	27.0 (23–33)	0.28
Pulmonary hypertension††; n/total assessed	100/314 (32%)	4/13 (31%)	13/55 (24%)	0.59
Left ventricular hypertrophy; n/total assessed	127/420 (30%)	3/13 (23%)	20/53 (38%)	0.32

Values are mean ± SD, n (%), or median (interquartile range).

* P value for comparison between SCD and AIDS Deaths;

† Stage II–III diastolic dysfunction;

†† Pulmonary artery systolic pressure > 30 mmHg

SCD = Sudden Cardiac Death