The Changing Paradigm of HIV-Related Heart Failure

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Over the past 30 years, there has been a dramatic evolution of the human immunodeficiency virus (HIV) epidemic around the world. As a consequence of substantial improvements in antiretroviral therapy (ART), the mortality associated with HIV has decreased significantly [1]. The reduction in mortality has transformed HIV into a long-term chronic illness for many people, characterized by a heavy burden of comorbidities associated with aging, including cardiovascular disease (CVD). It has been estimated that by 2030, the prevalence of CVD in HIV-infected people receiving ART may be >75% [2—4]. The majority of recent studies of HIV-related CVD have focused on atherosclerosis, coronary artery disease (CAD), and acute coronary syndromes [5,6]. However, on the basis of projected future rates of CVD in this population, there may likely be a tsunami of another worldwide epidemic in HIV-infected people—heart failure.

HIV AND LV SYSTOLIC DYSFUNCTION

Since the earliest reports of HIV-related cardiomyopathy in the mid-1980s, the patterns of HIV-related left ventricular (LV) dysfunction have evolved [7—18]. In studies published from 1989 to 2000, a period before the development and widespread use of effective combination ART, the prevalence of systolic dysfunction ranged from approximately 2% to 20% [7—18]. Key observations from these studies were that systolic dysfunction was associated with the extent of immunodeficiency, and there was a higher incidence and prevalence of cardiomyopathy in subjects with CD4 <400 cell/mm^3 and progression to acquired immunodeficiency syndrome (AIDS). In addition, nucleoside reverse transcriptase inhibitors, such as zidovudine, were associated with a higher prevalence of systolic dysfunction. In subjects treated with zidovudine, it was observed that there was a higher incidence of cardiomyopathy in subjects with CD4 counts <300 cells/mm^3, suggesting that the degree of immunodeficiency influences the development of systolic dysfunction more than the type of ART does [17].

The hypothesized etiologies of HIV-related systolic dysfunction include primary HIV myocarditis, in which myocytes are directly damaged by HIV, and secondary HIV myocarditis, in which myocytes are damaged by proteolytic enzymes released through HIV replication in the cardiac interstitium [16,17]. HIV-associated myocarditis has also been attributed to an increased susceptibility to other cardiotropic viruses such as Coxsackievirus group B, Epstein-Barr virus, and cytomegalovirus, and opportunistic infections such as *Toxoplasma gondii*, *Cryptococcus neoformans*, and *Mycobacterium avium intracellulare*. Cell-mediated and humoral immunity have also been postulated to have a pathogenic role in the initiation and the progression of HIV-associated cardiomyopathy. Other proposed mechanisms include excessive activation of cytokines such as tumor necrosis factor and interleukins, selenium deficiency, and nucleoside reverse transcriptase inhibitors toxicity, which has been associated with a reversible, dose-dependent skeletal and cardiac myopathy [18,19].

HIV AND LV DIASTOLIC DYSFUNCTION

Contemporary studies evaluating LV dysfunction in the setting of modern ART regimens have demonstrated lower rates of systolic dysfunction with lesser degrees of systolic impairment [20—29]. These recent studies have also revealed higher rates of preserved LV function and strikingly high rates of diastolic dysfunction, ranging from 26% to 50% [20—29]. The mean age of HIV-infected subjects in these studies ranged from 38 to 49 years. In comparison, the prevalence of diastolic dysfunction in the general population aged 45 to 55 years has been reported to be 6.2% [30,31].

Echocardiographic findings from studies in HIV-infected subjects indicate they may have increased LV mass and more diastolic relaxation abnormalities such as lower peak E/A ratios, lower mitral annular E′ velocities, and higher E/E′ ratios than do noninfected control subjects [22—28]. In the general population younger than age 50, the prevalence of mild diastolic relaxation abnormalities has been reported between 2% and 6% [30]. Echocardiography studies in HIV subjects have also demonstrated higher pulmonary artery systolic pressures in HIV subjects than in noninfected subjects, but in pressure ranges more consistent with pulmonary hypertension associated with left heart disease rather than pulmonary arterial hypertension [22,23].

The pathogenesis of HIV-associated diastolic dysfunction is likely multifactorial. Several studies suggest that hypertension, a comorbidity frequently associated with diastolic dysfunction in the general population, may also be related to the use of ART [32—34]. The reported rates of hypertension in HIV subjects in the echocardiography studies reviewed ranged from 14% to 42% [20—29]. The increased LV mass in HIV subjects noted in several of the echocardiography studies may independently predispose to diastolic dysfunction, as increased LV mass and hypertrophy have been associated with delayed early LV relaxation in the general population [30,31]. The increased LV mass could be secondary to afterload excess from increased vascular stiffness associated with hypertension. In non-HIV populations, there is evidence to suggest that wave

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reflections from stiff peripheral arteries and concomitant increases in late systolic load may be causally linked to LV hypertrophy, fibrosis, and diastolic dysfunction [35–38]. In addition, CAD has been associated with diastolic dysfunction in the general population and there may be a greater burden of occult CAD in the HIV population at an earlier age [39–42].

Inflammation may be another intriguing pathogenic process that may lead to the increased rates of diastolic dysfunction in the HIV population. HIV-infected subjects receiving ART have been shown to have increased inflammation and immune activation, with higher levels of soluble inflammatory markers and more aortic inflammation on fludeoxyglucose 18F fluorodeoxyglucose positron emission tomography scans [43–46]. A new theoretical framework for understanding diastolic dysfunction and heart failure with preserved ejection fraction (HFPEF) postulates a central role for inflammation in the progression of disease [47–50]. It has been hypothesized that many of the cardiovascular abnormalities in HFPEF can be understood as the downstream consequence of the proinflammatory state associated with diseases such as obesity, hypertension, diabetes, chronic obstructive pulmonary disease, anemia, and chronic kidney disease. Because of their heightened state of inflammation that begins at the time of infection, HIV-infected people may present a unique model to better understand the inflammation hypothesis in HFPEF and might provide insight on the pathogenesis and progression of diastolic dysfunction and HFPEF in all populations.

The hypothesized mechanisms linking inflammation and the development of LV diastolic dysfunction are as follows. First, the proinflammatory state produced by comorbidities stimulates coronary microvascular endothelial cells to produce reactive oxygen species, which limits nitric oxide bioavailability for adjacent cardiomyocytes. Next, limited nitric oxide bioavailability decreases protein kinase G activity in cardiomyocytes, which leads to the hypophosphorylation of the cytoskeletal protein titin. This increases the resting tension of myocytes and stimulates cardiac hypertrophy and concentric LV remodeling. The proinflammatory state also induces endothelial cells to produce vascular cell adhesion molecules and E-selectin, which attract monocytes. These inflammatory cells secrete transforming growth factor beta, which stimulates conversion of fibroblasts to myofibroblasts; these cells in turn increase collagen deposition and fibrosis of the interstitium. The entire process leads to LV hypertrophy and stiffening and culminates in LV diastolic dysfunction, the major cardiac functional deficit in HFPEF [47–50].

Results from cardiac magnetic resonance imaging and biomarker studies further support the hypothesis that inflammation, leading to myocardial hypertrophy, stiffening, and fibrosis, may play a central role in the development of HIV-related diastolic dysfunction. Cardiac magnetic resonance imaging studies have demonstrated a significantly higher burden of LV fibrosis and more diffuse fibrosis in HIV-infected subjects than in noninfected control subjects [51,52]. In addition, biomarkers such as tissue inhibitor of metalloproteinases 1, ST-2, and growth differentiation factor 15, which have been associated with inhibition of collagen degradation, fibrosis, and diastolic dysfunction in the general population, have been demonstrated to be elevated in HIV-infected subjects receiving ART versus noninfected control subjects [22,52,53].

THE FUTURE OF HIV-RELATED HEART FAILURE

On the basis of the high prevalence of diastolic dysfunction in the HIV population and the known progression from diastolic dysfunction to heart failure in the general population, we hypothesize that a future major cardiovascular complication in the HIV-infected population will be HFPEF [54]. There are still many questions about the pathophysiology and epidemiology of HIV-related diastolic dysfunction that should be elucidated. Further knowledge of the mechanisms of HIV-related diastolic dysfunction including the role of inflammation and the links to derangements in nitric oxide signaling leading to LV hypertrophy and fibrosis is needed. Additional data from large cohorts about the incidence and prevalence of HIV-related diastolic dysfunction and rates of progression to HFPEF are also essential. Does HFPEF develop at a faster rate in HIV populations than in the general population or than in populations with comorbidities such as hypertension or diabetes? Is inflammation the primary driving factor in HIV-related diastolic dysfunction, or is it secondary to the metabolic abnormalities associated with ART such as hypertension, hyperlipidemia, and lipodystrophy [55]? Importantly, if the role of inflammation in HIV-related diastolic dysfunction could be definitively proven, HIV-infected populations might offer a unique, accelerated model to test the inflammation hypothesis of HFPEF and help solve the puzzle of how to treat this perplexing disease.

NEXT STEPS

In order to further our understanding of diastolic dysfunction in the HIV population, it is critical that scientists and clinicians in the field of heart failure become engaged in asking compelling questions and addressing critical challenges in this field. There is also a need for multidisciplinary collaboration with the HIV scientific community, whose tremendous accomplishments have led to a transformation of the HIV epidemic. If inflammation proves to be the key causative factor in HIV-related diastolic dysfunction, and if, as hypothesized, the progression of diastolic dysfunction to heart failure is accelerated in this population, then HIV-infected people may offer unique insights into HFPEF for the entire population and may represent a distinct group in which to test novel therapies for this, as of yet, untreatable form of heart failure. Through multidisciplinary collaboration, scientific inquiry, and creative approaches, together the cardiovascular and HIV scientific communities may be able to use lessons

learned from HIV-infected people to unravel the mysteries of HFPEF and ultimately to identify treatments that benefit all people suffering from this enigmatic disease.

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