Cardiovascular Complications of HIV Infection

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INTRODUCTION

Rapid development in the management and treatment of HIV infection has lengthened the lifespan of this patient population, but the increased frequency of cardiovascular diseases related to increased lifespan has emerged as an added potential burden to the cost of their healthcare.[1] Cardiovascular diseases commonly associated with HIV infection include pericardial effusion, dilated cardiomyopathy, endocarditis, coronary artery disease, systemic arterial hypertension, pulmonary hypertension, malignant neoplasms, and drug-related cardiotoxicity. This review discusses recent insights into the pathophysiology of cardiovascular diseases in HIV-infected patients.

In recent years, effective therapies for HIV-infected patients have led to increased survival and a longer lifespan. This has led to the increased recognition of the manifestations of late-stage HIV infection, including HIV-related cardiovascular diseases. The prevalence of cardiovascular disease in HIV/AIDS has a reported range of between 28% and 73%,[1] which includes manifestations such as pericardial effusion, dilated cardiomyopathy, myocarditis, endocarditis, coronary artery disease, systemic arterial hypertension, pulmonary hypertension, malignant neoplasms, and drug-related cardiotoxicity. The pathogenesis is multifactorial, and may result from the viral infection itself, opportunistic infections complicating the immunodeficiency, nutritional deficiencies, autoimmunity or drug therapy.[2] Dyslipidaemia associated with anti-retroviral therapy has recently emerged as an issue of concern as it possibly increases the risk of premature atherosclerosis and cardiovascular disease.[2,3]

PERICARDIAL EFFUSION

Pericardial effusion is common in patients with HIV (estimated to be up to 11% per year)[5] and has a variable presentation. It may be asymptomatic or manifest as pericarditis or as cardiac tamponade.[4]

This incidence was studied by Heidenreich *et al* who showed an increasing trend of pericardial effusion with progression of HIV infection (asymptomatic HIV positive patients showed an incidence of 0% whereas patients with AIDS had an incidence of 11% per year). This study also demonstrated a ninefold increase in 6-month mortality in HIV patients diagnosed with pericardial effusions compared to patients without effusions. Although a definitive cause is often not found, it may be related to opportunistic infections, malignancy or a cytokine mediated capillary leak syndrome seen in end-stage HIV disease (see Table 1).[5]

A low CD4 count is observed in HIV patients with pericardial effusions which reflects the functional status of their immune system. The effusion may serve as a marker for end-stage HIV infection associated with undiagnosed opportunistic infections or malignant neoplasms. In up to 42% of patients a pericardial effusion will spontaneously resolve and therefore, pericardiocentesis is only performed diagnostically or to relieve poorly tolerated effusions. However, despite this spontaneous resolution, the patient's mortality remains increased once an effusion has developed.[5]

DILATED CARDIOMYOPATHY

Dilated cardiomyopathy, a primary cardiac muscle disease associated with severe left ventricular dysfunction, is the most common life-threatening cardiovascular complication of HIV infection.[6] It has an estimated annual incidence of 15.9 per 1000 before highly active antiretroviral therapy (HAART), and its prevalence (determined by echocardiographic and autopsy studies) ranges from 10-30%,[7] with echocardiographic findings of four-chamber enlargement, left ventricular hypokinesis and decreased fractional shortening.[8] At post mortem gross findings include increased heart weight and a pale myocardium.[9]

Although some studies have shown a role for direct HIV-1-mediated injury of the myocardium,[10] the exact pathogenesis of cardiomyopathy is still unknown. HIV-1 infection of the myocardium seems to occur in a patchy distribution without any definite association between HIV-1 and cardiac myocyte dysfunction.[11] Coinfection with Coxsackie group B virus, *Cytomegalovirus* and Epstein-Barr virus has been observed in some HIV patients and these may be implicated in the pathogenesis of cardiomyopathy (Table 1).[12]

Autoimmune reactions may play a key role in the pathogenesis of HIV-associated cardiomyopathy as circulating cardiac autoantibodies (anti-α myosin autoantibodies) have been reported in up to 30% of patients.[13]

Therefore in HIV-positive patients with previously normal echocardiographic findings, these autoantibodies could then serve as a marker for left ventricular dysfunction.[13] Another marker which can potentially be used for detection is brain natriuretic peptide (BNP) as there has been growing evidence to support the hypothesis of increased levels of this peptide in association with HIV-related cardiomyopathy.[14]

Malnutrition has also been implicated in contributing to ventricular dysfunction in cardiomyopathy. An improvement of cardiac function was seen after selenium supplementation in case reports of pediatric AIDS patients and there may also be alteration in levels of vitamin B_{12}, carnitine, growth hormone and thyroid hormone in patients with HIV disease (Table 1) which have all been associated with left ventricular dysfunction independantly.[15,16]

Evidence to suggest a beneficial effect of HAART on HIV-associated cardiomyopathy has yet to emerge. In contrast, Zidovudine has shown to be associated with mitochondrial DNA replication inhibition and cardiac mitochondrial ultrastructure destruction by studies on transgenic mice. This mitochondrial dysfunction is linked to a lactic acidosis, which may further deteriorate myocardial function.[17]

Intravenous immunoglobulin has been shown to be efficacious as a specific therapeutic regimen for HIV-associated cardiomyopathy with a 10% improvement in contractility and a 15% improvement in peak wall stress in children who receive this treatment. This supports the theory that the ventricular dysfunction seen in HIV-associated cardiomyopathy is mediated by immunological means and would therefore be responsive to immunomodulatory therapy.[18]

ENDOCARDITIS

Adherent and friable vegetations of platelets and red blood cells characterize marantic endocarditis, or nonbacterial thrombotic endocarditis, which is seen in 3% to 5% of AIDS patients.[19] It is usually found in patients older than 50 years, and in association with the HIV-wasting syndrome.[20] Systemic embolization involving the brain, lung, spleen, kidney and coronary arteries may occur in up to 42% of patients.[21] This is, however, a rare cause of death in AIDS patients.[11]

Infective endocarditis in HIV-infected patients is most commonly seen to affect the tricuspid valve (this is probably because of the association of HIV with intravenous drug misuse) and has an estimated prevalence of 6.3% to 34% in this population. Causative organisms include *Staphylococcus aureus* (more than 75% of cases), *Streptococcus viridans*, *Hemophilus influenzae*, *Candida albicans*, *Aspergillus fumigatus* and *Cryptococcus neoformans*.[20] In general, the presentation and survival of patients with infective endocarditis is similar between HIV positive and HIV negative patients (85% versus 93%).[20] However, in the late stage of HIV-infected patients, a significantly increased mortality (30%) has been reported.[22]

CORONARY ARTERY DISEASE

An increasing frequency of coronary artery disease has been reported in patients with HIV who are taking protease inhibitors (PIs) as a part of the HAART regimen.[11] Class-specific metabolic side effects of PIs such as dyslipidaemia and insulin resistance add to pre-existing cardiovascular risk factors and contribute to premature arteriosclerosis. In addition to this, HIV associated chronic inflammation with increased levels of C-reactive protein may accelerate atherosclerosis in these patients.[23] A study by Dressman *et al*[24] on the effects of PIs in mice showed that PIs induce CD36 gene expression on macrophages, which promotes the development of foam cells and subsequent atherosclerosis. The induction of CD36 on macrophages is related to the activation of peroxisome proliferator-activated receptor-γ (PPARγ), opening up therapeutic options for the use of thiazolidinediones (PPARγ inhibitors) to modulate the proliferative & inflammatory cascades involved in the atherogenic process.[25]

It has been suggested in recent findings that non-nucleoside reverse transcriptase inhibitors (NNRTIs) may increase the levels of high-density lipoprotein (HDL) cholesterol and these drugs would therefore be expected to be associated with decreased coronary artery disease incidence.[26] A HAART regimen based on NNRTIs may then be preferred in patients who are at high risk of coronary artery disease.

No correlation has been found between the development and progression of coronary artery disease and a patient's CD4 count or HIV-related opportunistic infections. However, on histology endoluminal protrusions resulting from diffuse vessel involvement of smooth muscle cell proliferation with an abundance of elastic fibers can be seen and this is a unique characteristic of HIV-related coronary arteriopathy.[27]

The incidence of acute myocardial infarction in HIV-infected patients has been reported at 5-5.5 per 1000 person-years, a threefold increase compared to non HIV-infected patients (1.52 per 1000 person-years).[28] Patients are predominantly male, with an average age of less than 50 years, and have a benign in-hospital course. However, after discharge HIV-infected

patients have a higher incidence of re-infarction, restenosis and stent thrombosis.[29]

SYSTEMIC HYPERTENSION AND COAGULATIVE DISORDERS

Elevated blood pressure has been linked to metabolic disorders and the lipodystrophy induced by protease inhibitors (Table 1).[30] With an estimated prevalence of 20% to 25% before the introduction of HAART,[31] systemic hypertension now has a prevalence of up to 74% in patients with HAART-related metabolic syndrome.[30] An increased risk of coagulative disorders is an issue of concern in patients receiving protease inhibitor-containing HAART therapy that include a protein S deficiency, increased levels of fibrinogen, D-dimer, plasminogen activator inhibitor-1 and tissue-type plasminogen activator antigen.[32,33] Documented thromboses in both veins and arteries have been associated with these disorders.[33]

PULMONARY HYPERTENSION

The incidence of pulmonary hypertension associated with HIV had been reported at 1 in 200 compared with 1 in 200,000 in the general population before the introduction of HAART.[34] It is seen most frequently in young male patients and is associated with intravenous drug users, homosexuals and haemophiliacs. Symptoms can range from dyspnoea to right-sided heart failure, cor pulmonale or death.[35]

The pathogenesis of the pulmonary arterial disease associated with HIV infection is unknown, and the hypothesis of a direct impact of the virus on the pulmonary vascular smooth muscle and/or endothelial cells has not been demonstrated.[36] However, histology frequently shows the presence of HIV-1 in alveolar macrophages which in turn release proteolytic enzymes, oxide anions and TNF-α in response to infection.[35] This supports the theory of HIV's indirect role in producing growth factors which lead to abnormal endothelial and smooth muscle cell proliferation.[37] The current treatment regime includes anti-coagulation and the use of vasodilator agents such as epoprostenol which is limited to use in very ill patients.[38] The effects of HAART on pulmonary hypertension in HIV-infected patients remains unknown.

MALIGNANT NEOPLASMS

Kaposi's sarcoma involving the heart in AIDS patients has an estimated incidence of 12% to 28% in retrospective autopsy studies.[20] Such cardiac involvement usually occurs as a part of disseminated Kaposi's sarcoma and is not usually linked to cardiac dysfunction, morbidity, or mortality.[11]

Malignant lymphoma in AIDS is usually derived from B cells, is typically of a high grade nature and disseminates early.[20] A primary cardiac lymphoma may also occur although this is extremely rare.[39] Patients present with a varied spectrum of clinical manifestations ranging from non-specific symptoms to congestive heart failure, pericardial effusion, cardiac arrhythmia or cardiac tamponade.[40,41,42] Despite the poor prognosis of patients with HIV-associated cardiac lymphoma, combination chemotherapy has yielded clinical remission in some cases.[43]

DRUG-RELATED CARDIOTOXICITY

The many medications to which HIV-infected patients are exposed in treating HIV-associated diseases (such as cancer and opportunistic infections) allows much more opportunity for drug toxicities and interactions (Table 2). Dilated cardiomyopathy has been seen in patients on amphotericin B, doxorubicin and foscarnet sodium.[44,45,46] Hypertension has been associated with erythropoeitin therapy (47% prevalence) and cardiotoxicity has been reported with interferon alpha in a review of cases by Sonnenblick and Rosin.[47,48] The most common manifestation of cardiotoxicity was arrhythmia, followed by myocardial infarct, cardiomyopathy, sudden death, AV block and congestive heart failure. Ganciclovir has been associated with ventricular tachycardia and QT prolongation has been seen with the use of pentamidine, pyrimethamine and trimethoprim-sulfamethoxazole.[49,50,51,52]

RISK STRATIFICATION FOR HIV-INFECTED PATIENTS

With the frequency of cardiovascular complications seen in the HIV-infected population, appropriate preventive screening and therapeutic strategies should be implemented in order to improve the quality of life and survival in this group of individuals. Dilated cardiomyopathy can be visualized and diagnosed by echocardiography and has been shown in association with increased levels of BNP.[14] In a study by Hervas *et al*, BNP showed a positive correlation with ventricular diameter and pulmonary artery systolic pressure and may, therefore, also play a role in the identification of patients with pulmonary hypertension.[53]

As NNRTIs have shown to be potentially beneficial on lipid profiles, a NNRTI-based HAART regimen may be favourable in patients who have an increased cardiovascular risk.[26] PI-containing HAART has been associated with vascular risk factors such as dyslipidaemia and metabolic syndrome, and therefore all patients

receiving HAART should be assessed for lipid and other metabolic abnormalities both before and at regular intervals after initiation of therapy.

Lipid abnormalities can be treated by dietary and pharmacological means with potential drug interactions taken into consideration.[54] Fibrates and statins are useful in lowering cholesterol and triglyceride levels although it should be noted that many statins are metabolized by the cytochrome P450 CYP3A4 enzyme pathway which is inhibited by protease inhibitors. This interaction may lead to a several fold increase in statin concentration and potentiate the risk of hepatic and skeletal muscle toxicity.[11]

CONCLUSION

Aggressive use of HAART therapy regimens for HIV-infected patients has decreased the incidence of opportunistic infection, pericardial effusions and HIV-associated malignancies which has helped to maximize patient survival and quality of life. Evidence has shown that protease inhibitors play a role in promoting and accelerating atherosclerosis and coronary heart disease which increases the mortality from myocardial infarction and effects of cerebrovascular disease such as stroke. To prevent the significant morbidity and mortality from cardiac involvement associated with HIV, prompt intervention of cardiac disease with screening and early recognition is important.

Table 1. Major cardiovascular manifestations associated with HIV-infection.

Type	Incidence	Cause
Pericardial Effusion	11% per year (5)	Infective: Bacterial, Mycobacterial, Viral, Fungal Malignancy: Kaposi's sarcoma, Malignant lymphoma Hypothyroidism Malnutrition Cytokine mediated capillary leak
Dilated Cardiomyopathy	1.59% before the introduction of HAART	Infective: HIV, Coxsackievirus Group B, Epstein-Barr Virus, Cytomegalovirus Autoimmune Nutritional deficiency Selenium, Vitamin B12, Carnitine Endocrine Thyroid hormone, growth hormone Hypothermia/hyperthermia High HIV viral load, immunosuppression
Coronary Artery Disease	Case reports limited to HAART with use of Pis	Adverse effects of protease inhibitors: Metabolic, Coagulative Arteritis
Systemic hypertension	20%-25% before introduction of HAART. Up to 74% in relation to HAART metabolic syndrome	HIV-induced endothelial dysfunction Premature atherosclerosis secondary to HAART Adverse effects of protease inhibitors: Insulin resistance, increased sympathetic Activity, sodium retention
Pulmonary hypertension	0.5% before the introduction of HAART	Mediators released from the endothelium Recurrent bronchial infections Multiple pulmonary emboli fragments (possibly from endocarditis)
Malignant tumors	12%-28% before introduction of HAART	Kaposi's Sarcoma Non-Hodgkin lymphomas

Table 2. Cardiovascular toxicities associated with common HIV medications.

Drug	Use	Cardiac Side Effects
Amphotericin B	Anti fungal	Dilated Cardiomyopathy, hypertension, bradycardia
Doxorubicin	Kaposi's sarcoma Non-Hodgkin's lymphoma	Dose related dilated cardiomyopathy
Erythropoeitin	Anemia	Hypertension
Foscarnet sodium	Cytomegalovirus (CMV) Esophagitis	Dilated cardiomyopathy
Ganciclovir	CMV	Ventricular tachycardia
Interferon alfa	Anti neoplastic, anti viral	Arrhythmia, myocardial infarction, cardiomyopathy, sudden death, AV block, congestive heart failure
Pentamidine	*Pneumocystis carinii*	QT prolongation, Torsades de pointes, severe hypotension
Pyrimethamine	Toxoplasmosis	QT prolongation
Trimethoprim-sulfamethoxazole	*P. carinii*	QT prolongation, Torsades de pointes
Zidovudine	Anti retroviral	Myocarditis, dilated cardiomyopathy

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