

Left ventricular dysfunction in patients with human immunodeficiency virus infection

Alexander Valdés Martín^a✉, MD; and Angélica M. Reyes Pérez^b, MD

^a Institute of Cardiology and Cardiovascular Surgery. Havana, Cuba.

^b Pedro Kouri Institute of Tropical Medicine. Havana, Cuba.

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Acronyms

AIDS: acquired immunodeficiency syndrome

DCM: dilated cardiomyopathy

HAART: highly active antiretroviral therapy

HIV: human immunodeficiency virus

LV: the left ventricle

LVD: left ventricular dysfunction

TDI: Tissue Doppler Imaging

TNF- α : tumor necrosis factor alpha

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✉ A Valdés Martín

ICCCV - Calle 17 N^o 702

El Vedado, Plaza CP 10400

La Habana, Cuba.

E-mail address:

avaldes@infomed.sld.cu

ABSTRACT

Infection with the human immunodeficiency virus is a major cause of acquired heart disease, especially symptomatic left ventricular dysfunction. A literature review was conducted to deepen the understanding of the various clinical, pathophysiological and diagnostic aspects that characterize these patients. The pathogenesis of left ventricular dysfunction is related to various causative agents such as: myocardial infection by the virus itself, opportunistic infections or by other viruses, autoimmune mechanisms, nutritional deficiencies, overexpression of cytokines and drug induced toxicity. Symptomatic systolic dysfunction is a late manifestation of cardiac involvement, while a significant proportion of patients have clinically silent abnormalities. Diastolic dysfunction presents with early alterations in myocardial relaxation and in left ventricular filling dynamics. Echocardiography is useful for its diagnosis. Current antiretroviral therapy increases the survival of patients infected with human immunodeficiency virus, which presumably would lead to an increase in the prevalence of cardiac complications. New prospective observational studies to determine the susceptibility of developing symptomatic heart disease in patients infected with this virus are required.

Key words: Human immunodeficiency virus, Echocardiography, Highly active antiretroviral treatment

Disfunción ventricular izquierda en pacientes con infección por virus de inmunodeficiencia humana

RESUMEN

La infección por el virus de inmunodeficiencia humana es una de las principales causas de cardiopatía adquirida, especialmente de disfunción ventricular izquierda sintomática. Se realizó una revisión bibliográfica para profundizar en los diversos elementos clínicos, fisiopatológicos y diagnósticos que caracterizan a estos pacientes. La patogénesis de la disfunción del ventrículo izquierdo se relaciona con diversos agentes causales como: la infección miocárdica por el propio virus, las infecciones oportunistas o por otros virus, mecanismos autoinmunes, deficiencias nutricionales, sobreexpresión de citocinas y toxicidad inducida por fármacos. La disfunción sistólica

sintomática es una manifestación tardía de afectación cardíaca mientras que una proporción importante de pacientes presentan alteraciones clínicamente silentes. La disfunción diastólica cursa con una alteración precoz de la relajación miocárdica y de la dinámica de llenado del ventrículo izquierdo. La ecocardiografía es útil para el diagnóstico. El tratamiento antirretroviral actual incrementa la supervivencia de pacientes con infección por el virus de inmunodeficiencia humana, lo cual presumiblemente producirá un aumento en la prevalencia de complicaciones cardíacas. Se requiere de nuevos estudios prospectivos observacionales que determinen la susceptibilidad de desarrollar enfermedad cardíaca sintomática en los pacientes infectados por este virus.

Palabras clave: Virus de inmunodeficiencia humana, Ecocardiografía, Tratamiento antirretroviral altamente activo

INTRODUCTION

In 1983, as Anglaret X¹ reported, the French physician and virologist Luc Montagnier discovered the retrovirus that causes Acquired Immunodeficiency Syndrome (AIDS) in humans, which was first called lymphadenopathy-associated virus (LAV), and then, in 1986, received the international designation of human immunodeficiency virus (HIV).

The HIV belongs to the lentivirus group, a subfamily of retroviruses. The members of this group can infect humans and primates. These viruses have several features in common: long incubation period before the onset of symptoms of the disease, infection of blood and nervous system cells, and immune system involvement². The unique feature that distinguishes the retroviruses and allows their classification is the need to transform their genetic information, which is in the form of ribonucleic acid, into deoxyribonucleic acid (reverse transcription process) using an enzyme known as reverse transcriptase. Two types of HIV have been identified, known HIV-1 and HIV-2. HIV-1 is the most widespread in the world and has a greater virulence. The geographical distribution of HIV-2 is more limited, and has its epicenter in West Africa, but it also exists and spreads slowly in India, Portugal, Angola, Mozambique and Brazil. Both HIV-1 and HIV-2 are able to decrease the number of CD4+ helper T cells and cause AIDS in infected persons, although they differ in their natural history³.

HIV infection is characterized by causing a severe acquired immunosuppression, which predisposes patients to multiple opportunistic infections, malignancies, and progressive multiorgan dysfunction. Initially, cardiovascular involvement did not seem to be a com-

mon complication of HIV infection, but in recent years it has been described more frequently⁴. Its prevalence varies from 25 to 75% in infected individuals, and is more commonly seen in advanced stages⁵. The introduction in 1996 of the highly active antiretroviral therapy (HAART) changed the course of infection as it improved survival rates and the quality of life of patients⁶⁻⁸. However, the infection itself, the metabolic disturbances resulting from such treatment and pre-existing cardiovascular risk factors can make this group of patients face, in a few years, an epidemic of cardiovascular diseases⁹.

In HIV patients, left ventricular dysfunction (LVD), and therefore its broad clinical spectrum, is one of the most common findings during a cardiology assessment. For this reason, this review aims to go more deeply into the various clinical, pathophysiological and diagnostic aspects that characterize LVD in these patients, to facilitate an adequate treatment by the assisting doctors.

DOCUMENTARY ANALYSIS

An exhaustive and automated review was conducted covering the articles related to the topic, published in English and Spanish in the last five years and available in the databases of Medline, Hinari and international repositories of Dialnet and Imbiomed. For this, the descriptors were previously defined, and studies that explored LVD from the clinical, epidemiological and echocardiographic standpoint were included. All information obtained was organized, for analysis and synthesis.

PATHOGENESIS

A range of possible causative agents in LVD secondary to HIV infection has been suggested, including myocardial infection by HIV itself, opportunistic infections, other infections also of viral origin, autoimmune response, cardiotoxicity due to drug treatment or the use of illegal drugs, nutritional deficiencies, overexpression of cytokines and many others¹⁰.

Myocarditis is the best studied causal hypothesis. Its prevalence in infected individuals is 12.5 to 53%¹¹. HIV is the specific cause in less than 20% of the cases. Less common causes include toxoplasmosis, tuberculosis, candidiasis, cryptococcosis, histoplasmosis, cytomegalovirus and herpes simplex¹¹⁻¹². Cytokines seem to significantly influence the development of myocarditis, because high levels of tumor necrosis factor alpha (TNF- α) have been found in seropositive patients with acute myocarditis¹³. Most cases of myocarditis are clinically asymptomatic¹⁴. Cardiac inflammatory and functional lesions are similar to those found in the simian immunodeficiency virus, studied in Rhesus monkeys. Therefore, a similar mechanism of production is suggested, where intramyocardial cells infected with the viral protein were located with labeled macrophages, and it was found that these were very low in number and did not correspond to the amount of inflammation or necrosis detected. This study attributed an important role to the immune response in myocardial injury¹⁵.

The results of autopsies and biopsies show inflammatory cell infiltrates are scarce. HIV virions infect the cardiomyocytes following a patchy distribution. Infected cells are not surrounded by an inflammatory response and a clear association between infection and functional deterioration has not established¹⁶. However, myocardial biopsy may be clinically useful, since the presence of lymphocytic infiltrates may indicate the existence of myocarditis or treatable opportunistic infections (diagnosed with special stains), allowing appropriate therapy as soon as there is a diagnosis. The increase in TNF- α production alters intracellular calcium homeostasis and increases the production of nitric oxide, tumor growth factor-beta and endothelin 1^{17,18}. Furthermore, it has been experimentally demonstrated that nitric oxide in high concentrations has a negative inotropic effect, and is cytotoxic to myocytes.

Experts say that the introduction of HAART is asso-

ciated with cardiovascular complications such as the development of the metabolic syndrome, with a propensity towards developing hyperlipidemia and coronary atherosclerosis¹⁹. Hruz *et al.*²⁰, in their investigations, have shown that the clinical use of HIV protease inhibitors is associated with insulin resistance and other metabolic changes that prevent the uptake of glucose by the heart muscle and increase the long-term cardiovascular risk. Studies with transgenic mouse models with dilated cardiac chambers have shown that exposure to ritonavir, atazanavir and lopinavir precipitated acute heart failure and death of mice with acute pulmonary edema^{21,22}. The mechanism responsible for cardiac dysfunction was cardiac muscle overexposure to the action of the enzyme Cre-recombinase²³. These studies finally show that HIV protease inhibitors affect glucose transport and induce acute heart failure^{23,24}.

Mayosi²⁵, in epidemiologic studies of cardiac dysfunction in sub-Saharan Africa, states that it is mainly due to nonischemic causes such as hypertension, pericarditis, rheumatic carditis and cardiomyopathy. The two endemic diseases that contribute most to the LVD in Africa are cardiomyopathy and pericarditis. The most common endemic forms are dilated cardiomyopathy (DCM), peripartum cardiomyopathy and endomyocardial fibrosis. The DCM is more commonly associated with HIV patients and progresses with immunosuppressive therapy in patients with HIV who suffer from pericarditis, which is associated with a large pericardial effusion and tuberculosis²⁶.

Nutritional deficiencies are common in HIV infection, especially in cases of advanced disease. Malabsorption and diarrhea episodes cause electrolyte disturbances and elemental nutrient deficiencies. Selenium deficiency increases the virulence of the Coxsackie viruses in the cardiac tissue²⁷. Treatment with selenium reverses cardiomyopathy and normalizes the functioning of the left ventricle (LV) in nutritionally depleted patients. The levels of B12 vitamin, carnitine, and thyroid and growth hormones can also be altered in patients with HIV infection, and may be associated with LVD²⁶.

Two pathogenic mechanisms have been described in children with vertically transmitted HIV infection. One is the expansion of LV with a reduction of the ratio between the thickness and diastolic ventricular size, and the other is the concentric hypertrophy of the muscle with ventricular dilation. The ratio between

the thickness and diastolic size is normal or increased²⁸.

CLINICAL PRESENTATION AND ECHOCARDIOGRAPHIC CORRELATION

HIV patients with LV systolic dysfunction may be asymptomatic, or present a New York Heart Association (NYHA) functional class III or IV as part of the clinical symptoms of a DCM²⁹. The annual incidence of this disease is estimated at 15.9 per 1,000 patients before the era of HAART, and has been reduced by 30% after its introduction. DCM secondary to HIV infection accounts for 3-6% of all its cases³⁰.

DCM is characterized by a dilated LV cavity and an overall decrease of systolic function. Dimensions and end-diastolic and systolic volumes are moderately or markedly increased, and the variables of systolic function (LV ejection fraction, fractional shortening, stroke volume and cardiac output) are uniformly decreased³¹. According MacNeil *et al.*³, Bárbaro noted that of 952 HIV-infected patients who were asymptomatic, 76 (8%) had DCM at 60 months of follow-up. Transthoracic echocardiography in these patients showed a global LV hypokinesis with an ejection fraction of less than 45%, and a dilatation with a volume rate at LV end-diastole greater than 80 ml/m². Other secondary features found in patients with DCM include dilation of the mitral annulus and incomplete coaptation of mitral leaflets, which are responsible for associated functional mitral regurgitation, growth of the atrial chambers, enlarged right ventricle and apical mural thrombi³².

The DCM appears in the advanced stages of the disease and is associated with low counts (<400/ml) of helper and inducer T-cells (CD4+ T cells). Lohse *et al.*³³, showed that the mortality of HIV-infected patients with DCM increases regardless of the count of CD4+ T cells, age, sex or risk group. The median survival to death associated with AIDS is 101 days in patients with LVD, and 472 days in patients with a normal heart, for a similar stage of infection.

In the P2C2 study, cited by Bradley *et al.*³⁴, the median age of HIV-infected children was 2.1 years and the cumulative survival at 5 years was 64%. Mortality was higher in children who at baseline had a decrease of LV fractional shortening, or enlargement of the LV, increased thickness, mass, wall stress, heart rate or

blood pressure. The decrease in LV fractional shortening and increased wall thickness were also factors that determined survival after adjusting them for age, height, CD4+ lymphocyte count, HIV viral load, hospital and presence or absence of encephalopathy. Fractional shortening was abnormal from three years before death, while wall thickening identified risk population only 18 to 24 months before death. The rapid onset of heart failure has a poor prognosis in both adults and children with HIV infection, since more than half of patients die due to primary heart failure between 6 and 12 months after diagnosis.

LVD is not limited to an impairment of ventricular systole. Clinical and echocardiographic findings suggest that diastolic dysfunction is relatively common in long-term survivors with HIV infection. This dysfunction may precede LV systolic dysfunction. Therefore, a noninvasive analysis of diastolic function in HIV-infected patients, who are asymptomatic from the cardiovascular point of view, can be used as a screening tool to detect early changes in ventricular filling suggesting myocardial involvement³⁵.

There are several echocardiographic techniques to assess LV diastolic function. Currently, the most useful ones are Doppler techniques that assess mitral flow and pulmonary veins flow, as well as the use of Tissue Doppler Imaging (TDI) at the mitral valve annulus³² (Figure 1). Normal mitral flow is a two-phase flow from the left atrium to the left ventricle. In a healthy individual, the initial flow, which coincides with mitral E wave, exceeds the late flow, which occurs with atrial systole (A wave), both in speed and volume³⁶. The magnitude of these flows, and their relationship, varies with age in the normal population. In healthy young people, E wave is greater than A wave, hence the E/A ratio is greater than 1 (Figure 2). In young adults, there may be a disproportionate contribution of active ventricular relaxation to ventricular filling, resulting in an increased E wave velocity. In this case the E/A ratio may exceed a value of 2. In various clinical conditions, such as HIV infection, a ventricular stiffness occurs, which results in a delayed relaxation. This generates a progressive decrease of E wave velocity and an increase in A wave velocity, so that the E/A ratio can reach a value below 1³⁷. Moreover, the above is accompanied by a prolongation of E-wave deceleration time and a lengthening of isovolumic relaxation time. This time represents the first phase of diastole; it is defined as the time elapse from the

closing of the aortic valve until the opening of the mitral valve. In adults, it usually has an average of 76 ± 13 m/s³⁸. In a multicenter HIV-heart study³⁹, asymptomatic patients with HIV infection underwent an echocardiography, and they were found to have an E/A ratio 34.6% lower than normal, and an isovolumic relaxation time 19.7% higher than normal compared to healthy adults.

Patients with very advanced or decompensated DCM may display a restrictive diastolic filling pattern because of the reduced distensibility and increased left ventricular filling pressure. As the heart failure of DCM patient is treated, diastolic filling becomes less restrictive. The persistence of a restrictive filling after treatment is associated with high mortality and transplant rate⁴⁰.

The pressure in the pulmonary artery, which is estimated based on the speed of the tricuspid valve regurgitation, is also of predictive value in the DCM secondary to HIV infection³⁷. Patients with tricuspid regurgitation velocity higher than 3 m/s have a higher mortality, a higher incidence of heart failure and are hospitalized more frequently than those with a lower velocity.

In the field of diastology, the TDI of medial and lateral mitral annulus, or both, has become an adequate technique to assess LV diastolic function. In patients with chronic HIV infection and abnormal LV relaxation, the time constant of isovolumic relaxation (*tau*) is prolonged. The pattern of mitral annular velocity varies with TDI, and shows a decrease of the E wave and a predominant A wave. The mitral annulus TDI reflects the alteration of the diastolic function with a higher sensitivity than the transmitral Doppler or the Doppler study of pulmonary venous return, and it is not altered by variations in the preload⁴¹.

There are few works studying diastolic function in HIV infection. Little *et al.*⁴² described the altered pattern of initial filling of the LV and the prolonged isovolumic relaxation time in patients younger than 50 years with HIV (asymptomatic and symptomatic patients), compared to a healthy control group, but did not mention the immune status or the CD4+ lymphocyte count. By contrast, Aljaroudi *et al.*⁴³ included in their study asymptomatic African patients with CD4+ lymphocyte values $< 300/\text{ml}$, and confirmed the altered pattern of LV filling and that it is significantly associated with immune status. This alteration was restrictive and was attributed to the presence of

concentric left ventricular hypertrophy or cardiac infiltration during systemic amyloidosis.

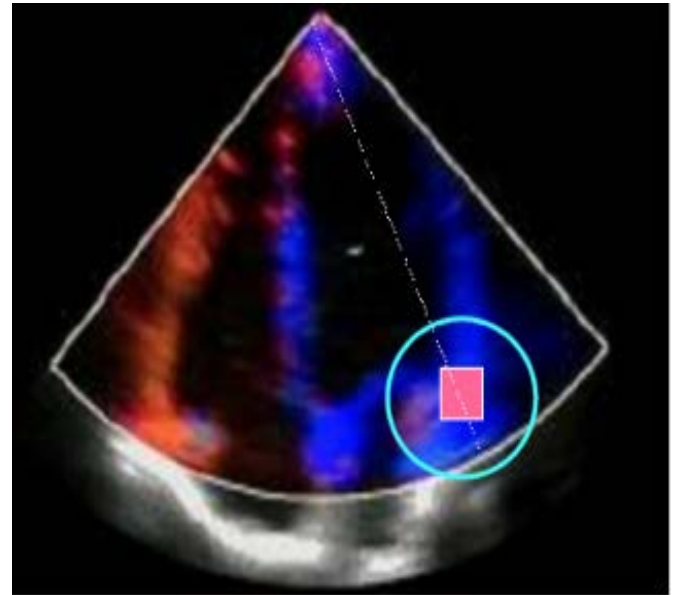


Figure 1. Echocardiogram. Apical four-chamber view. The square is the site of sample volume placement during TDI of the mitral annulus.

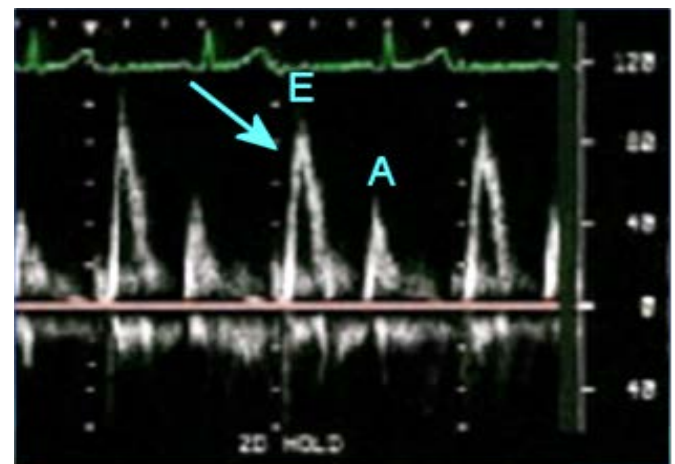


Figure 2. Mitral flow chart of a young patient where there is an E/A ratio higher than 1.

TREATMENT

The treatment of LVD secondary to DCM due to HIV is

similar to the treatment of the idiopathic form, and includes the use of diuretics, digoxin and inhibitors of angiotensin converting enzyme, as they are tolerated. There is no report of studies investigating the efficacy of specific treatments for the heart, except with intravenous immunoglobulin. On the other hand, HAART reduces the mortality rate due to heart failure⁴⁴.

Immunoglobulins have had some success in acute congestive cardiomyopathy and nonspecific myocarditis in patients without HIV infection. This treatment is beneficial in patients with Kawasaki disease, an immune-mediated disorder with cardiac dysfunction similar to that of VIH infection⁴⁵. The monthly infusion of immunoglobulins in pediatric patients with HIV-associated cardiomyopathy has managed to minimize LVD, increase ventricular wall thickness and reduce the maximum stress of LV wall, suggesting that both, the abnormal growth of myocardium and LVD, may have an immune mediator. The apparent effect of the immunoglobulins may be due to its capacity to remove heart autoantibodies and decrease the secretion or effects of cytokines and cellular growth factors. Cases with high plasma concentrations of proinflammatory cytokines have a poor prognosis. Immunomodulatory treatment may be useful in special situations, or in children with progressive deterioration of LV function. It will be necessary to conduct a multicenter, randomized study to evaluate the effectiveness of this treatment⁴⁵.

Aggressive treatment of infections (opportunistic or not) can improve the outcome and prognosis of DCM. Moreover, it is important to conduct a thorough study of the nutritional status of patients and provide supplements if there is any deficit (selenium, carnitine, multivitamins, alone or in combination, in anorexic patients or those with cachexia or diarrheal syndromes)⁴⁶. After initiation of medical treatment, it is necessary to perform serial echocardiographies every four months; if cardiac function or clinical course deteriorates, a biopsy of the right ventricle must be considered.

CARDIOTOXICITY BY DRUGS

Patients with opportunistic infections or cancer receive drugs that may cause cardiovascular toxicity. It is reported that there is a relationship between ad-

ministration of zidovudine and DCM; this antiretroviral drug is related to diffuse destruction of cell ultrastructures and the inhibition of mitochondrial DNA replication, causing lactic acidosis which contributes to myocardial dysfunction⁴⁷. Ventricular arrhythmias have also been described, for example, tachycardia, fibrillation and atypical ventricular tachycardia (related to QTc interval prolongation). Also, impaired atrioventricular conduction linked to the use of drugs as amphotericin B, ganciclovir, trimethoprim-sulfamethoxazole and pentamidine⁴⁸. Furthermore, cases of atrioventricular block have been reported with the combination lopinavir-ritonavir, particularly when administered with drugs that prolong the QT interval in the electrocardiogram⁴⁹.

Co-administration of atazanavir and macrolides may prolong corrected QT interval⁵⁰. Doxorubicin, interferon α and foscarnet are cardiotoxic; and alcohol and cocaine can exacerbate ventricular dysfunction in these patients⁵¹.

EPILOGUE

It is important to note that current antiretroviral therapy increases survival in patients with HIV infection, which presumably will lead to an increase in the incidence and prevalence of cardiac complications; therefore, new observational prospective studies are required to determine the susceptibility to symptomatic heart disease in patients infected with HIV.

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