Echocardiographic Assessment of Systolic Pulmonary Arterial Pressure in HIV-Positive Patients

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Abstract- Pulmonary hypertension is rare but is one of the complications that occur due to HIV infection. Symptoms of HIV-associated pulmonary arterial hypertension are often non-specific but the main symptom of the disease is dyspnea. In this cross-sectional study, we measured systolic pulmonary arterial pressure (SPAP) by echocardiographic methods among HIV-positive patients who received ART. This research is a descriptive, cross-sectional study of 170 HIV-positive patients that was conducted in Imam-Khomeini hospital, Tehran, Iran during 2011-2013. All patients regularly received antiretroviral therapy at least for recent 2 years. There were not any cardiopulmonary symptoms (cough, dyspnea, exertional fatigue and chest discomfort) in these patients. All participants underwent echocardiography to estimate SPAP. The participants comprised 108 males (63.5%) and 62 females (46.5%). The mean age of patients was 41 years old, and the mean duration of HIV infection was 5.5 years. The mean CD4 cell count was 401cell/µl. The principal regimen of antiretroviral therapy included two nucleoside reverse transcriptase inhibitor (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) in the hospital. The mean of systolic pulmonary arterial pressure was 25 mmHg in the participants; 156 (93.4%) of them had SPAP ≤30mmHg (normal), six (3.6%) had SPAP: 31-35mmHg (borderline) and five (3%) had SPAP > 35 mmHg (pulmonary hypertension). Our results indicated a significant increase of pulmonary hypertension in asymptomatic HIV-positive patients that had no association with any other risk factor. Also, antiretroviral therapy was not a risk factor for pulmonary hypertension in this study.

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Keywords: Echocardiography; HIV; Highly active Antiretroviral therapy; Pulmonary hypertension

Introduction

Although opportunistic infections are still main clinical manifestations in HIV-Positive patients, but cardiopulmonary symptoms are increasing in developing countries (1). The cardiopulmonary diseases have two main forms in HIV-positive patients: 6-7% of patients are symptomatic, and the remaining are asymptomatic (2). The most common cardiac diseases among HIV-positive patients include pericardial diseases, cardiomyopathy and myocarditis, pulmonary arterial hypertension (PAH) and valvular dysfunctions (2-4).

Pericardial effusion, PAH and cardiomyopathy are most common cardiac complications in AIDS patients in poor countries where coverage of antiretroviral therapy (ART) is less than 5% of patients (1,5). The pattern of cardiac diseases has altered in developed countries to coronary artery disease (CAD) and atherosclerosis (1).

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PAH is unusual and one of the complications because of HIV infection (6, 7). Since the introduction of ART, HIV-related pulmonary arterial hypertension has not exactly evaluated, but the prevalence of the disease among these patients is estimated about 0.5%. The patients are often men with a history of intravenous drug use. The disease can appear as independent predisposing factor resulting to death, associated with right-sided heart failure in HIV-positive patients (6-8). In the past, studies have displayed that more than 35-57% of HIV-positive patients had systolic pulmonary arterial pressure (SPAP) > 30 mmHg (9,10).

PAH usually arises from chronic obstruction of pulmonary arterioles that finally results in right-sided heart failure (7). It has been reported without thromboembolic diseases, endocarditis, history of intravenous drug use and pulmonary infections among HIV-positive patients. It seems that progress of PAH is not related to immune deficiency state in the patients (10).

The pathogenesis of PAH is not entirely obvious in AIDS patients, but it is postulated that HIV makes endothelial damage through release of endothelin-1, interleukin-6 and TNF-α (8,11,12). There is plexogenic pulmonary arteriopathy in pathologic examinations of these patients (10).

Symptoms of HIV-related pulmonary arterial hypertension are often non-specific but the main symptom of the disease is dyspnea. In recent years with improvement in survival of HIV-positive patients due to ART, the clinicians should attention to PAH, especially when these patients have dyspnea (7).

PAH can result in the high rate of morbidity and mortality among people living with HIV. The median time of diagnosis to death in these patients is approximately equal to 6 months; therefore early diagnosis of PAH may lead to timely treatment and decrease in symptoms and rate of mortality (8). In this cross-sectional study, we measured SPAP by echocardiographic methods among HIV-positive patients who received ART.

Materials and Methods

Participants

This research is a descriptive, cross-sectional study of 170 HIV-positive patients who have been monitored in Imam-Khomeini Hospital affiliated to Tehran University of Medical Sciences in Iran. All patients regularly received antiretroviral therapy at least for recent 2 years (2011-2013). There were not any cardiopulmonary symptoms (cough, dyspnea, exertional fatigue and chest discomfort) in these patients.

Measurements

Duration of HIV infection was defined based on the time interval between positive western blot test and echocardiographic assessment day (reported by year). Body mass index was estimated by weight/height^2 (Kg/m^2). smoking and injection drug use history was recorded by Interview and took smoking was reported as pack-year (PY). Fasting blood samples of all participants was tested for fasting cholesterol, triglyceride, plasma glucose and creatinine. Hypercholesterolemia (fasting cholesterol > 200 mg/dl) and hypertriglyceridemia (fasting triglyceride > 200 mg/dl) formed hyperlipidaemia (12) and these tests were done for all of the participants. Diabetes mellitus was diagnosed by fasting plasma glucose ≥ 126 mg/dl (13). Glomerular filtration rate was estimated by Cockcroft-Gualt formulation (ml/min), and glomerular filtration rate < 60 ml/min was considered chronic renal disease (14).

Hepatitis C virus (HCV) co-infection was assessed through positive HCV antibody test. HIV test was confirmed by positive western blot test. Absolute CD4 cell count was measured by flow cytometry.

All participants underwent transthoracic echocardiography with a machine (Fucuda, Denshi, CFsonic, model: UF-770) and by an expert cardiologist that was blind to patient's conditions. Systolic pulmonary arterial pressure (SPAP) was measured by calculation of right ventricular systolic pressure (RVSP) that was estimated by the formula: 4V2 + 10= RVSP in which V was velocity of the systolic tricuspid regurgitation jet. SPAP was classified to three groups: 1. SPAP ≤ 30mmHg (normal), 2. SPAP: 31-35mmHg (borderline) and 3. SPAP>35 mmHg (PAH) (15).

Statistical analysis

The collected data were analyzed by SPSS version 18.0 (Chicago, USA). We calculated mean, median, proportions of risk factors, ART and SPAP, as well as the associations between SPAP with risk factors and type of ART, were investigated.

Ethical considerations

Informed oral consent was obtained, and Institutional Review Board (IRB) of Tehran University of Medical Sciences also approved the study protocol.

Results

This study included 108 males (63.5%) and 62 females (46.5%).The mean age of patients was 41 years old, and the mean duration of HIV infection was 5.5 years. The mean CD4 cell count was 401cell/µl. Smokers were 48% in this study (12%:1-10 PY, 24%: 11-20 PY and 12%: >20 PY). Table 1- shows the characteristics of the participants.

The principle regimen of antiretroviral therapy included two nucleoside reverse transcriptase inhibitor (NRTI) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI) in the hospital and the most widely used drug were lamivudine (100%), zidovudine (86.5%) and efavirenz (83%). Additional information about antiretroviral medications is shown in Table-2.

The mean of SPAP was 25 mmHg. One hundred fifty six (93.4%) of them had SPAP ≤30mmHg (normal), six (3.6%) had SPAP: 31-35mmHg (borderline) and five (3%) had SPAP > 35 mmHg (PAH).

There were not any associations between SPAP and risk factors in our study (P>0.05) and there was not any relation between SPAP and antiretroviral therapy (P>0.05). Also, there was no correlation between CD4 and SPAP (P>0.05). The smoking and SPAP did not correlate with each other (P>0.05), but in heavy smoker participants (>20PY), the mean of SPAP was higher; however, the different was not significant (P>0.05).

Table 1. Characteristics of participants in the study

Characteristics		Number (Percent)
Female	**Gender**	108 (63.5)
	Male	62 (46.5)
Smoking		81 (48)
IV drug use		86 (50.5)
History of diabetes		8 (4.5)
Hyperlipidemia		
	Hypercholesterolemia	11 (6.5)
	hypertriglyceridemia	18 (10.5)
	Hypercholesterolemia & hypertriglyceridemia	23 (13.5)
Chronic renal disease		17 (10)
HCV co-infection		81 (48)

Table 2. Characteristics of antiretroviral therapy in the participants

Type of ART	Participants (%)	Mean time of drug received (month)
Lamivudine	170 (100)	45
Zidovudine	147 (86.5)	36
Efavirenz	141 (83)	70
Tenofovir	30 (17.6)	4.5
Stavudine	20 (11.8)	4
Nevirapine	15 (8.8)	3
Kaletra (Lopinavir / ritonavir)	27 (16)	5.5

Discussion

There are several points in this cross-sectional study. First of all, antiretroviral therapy use in the Participants was regular. Secondly, their mean CD4 cell counts (401cell/µl) were relatively high. Third, the prevalence of PAH compared to the general population (1-2 cases per million people) was higher (3%), but in comparison with similar studies in HIV-positive patients was lower (5,9,15). Finally, the mean SPAP in our study was lower than other similar studies (9,16).

The lower rate of PAH is due to relatively high immune status of participants in our research, although in the study conducted by Sitbon. *et al.,* in France on 277 patients with complaint of dyspnea, mean of CD4 count were less than 200 cell/µl and prevalence of PAH was 0.46% (7). In the previous reports, it has been shown that HIV-related pulmonary hypertension happened in each state of immune suppression and did not necessarily correlate with the level of immune suppression (8). The main complaint of PAH is dyspnea but in our study all participants were asymptomatic and five patients had PAH. So it seems to regard to improvement of survival with early diagnosis, perhaps in HIV-positive patients

we need more assessment for diagnosis of PAH even in asymptomatic cases (8,17).

The data about relation between PAH and antiretroviral therapy is dispute. Some studies have mentioned pulmonary hemodynamic improvement in patients receiving antiretroviral therapy, and several others have demonstrated that antiretroviral therapy is a risk factor for pulmonary hypertension (8-11). Our study showed that there was not any relation between SPAP and antiretroviral therapy and also ART was not a risk factor for PAH. Currently, there is no definite risk factor for HIV-related pulmonary hypertension; although ritonavir has been mentioned as a risk factor of pulmonary hypertension in a study but this result has not been repeated in our results as well as other studies (15).

In some studies, viral load of participants had been measured that about our limitation, it was not possible. Golden method for pulmonary arterial pressure measurement is right heart catheterization but this method has probable complications, high cost and also the impossibility of repetition; therefore, it is not routinely used in patients. Currently, Doppler echocardiography is used as a noninvasive and reliable tool for pulmonary arterial pressure measurement (17). We also used this modality with respect to our limitations in this study.

In conclusion, our results indicated a dramatic increase of pulmonary hypertension in asymptomatic HIV-positive patients that had no correlation with any other risk factor. Also, antiretroviral therapy was not risk factor for pulmonary hypertension.

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