A STUDY OF THE CARDIAC MANIFESTATIONS IN HIV POSITIVE INDIVIDUALS AND ITS CORRELATION WITH DISEASE SEVERITY AND FRAMINGHAM RISK SCORE

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ABSTRACT: BACKGROUND AND OBJECTIVES: HIV infection is characterized by an acquired, irreversible, profound immunosuppression that predisposes patients to multiple opportunistic infections, malignancies, and progressive dysfunction of multiple organ systems. Studies have suggested that HIV may exhibit a cardiac tropism and cardiac disease associated with HIV may be multifactorial, and can be caused by infectious or neoplastic complications or their treatments or by HIV infection of the myocardium itself. Pericardial effusion and myocarditis are among the most commonly reported abnormalities though cardiomyopathy, endocarditis and coronary vasculopathy have also been reported. The present study was done to evaluate the relative frequency of cardiac manifestations in patients with HIV.

METHODS: The study included 100 HIV positive patients who were selected from the outpatient department and inpatient of the Sri Ramachandra Medical College and Hospital from the year 2011 to 2013. All routine laboratory parameters, CD4 count, Chest X ray, ECG and 2D echo was done for all patients. They were divided into two groups based on Framingham 10 year cardiovascular risk score and CD4 count.

RESULTS: 62 patients were in low risk category, 30 were in moderate risk category and 8 were in high risk category for Framingham 10 year absolute risk for coronary heart disease. Twelve (12%) patients had ECG abnormalities (8 in low risk category, 4 in moderate risk category). Echocardiographic abnormalities were seen in 24 patients, (13 in low risk category, 6 in moderate risk category and 5 were in high risk category). Significant correlation was found between CD4 count, duration of HIV infection, cardiac symptoms, Anti-Retroviral Therapy and cardiac abnormalities.

KEYWORDS: HIV infection, CD4 count, Echocardiography, Framingham risk score.

INTRODUCTION: From the beginning of the AIDS epidemic, it was recognised that HIV infection can cause cardiac abnormalities. However cardiac abnormalities in AIDS patients appear to be more common than previously thought. Although most manifestations are clinically quiescent, some may have devastating and fatal outcomes. Pericardial effusion and myocarditis are among the most commonly reported abnormalities though cardiomyopathy, endocarditis and coronary vasculopathy have also been reported.¹

Almost any agent that can cause disseminated infection in patients with AIDS may involve the myocardium, but clinical evidence of cardiac disease is usually overshadowed by manifestations in other organs, primarily the brain and lungs. Thus, the number of patients with AIDS and cardiac involvement at necropsy greatly exceeds the number with significant cardiac...
disease during life. Estimates of prevalence vary widely from 28-73% according to the screening methods elected. There are varied reasons for the paucity of knowledge about the etiology of HIV associated cardiovascular diseases. Because cardiomyocytes do not have CD4 receptors, the heart was thought to be unaffected by HIV infection. Presence of cardiovascular risk factors like poor nutrition, alcohol and drugs can lead to cardiac disease in HIV infected individuals. Cardiac disease remains relatively asymptomatic in early stages of HIV infection. Heart disease can be overlooked in HIV-positive patients, because symptoms of breathlessness, fatigue and poor exercise intolerance are frequently ascribed to other conditions associated with HIV infection. Echocardiography is a very useful tool for the identifying cardiac abnormalities in HIV patients.

The advent of HAART (Highly active anti-retroviral therapy) has changed the pattern of disease in developed countries where premature coronary artery disease and other manifestations of atherosclerosis are now the most common cardiovascular disorder. This is partly caused by HAART-induced metabolic problems, particularly insulin resistance and hyperlipidemia, but also reflects a high prevalence of conventional risk factors such as smoking.

HIV neither has been universally accepted nor unambiguously proven causative agent of myocarditis in AIDS. Although HIV can clearly infect monocytes/macrophages and myocardial interstitial cells, evidence proving that HIV can infect human cardiac myocytes which do not possess CD4 receptor is less clear. HIV gene sequences have been detected by PCR in micro dissected endomyocardial biopsies from HIV-positive patients some of whom had cardiac symptoms. HIV has also been shown gain entry into human fetal cardiac myocyte by ingestion through a specific crystallizable fragment (of immunoglobulin) (Fc) receptor, and it remains possible that this or other, unidentified mechanisms can promote HIV entry into the myocyte and facilitate a primary HIV myocarditis.

Interstitial lymphocytes and macrophages can form contact with myocytes causing focal loss of basement membrane through a local reaction. Proteolytic enzymes released through HIV replication in the interstitium could also damage myocytes. The HIV envelope glycoprotein group 120 can induce tumor necrosis factor-α (TNF-α) expression from macrophages and has been shown to enhance IL-1 induced nitric oxide production in neonatal rat cardiac myocytes. Cytokine IL-6 which has some effect on immune response and viral replication in murine myocarditis, has been found in excess in small number of HIV-positive patients with biopsy proven myocarditis.

Many autoimmune processes have been described in association with HIV/AIDS infection. HIV infection can itself trigger autoimmune phenomenon in susceptible patients. The presence of auto antibodies along with hypergammaglobulinemia and elevated circulating immune complexes suggests that yet unidentified autoimmune process can take place in HIV positive patients. Usefulness of Echocardiography to identify cardiac abnormalities has been well studied. Primary pulmonary hypertension, accelerated atherosclerosis, autonomic dysfunction and rhythm disturbances including torsades de pointes have been described in association with HIV infection.

The present study was undertaken to find out cardiac abnormalities in various group of HIV infected patients and its relationship to CD4 count and to find out the predictors of cardiovascular disease risk in HIV patients based on Framingham 10 year absolute cardiovascular disease risk scoring.
MATERIAL AND METHODS: This study was a cross sectional study of 100 HIV positive patients conducted at Sri Ramachandra Medical College in the Department of Medicine from July 2011 to August 2013, after approval of Hospital ethics committee. All patients fulfilling inclusion criteria (All HIV seropositive patients, seropositivity being confirmed by ELISA) were screened and investigations done. Patients with age less than 18 years, patients previously known to have ischemic heart disease, rheumatic heart disease and congenital heart disease were excluded from the study.

A questionnaire for detailed history was taken from all patients and a thorough physical examination with detailed cardiac examination was done. Complete blood count, blood urea, sugar, serum creatinine, liver function tests and urine routine analysis were done for all patients. Fasting serum lipid profile and thyroid profile were also done. The CD4 lymphocyte count was done by Flow cytometry method.

An erect chest X-Ray (Posterior-anterior view) on deep inspiration was taken and analysed for cardiomegaly, pleural effusion, pulmonary hypertension and pulmonary edema. A standard twelve lead resting electro-cardiogram was done for all patients. The various aspects of the P wave and the QRS complexes, ST-T changes and other electro-cardiographic features suggestive of pericarditis, myocarditis, pericardial effusion, pulmonary hypertension and left ventricular dilatation were noted. Two dimensional echocardiography with colour flow Doppler was done for all patients to evaluate the presence of pericardial effusion, chamber dilatation, myocardial dysfunction, ejection fraction, pulmonary hypertension and valvular lesions.

The collected data was analyzed using Statistical Package of Social Sciences (SPSS) 17.0 for windows. Data were expressed as the mean+standard deviation. A p value of less than 0.05 was considered statistically significant.

RESULTS: Total of 100 HIV patients were studied. They were divided into two groups based on:
1) CD4 count.
2) Framingham 10 year cardiovascular risk score.

| CD4 group | No. of Patients | CD4 count | Mean CD4 count |
|-----------|----------------|-----------|----------------|
| I         | 36             | >350      | 423.64         |
| II        | 64             | <350      | 188.86         |
| Total     | 100            |           | 273.38         |

Table 1: CD4 group

| Framingham group | Total |
|------------------|-------|
| Low risk         | 62    |
| Moderate risk    | 30    |
| High risk        | 8     |

Table 2: Framingham Group
A Framingham 10 year absolute risk for developing CHD was calculated in all patients and were categorised as per NCEP guidelines. Out of 100 HIV patients, 62 were in low risk category, 30 were in moderate risk category and 8 were in high risk category.

| Duration Of HIV (Years) | CD4 GROUP I | CD4 GROUP II |
|-------------------------|-------------|--------------|
|                         | Cardiac abnormalities | Cardiac abnormalities |
|                         | Present | Absent | Total | Present | Absent | Total |
| <1                      | 2(5.6%) | 18(50%) | 20(55.6%) | 15(23.4%) | 21(32.8%) | 36(56.3%) |
| 1 - 3                   | 1(2.8%) | 10(27.8%) | 11(30.6%) | 5(7.8%) | 9(14.1%) | 14(21.9%) |
| > 3                     | 1(2.8%) | 4(11.1%) | 5(13.9%) | 0(0%) | 14(21.9%) | 14(21.9%) |
| TOTAL                   | 4(11.1%) | 32(88.9%) | 36(100%) | 20(31.3%) | 44(68.8%) | 64(100%) |
| P value                 | 0.790    | 0.016      |

Table 3: Duration of HIV Infection in Relation to Cardiac Abnormalities and CD4 Count

| Framingham group       | Mean HIV Duration |
|------------------------|-------------------|
| Low risk               | 1.563             |
| Moderate risk          | 2.110             |
| High risk              | 2.575             |
| P value                | 0.404             |

Table 4: Duration of HIV Infection in Relation to Framingham Risk Score

| Symptom | Present | Absent |
|---------|---------|--------|
|         | Cardiac abnormalities | Cardiac abnormalities |
|         | Present | Absent | Total | Present | Absent | Total |
| Group I | 2(4.4%) | 14(31.1%) | 16(35.6%) | 2(3.6%) | 18(32.7%) | 20(36.4%) |
| Group II| 7(15.6%) | 22(48.9%) | 29(64.4%) | 13(23.6%) | 22(40%) | 35(63.6%) |
| Total   | 9(20%) | 36(80%) | 45(100%) | 15(27.3%) | 40(72.7%) | 55(100%) |
| P value | 0.35    | 0.03    |

Table 5: Cardiac Symptoms In Relation To Cardiac Abnormalities And CD4 Count

| ART | Group I | Group II |
|-----|---------|----------|
|     | Cardiac abnormalities | Cardiac abnormalities |
|     | Present | Absent | Total | Present | Absent | Total |
| Yes | 3(8.3%) | 15(41.7%) | 18(50%) | 4(6.2%) | 24(37.5%) | 28(43.8%) |
| No  | 1(2.8%) | 17(47.2%) | 18(50%) | 16(25%) | 20(31.2%) | 36(56.2%) |
| Total | 4(11.1%) | 32(88.9%) | 38(100%) | 20(31.2%) | 44(68.8%) | 64(100%) |
| P value | 0.280 (not significant) | 0.010 (significant) |

Table 6: ART In Relation To Cardiac Abnormalities And CD4 Count
### Table 7: ECG in Relation To Cardiac abnormalities and CD4 Count

| ECG       | Group I | Group II |
|-----------|---------|----------|
|           | Cardiac abnormalities | Cardiac abnormalities |
|           | Present | Absent | Total | Present | Absent | Total |
| Normal    | 3(8.3%) | 32(88.9%) | 35(97.2%) | 10(15.6%) | 43(67.2%) | 53(82.8%) |
| Abnormal  | 1(2.8%) | 0(0%) | 1(2.8%) | 10(15.6%) | 1(1.6%) | 11(17.2%) |
| Total     | 4(11.1%) | 32(88.9%) | 36(100%) | 20(31.2%) | 44(68.8%) | 64(100%) |
| P value   | 0.004 (significant) | 0.0001 (significant) |

### Table 8: Echocardiographic findings

| Echo findings         | No. | % |
|-----------------------|-----|---|
| Chamber dilatation    | 14  | 14 |
| Myocardial dysfunction|     |   |
| RV dysfunction        | 1   | 1 |
| Grade I diastolic dysfunction | 33  | 33 |
| LV systolic dysfunction | 6  | 6 |
| Pericardial effusion  | 7   | 7 |
| Pulmonary hypertension| 12  | 12 |

### Table 9: Cardiovascular Risk Profile In HIV Patients

| Characteristics       | N (100) | Low (62) | Moderate (30) | High (8) | P value |
|-----------------------|---------|----------|---------------|----------|---------|
| Age (mean)            | 40.02   | 39.89    | 40.57         | 39.0     | 0.906   |
| Sex                   |         |          |               |          |         |
| Male                  | 55      | 35       | 14            | 6        | 0.335   |
| Female                | 45      | 27       | 16            | 2        |         |
| Symptoms              | 100     | 27       | 13            | 5        | 0.584   |
| HIV duration          | 1.808   | 1.563    | 2.110         | 2.575    | 0.404   |
| ART                   | 46      | 26       | 16            | 4        | 0.573   |
| Rbs                   | 110.47  | 111.39   | 110.63        | 102.75   | 0.726   |
| FLP                   |         |          |               |          |         |
| Cholesterol           | 141.77  | 145.73   | 136.07        | 132.07   | 0.253   |
| Triglycerides         | 146.83  | 149.37   | 144.20        | 137.00   | 0.732   |
| HDL                   | 41.67   | 42.85    | 40.63         | 36.38    | 0.174   |
| LDL                   | 101.85  | 101.53   | 101.63        | 105.13   | 0.888   |
| CD4 count             | 273.38  | 272.42   | 280.27        | 255      | 0.903   |
| ECG                   | 12      | 8        | 4             | 0        | 0.552   |
| Echo                  | 24      | 13       | 6             | 5        | 0.05    |
A Framingham 10 years absolute risk for coronary heart disease was calculated in all patients. Out of 100 patients, 62 were in low risk category, 30 were in moderate risk category and 8 were in high risk category. 38% of the patients were in either the moderate or high risk category by Framingham absolute 10 year cardiovascular risk scoring. Echocardiographic abnormalities were seen in 24 patients, of which 13 were in low risk category, 6 were in moderate risk category and 5 were in high risk category. There was significant correlation between the echocardiographic abnormalities in predicting the 10 year cardiovascular risk.

**DISCUSSION:** Cardiovascular manifestation in HIV infection has not attracted much attention in the Indian sub-continent. This is partly because of the clinical picture of HIV infection is still dominated by opportunistic infection and symptoms of breathlessness, fatigue and poor exercise intolerance are frequently ascribed to other conditions associated with HIV infection. With the advent of ART medication, more patients may live longer with HIV infection and present with end organ disorder.

Present study was undertaken based on the above considerations, to find out various unsuspected cardiac abnormalities in various group of HIV infected patients and its relationship to CD4 count and to find out the predictors of cardiovascular disease risk in HIV patients based on Framingham 10 year absolute cardiovascular disease risk scoring.

Based on Framingham cardiovascular risk scoring, study population was divided into three groups (Low risk, Moderate risk and High risk). Out of 100 HIV patients, 62 were in low risk category, 30 were in moderate risk category and 8 were in high risk category. In our study, 38% of patient was in either moderate or high risk categories.

There was no significant correlation between age and cardiac abnormalities similar to the study conducted by Caggese et al. In relation with Framingham group, there were 35 males and 27 females in low risk category, 14 males and 16 females in moderate risk category and 6 males and 2 females were in high risk category with P value of 0.335 which was statistically insignificant. So gender did not play a significant role in assessing the cardiovascular risk in HIV patients.

In this study, mean duration of HIV infection was 1.8 years. Mean duration of HIV infection in Group I and Group II was 1.58 and 1.93 years respectively. There was statistically significant correlation was observed between duration of HIV infection and cardiac abnormalities in Group II who has lower CD4 count.

In relation with Framingham group, mean duration in low risk category was 1.563 years, 2.110 years in moderate risk category and 2.575 in high risk category with P value of 0.404 which was statistically insignificant. Though it is statistically insignificant, there is increase in duration of HIV infection in high risk category when compared with moderate and low risk category. Hence, increase in duration of HIV infection increases the cardiovascular risk in HIV patients.

Most patients were asymptomatic (55 patients), cardiac symptoms were found in 45 patients in which dyspnea was the most predominant symptoms. There is a significant correlation between symptoms and cardiac abnormalities in Group II who had lower CD4 count. There is no relation between presence of symptoms in assessing the cardiovascular risk in HIV patients. In a study by Cardosa JS et al, 7.3% (10/137) of patients were symptomatic. In a study by Ewig S. et al, nine out of 14 patients (64%) with cardiac abnormalities had symptoms.
Out of 100 HIV patients, 46 patients were on antiretroviral therapy. In relation with cardiac abnormalities and CD4 count, among 4 patients with cardiac abnormalities in Group I, 3 patients were on antiretroviral therapy. In Group II, out of 20 patients with cardiac abnormalities, 4 patients were on antiretroviral therapy. P value for Group I and Group II was 0.280 and 0.010 respectively. Hence relation between antiretroviral therapy and cardiac abnormalities were statistically significant in Group II who had low CD4 count.

Electrocardiographic abnormalities were seen in 12 patients. In Joshi et al study, among 74 patients, 20.27% had electrocardiographic abnormalities. Only one patient had ECG abnormalities without echocardiographic abnormalities and 13 patients had normal ECG in spite of echocardiographic abnormalities. There was a significant correlation between CD4 count and ECG abnormalities but there is no relation between ECG abnormalities in assessing the cardiovascular risk in HIV patients.

Prevalence of cardiac abnormality in our study was 24%. Echocardiographic findings were Pulmonary hypertension (12%), Pericardial effusion (7%), Left ventricular systolic dysfunction (6%), Diastolic dysfunction (23%), Right ventricular dysfunction (1%) and Chamber dilatation was noted in 14% of patients. In a study by Joshi et al, among 74 patients 10.6% had dilated cardiomyopathy, 8.5% had pericardial effusion, 4.2% had vegetations, 2.1% had constrictive pericarditis and 10.6% had incidental valvular, left ventricular hypertrophy, ischemic heart disease. In a study by Mishra et al at AIIMS, 36.7% had diastolic dysfunction and 23.3% had systolic dysfunction. In P Kannan et al study, out of 200 patients, 28 patients had left ventricular dysfunction, 6 patients had pulmonary hypertension and one patient had dilated cardiomyopathy. In Mirri A et al study, 17% had echocardiographic abnormalities.

There was a significant correlation between CD4 count and Echocardiographic abnormalities. As the CD4 count decreases, the cardiac abnormalities increase proportionally. Cardiac abnormalities are inversely proportional to CD4 count. This finding correlated well with Cardoso JS et al study and Caggese et al study. In a study by S Mishra et al, there was no correlation between CD4 count and diastolic dysfunction. In Framingham group, there were 13 patients with echocardiographic abnormality in low risk category, 6 patients in moderate risk category and 5 patients in high risk category with P value of 0.05 which was statistically significant. Hence there is a significant relation between echocardiographic abnormalities in assessing the cardiovascular risk in HIV patients.

Though there are limitations in this study (This was not a case control study, CD4 group was not well matched as there are more number of HIV patients with low CD4 count in our study and the study population was very less which does not reflect the entire scenario of HIV infected individual globally to implicate our results) but this study could strongly recommend to do electrocardiography and echocardiography for screening of cardiac abnormalities in HIV patients.

CONCLUSION: Cardiac abnormalities in HIV are common. Pulmonary hypertension was the most common echocardiographic abnormality. Cardiac abnormalities correlated well with CD4 count. Only echocardiographic abnormalities had significant correlation in assessing cardiovascular risk in HIV patients by Framingham risk scoring. Hence present study recommends...
doing electrocardiography and echocardiography for screening of cardiac abnormalities in HIV patients to identify early cardiac involvement and minimize complications by early intervention.

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Date of Submission: 06/08/2015.
Date of Peer Review: 07/08/2015.
Date of Acceptance: 13/08/2015.
Date of Publishing: 21/08/2015.