Cardiovascular magnetic resonance characterisation of myocardial involvement in tuberculous pericardial constriction with and without HIV co-infection

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Declaration

This research report is my original work. Neither the whole work nor any part of it has been, is being, or is to be submitted for another degree to any other university. None of this work has been published in any format prior to the registration of the above-mentioned degree.

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Abstract

Background:Tuberculous pericarditis includes the spectrum of pericarditis caused by *Mycobacterium tuberculosis* manifesting with pericardial effusion, cardiac tamponade, effusive-constrictive and constrictive pericarditis. In patients with pericardial tuberculosis, co-infection with human immunodeficiency virus (HIV) is associated with increased incidence of haemodynamic instability, electrocardiographic (ECG) ST elevation and mortality, suggesting an aggressive myopericarditis. However, little is known about myocardial involvement in patients with pericardial tuberculosis. Cardiovascular magnetic resonance (CMR) can assess non-invasively cardiac function, myocardial oedema, inflammation and fibrosis.

Objectives: To assess cardiac and pericardial structure and function in patients with TBPC with and without HIV co-infection and to assess the relationship of left ventricular (LV) function with other imaging biomarkers.

Methods: 72 patients with TBPC (37 male (51.3%), mean age 40 ± 14.3) were included in the study. Of these, 35 were HIV infected (17 male (48.6%), mean age 34 ± 8) and 37 were HIV uninfected (20 male (54.1%), mean age 51 ± 16). Assessments included clinical examination, ECG, echocardiography, serum and pericardial biomarkers and CMR (biventricular volumes and function, oedema, and late gadolinium enhancement - LGE).

Results: HIV infected TBPC patients were younger ($p<0.001$), had lower serum haemoglobin ($p<0.001$) and were more likely to have NYHA class III and IV symptoms ($p<0.001$). There were no differences on ECG and echocardiography between HIV infected and uninfected TBPC patients. There were also no differences in global systolic function between HIV infected and uninfected TBP patients. Focal fibrosis on LGE was found more commonly in

those with HIV infection ($p<0.001$). Pericardial effusions were frequent (>50%) in both groups of TBPC patients. Determinants of LV ejection fraction in TBPC included heart rate, LV size, E/A ratio, pericardial LGE and pericardial thickness (all $p<0.01$).

Conclusions: HIV co-infection is associated with increased focal myocardial fibrosis in TBPC patients suggesting increased myocardial inflammation in those with HIV co-infection. In the future, it will be important to assess the prognostic significance of these findings.

Keywords

HIV-associated cardiovascular disease, tuberculous pericardial constriction, cardiovascular magnetic resonance, pericarditis, heart failure

Abbreviations

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
CMR	Cardiovascular magnetic resonance
CVD	Cardiovascular disease
ECG	Electrocardiography
ECP	Effusive-constrictive pericarditis
HIV	Human immunodeficiency virus
LA	Left atrium
LBBB	Left bundle brunch block
LGE	Late gadolinium enhancement
LV	Left ventricle/ventricular
SI	Signal intensity
SSFP	Steady state free precession
SSA	Sub-Saharan Africa
TBPC	Tuberculous pericardial constriction

Introduction

In 2013, 9 million people developed tuberculosis and 1.5 million people died in the same year from tuberculosis, 360,000 of whom were HIV infected.[1] Globally, the incidence of tuberculosis is declining each year, but continues to increase in many parts of the world, including sub-Saharan Africa (SSA).[2] Tuberculosis has a complex interaction with the human immunodeficiency virus (HIV) infection, occurring at a multiplicity of levels.[3]Tuberculous pericarditis, caused by *Mycobacterium tuberculosis*, is the most common cause of a large pericardial effusion in the developing world, accounting for 69.5% of effusions in a case series from the Western Cape, South Africa;[4] and has a high mortality related to pericardial tamponade, constrictive pericarditis, arrhythmias and heart failure.[5]

Cardiovascular manifestations of tuberculosis include pericarditis with pericardial effusion, cardiac tamponade, effusive-constrictive and constrictive pericarditis, calcific pericardial constriction, tuberculomas and vasculitis.[6,7]There has been a dramatic resurgence in tuberculous pericarditis in the context of co-infection with HIV. Over 90% of pericardial effusions in those infected with HIV in SSA are due to tuberculosis, compared with 50–70% in those without HIV and less than 5% in industrialised nations.[8]

In patients with tuberculous pericarditis, co-infection with HIV is associated with increased incidence of haemodynamic instability, electrocardiographic (ECG) ST elevation and mortality, suggesting an aggressive myopericarditis in the context of HIV co-infection.[9] However, little is known about myocardial involvement in patients with tuberculous pericarditis, and in particular, in those with tuberculous pericardial constriction (TBPC).

TBPC is a serious complication of tuberculous pericarditis, occurring in 30 to 60% of patients, despite prompt and adequate antituberculous treatment and steroids,[10]and is associated with high mortality.[5] The mortality from TBPC is reduced by the use of corticosteroids in those without HIV infection.[11,12] Tuberculosis remains the commonest cause of pericardial constriction in SSA.[13] In SSA, many patients with TBPC present with a subacute variety of effusive-constrictive pericarditis (ECP), characterised by a thick, fibrinous exudate in the pericardial sac.[14]The diagnosis of ECP is considered probable if it is established on the basis of echocardiography or cardiovascular magnetic resonance (CMR). Currently, there are no published prospectively-derived consensus diagnostic criteria for ECP using these imaging modalities, but widely accepted criteria include presence of the following: (1) pericardial thickening; (2) abnormal or paradoxical motion of the interventricular septum; (3) a dilated inferior vena cava with reduced respiratory variation; and (4) marked respiratory variation of the mitral (and tricuspid) inflow Doppler patterns.[15]

CMR can assess non-invasively cardiac function, myocardial oedema, inflammation and fibrosis.[16]To date, there have been no systematic, prospective CMR studies of tuberculous pericarditis. Smith and colleagues published the first case report of TBPC confirmed on CMR in 2001.[17]Russell *et al* demonstrated the role of CMR in characterising tuberculous ECP and how the CMR findings correlated with invasive haemodynamics.[18] Further, our group has also demonstrated the role of CMR in monitoring of nodular myocardial tuberculosis following antituberculous therapy.[19] Similarly, Grigoratos*et al* published a case report showing CMR evidence of focal oedema and late gadolinium enhancement (LGE), which resolved following antituberculous therapy.[20] A single centre retrospective study of 11

Moroccan patients with pericardial constriction (only 4 of whom were suspected to be tuberculous) found LGE in 3 of 11 patients.[21]

We hypothesised that HIV co-infection would be associated with increased myocardial pathology on CMR in patients with TBPC. Therefore, our study objectives were (1) to assess myocardial and pericardial structure and function in patients with TBPC with and without HIV co-infection, and (2) to assess the relationship of left ventricular (LV) function with other imaging biomarkers.

Methods

Study subjects

The study subjects consisted of a prospectively acquired South African cohort, from the Western Cape Province, that were referred for investigation of tuberculous pericardial constriction at Groote Schuur Hospital between 2006 and 2014. In this study, we included those who underwent imaging with CMR (n=72). Patients were included into the study regardless of HIV-infection status. Patients with non-sinus rhythm were excluded from the study. All subjects gave written informed consent to participate in the study. Ethical approval was granted for all study procedures by the University of Cape Town Human Research Ethics Committee and all participants gave informed consent to participate in the study.

Study metadata

Patient demographics, including age, sex, weight and height were obtained from the patients' clinic folders. Information such as patients' history and symptoms were also obtained from the clinic folders and documented as dyspnea, paroxysmal nocturnal dyspnea, orthopnea, oedema, chest pain, palpitations, syncope, night sweats, fever, loss of weight, cough, and previous pulmonary tuberculosis. Past medical history was documented in detail, as were co-morbid conditions. Investigations included electrocardiography (ECG), echocardiography, serum biomarkers and CMR.

CMR assessments

CMR studies were performed using a single 1.5 T MR system (Symphony, Siemens Healthcare, Germany). A 20-channel phased-array chest coil was used for all data acquisition, except for STIR imaging, for which the body coil was used. A complete stack of short axis images were obtained during breath hold and cardiac gating for cine,T2-weighted and LGE imaging. T2 weighted-CMR was performed with the black blood short-Tau inversion recovery (STIR) sequence, before administration of contrast agent. LGE imaging was performed using a T1-weighted phase-sensitive inversion recovery sequence about 6 minutes after intravenous administration of contrast agent (Omniscan; 0.15 mmol/kg body weight).

CMR image analysis

All CMR images were analysed offline in a blinded fashion.

Cine images

Analysis of left ventricular ejection fraction was performed using Argus software (Siemens Medical Solutions, Erlangen, Germany). Left ventricular (LV) short axis epicardial and endocardial borders were manually contoured at end-diastole and end-systole. LV end systolic (LVESV) and end diastolic (LVEDV) volumes were used to calculate stroke volume (SV) and ejection fraction (EF) – (EF = SV/EDV). Myocardial mass was also calculated by subtracting the endocardial volume from the epicardial volume, based on prior knowledge of myocardial specific gravity

STIR images

Quantitative analysis was performed by comparing the LV myocardium in short axis against adjacent skeletal muscle in the same slice, verified on a corresponding balanced steady state free precession (SSFP) image. The T2 signal intensity (SI) ratio was defined as $SI_{myocardium}/SI_{remote\ skeletal\ muscle}$. Myocardial oedema was diagnosed when myocardial T2 SI ratio is > 1.9. Care was taken to exclude non-suppressed blood pool signal due to slow flow adjacent to the subendocardium and to avoid using areas with abnormally low signal for normalisation.

LGE images

Images were evaluated qualitatively for the presence or absence, pattern (subendocardial, midwall, subepicardial, transmural) and regional distribution of LGE areas by two observers, each with at least 5 years of CMR experience. The detection of LGE was made by consensus of both observers.

Statistical considerations

Normality of data was tested using the Kolmogorov-Smirnov test. Normally distributed data are presented as mean ± standard deviation (SD) or, where highly skewed, as median (interquartile range); non-parametric data are presented as numbers (percentages). The chi-square test or the Mann-Whitney U test was utilized for non-parametric data. Unpaired samples between groups were assessed by the unpaired 2-tailed Student t test. Correlation was assessed using the Pearson "R" and Spearman "R_S" coefficient, as appropriate. All statistical tests were two-tailed, with p-values of less than 0.05 considered statistically

significant. All analyses were performed using SPSS version 20 (IBM, Armonk, New York, USA).

Results

Baseline characteristics

Of 72 patients included in the study, there was an almost even split between males (51.3%) and females (48.7%) with TBPC (Tables 1 and 2). Of the study population, 35 participants were HIV infected, with only 6 (17%) of these receiving combination antiretroviral therapy (ART). None of the HIV infected persons on ART were on a protease inhibitor.The median CD4 count was 165 (IQR 29-268). The mean age of the total study population was 40 ± 14 years; however the HIV infected patients were younger with an average age 34 ± 8 years ($p<0.001$). There were no significant differences between HIV infected and uninfected persons when comparing body mass index, systolic and diastolic blood pressure and heart rate. Importantly, the prevalence of cardiovascular risk factors and comorbidities were low in this cohort.

Table 1: Demographic details (N=72)

Age, years	40.0 ± 14.3
Male sex, n (%)	37 (51.3)
BMI, kg/m^2	22.9 ± 5.5
Systolic BP, mmHg	110.4 ± 19.2
Diastolic BP, mmHg	70.7 ± 11.6
Heart rate, bpm	115.1 ± 22.3
HIV infected, n (%)	35 (48.6)
Receiving ART, n (%)	6 (8.3)
On diuretic therapy, n (%)	9 (12.5)

Continuous data are mean ± SD unless otherwise indicated
ART, antiretroviral therapy; BMI, body mass index; BP, blood pressure; HIV, human immunodeficiency virus

Table 2. Demographic characteristics separated by HIV infection status

	HIV infected (N=35)	***HIV uninfected (N=37)***	***P value***
Age, years	33.7 ± 7.8	51.4 ± 15.8	<0.001
Male sex, n (%)	17 (48.6)	20 (54.1)	0.46
BMI, kg/m^2	22.2 ± 4.8	23.8 ± 8.2	0.59
SBP, mmHg	110.0 ± 20.2	111.5 ± 20.9	0.83
Diastolic BP, mmHg	70.8 ± 9.6	71.2 ± 17.05	0.95
Heart rate, bpm	116.2 ± 20.1	112.3 ± 22.6	0.57
Receiving ART, n (%)	6 (17.1)	0 (0)	–
On diuretic therapy, n (%)	5 (14.3)	4 (10.8)	0.13

Continuous data are mean ± SD unless otherwise indicated
ART, antiretroviral therapy; BMI, body mass index; BP, blood pressure

Dyspnoea was present in 83% and 41% in HIV infected and uninfected persons, respectively (p<0.001) − Table 3, in keeping with prior reports of greater degrees of dyspnoea in HIV-infected persons.[22,23] Interestingly, palpitations were more frequently reported in those with HIV infection (p=0.03). Constitutional features including cough (p=0.03), fever (p=0.04), weight loss (p=0.01) and night sweats (p=0.003) were more prevalent in those infected with HIV.

Smoking was more prevalent in those who were HIV infected (p=0.007) – Table 4. Previous pulmonary tuberculosis was evident in the history of 11% and 11%, respectively, in HIV infected and uninfected persons (p=0.001).

Table 3. Clinical features

	HIV infected (N=35)	***HIV uninfected (N=37)***	***P value***
Dyspnea, n (%)	29 (82.9)	15 (40.5)	0.004
NYHA FC, n (%) NYHA I NYHA II NYHA III NYHA IV	 0 (0) 17 (48.6) 21 (60.0) 6 (17.1)	 0 (0) 16 (43.2) 9 (24.3) 3 (8.1)	0.001
Orthopnea, n (%)	8 (22.9)	4 (10.8)	0.04
PND, n (%)	5 (14.3)	2 (5.4)	0.08
Palpitations, n (%)	6 (17.1)	2 (5.4)	0.03
Syncope, n (%)	1 (2.9)	0 (0)	–
Pedal oedema, n (%)	8 (22.9)	6 (16.2)	0.64
Cough, n (%)	29 (82.9)	11 (29.7)	0.03
Fever, n (%)	11 (31.4)	7 (18.9)	0.04
Night sweats, n (%)	18 (51.4)	7 (18.9)	0.003
Loss of weight, n (%)	16 (45.7)	9 (24.3)	0.01
Known TB contact, n (%)	2 (5.7)	1 (2.7)	0.55

Continuous data are mean ± SD unless otherwise indicated
NYHA, New York Heart Association; PND, paroxysmal nocturnal dyspnoea

Table 4. Comorbid cardiovascular risk factors

	HIV infected (N=35)	***HIV uninfected (N=37)***	***P value***
Smoking, n (%)	10 (28.6)	3 (8.1)	0.007
Hypertension, n (%)	1 (2.9)	1 (2.7)	0.70
Diabetes, n (%)	1 (2.9)	0 (0)	–
Dyslipidaemia, n (%)	0 (0)	0 (0)	–
COPD, n (%)	1 (2.9)	0 (0)	–
Previous PTB, n (%)	4 (11.4)	4 (10.8)	0.88
Alcohol use, n (%)	3 (8.6)	1 (2.7)	0.26

Continuous data are mean ± SD unless otherwise indicated
COPD, chronic obstructive pulmonary disease; PTB, pulmonary tuberculosis

Electrocardiographic and echocardiographic findings

There were no significant differences on ECG between TBPC patients with and without HIV infection (Table 5). Of note, on echocardiography, there were also no significant differences between the two groups (Table 6). Trivial to mild atrioventricular valve incompetence was reported in a third of patients, overall. Echocardiographic evidence of tamponade was not seen in this cohort. Most patients had a diagnosis of ECP. Pericardial effusion was a present in 77% of those with HIV infection and in 93% of those without HIV infection (p=0.41).

Table 5. Electrocardiographic features (N=48)

	HIV infected (N=34)	***HIV uninfected (N=14)***	***P value***
Heart rate, bpm	108.1 ± 28.4	109.0 ± 26.6	0.96
Rhythm Sinus rhythm Atrial fibrillation Atrial flutter	 31 (91.2) 3 (5.9) 0 (0)	 13 (92.9) 0 (0) 1 (7.1)	0.72
QRS axis, degrees	56.6 ± 35	58.4 ±28.3	0.89
PR interval, ms	147.2 ± 25.3	135.3 ± 20.5	0.17
PR elevation, n (%)	7 (20.6)	1 (7.1)	0.16
Pathological Q waves, n (%)	1 (2.9)	0 (0)	–
QRS duration, ms	78.3 ± 12.1	75.9 ± 10.4	0.68
ST elevation, n (%)	3 (8.8)	0 (0)	–
ST depression, n (%)	2 (5.8)	0 (0)	–
Repolarisation abnormalities, n (%)	10 (29.4)	5 (35.7)	0.46
QT interval, ms	422.3 ± 34.5	403.1	0.23
Poor R wave progression, n (%)	7 (20.6)	3 (21.4)	0.66
Microvoltage, n (%)	4 (11.8)	5 (35.7)	0.06
Electrical alternans, n (%)	22 (64.7)	10 (71.4)	0.25
Left ventricular hypertrophy, n (%)	1 (2.9)	1 (7.1)	0.43
Dominant R in V1, n (%)	1 (2.9)	0 (0)	–

Continuous data are mean ± SD unless otherwise indicated

Table 6. Echocardiographic features (N=48)

	HIV infected (N=34)	*HIV uninfected (N=14)*	*P value*
LVIDd, cm	4.8 ± 0.6	4.2 ± 0.9	0.09
LVIDs, cm	3.3 ± 0.7	3.2 ± 0.5	0.57
Dilated LV[24], n (%)	2 (5.9)	0	0.36
IVSd, cm	1.0 ± 0.2	1.2 ± 0.4	0.26
RV diameter, cm	2.3 ± 0.5	2.4 ± 0.2	0.89
LV wall motion abnormality (septal bounce), n (%)	3 (8.8)	4 (28.6)	0.12
E/A	1.5 ± 1.0	1.7 ± 0.7	0.71
LVEF, %	55.4 ± 17.1	47.8 ± 9.8	0.18
FS, %	29.8 ± 10.2	25.0 ± 8.8	0.24
PAP, mmHg	19.6 ± 10.0	16.4 ± 3.3	0.47
MR, n (%)	10 (29.4)	4 (28.6)	0.54
AR, n (%)	1 (2.9)	1 (7.1)	0.53
TR, n (%)	8 (23.5)	3 (21.4)	0.69
PR, n (%)	1 (2.9)	1 (7.1)	0.17
LA dimension, cm	3.1 ± 0.6	3.3 ± 0.5	0.36
RV/RA collapse, n (%)	3 (8.8)	2 (14.3)	0.62
Respiratory variation, n (%)	8 (23.5)	4 (28.6)	0.62
Dilated IVC, n (%)	3 (8.8)	2 (14.3)	0.53
Increased pericardial thickness, n (%)	9 (26.5)	7 (50.0)	0.11
Pericardial effusion, n (%)	26 (76.5)	13 (92.9)	0.41

Continuous data are mean ± SD unless otherwise indicated
AR, aortic regurgitation; IVC, inferior vena cava; IVSd, interventricularseptal thickness in diastole; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal dimension in diastole on echocardiography; LVIDs, left ventricular internal dimension in systole on echocardiography; MR, mitral regurgitation; PAP, pulmonary arterial pressure; PR, pulmonary regurgitation; RV, right ventricle; TR, tricuspid regurgitation

Serum biomarkers

Of the laboratory data, only the haemoglobin was found to be significantly lower in the HIV infected subjects (9.7g/dl vs. 12.7g/dl, p<0.001) – Table 7. *Mycobacterium tuberculosis* was cultured in 28.6% and 33.3% in the HIV infected and uninfected groups, respectively (p=0.57). Pericardial fluid adenosine deaminase (ADA) was found to be a sensitive marker for tuberculous pericarditis with mean values of 73 ± 23 and 99 ± 57 mmol/L in those with and without HIV infection, respectively (p=0.08). Positive Light's criteria on pericardial fluid were highly sensitive for the diagnosis of tuberculous pericarditis, and were positive in 97% and 100% of HIV infected and uninfected participants who underwent pericardiocentesis, respectively (p=0.92). In our study, 16 patients had a cardiac Troponin T and creatinine kinase (CK-MB) performed and all these biomarker results were within normal limits, ruling out active myocardial injury in the patients studied.

Cardiovascular magnetic resonance

On CMR, there were no differences between the HIV infected and uninfected patients when comparing LV chamber size, stroke volume, global ejection fraction and LV mass index (Table 8); also there were no differences in left atrial size (all p values >0.05). While the T2-weighted signal intensity ratios were higher in HIV infected patients (1.70 ± 0.21 vs. 1.49 ± 0.20 %), these were within the normal range and did not reach statistical significance (p=0.19). The presence of LGE was significantly higher in HIVinfected persons with TBPC (71% vs. 22%, p<0.001). Pericardial thickening (0.5 ± 0.2 vs. 0.7 ± 0.3 cm, p=0.16), frequency of pericardial effusions (67 vs. 52%, p=0.19) and pericardial LGE (31% vs. 22%, p=0.11) was similar in HIV infected and uninfected patients, respectively.

Table 7. Laboratory measurements

	HIV infected (N=35)	***HIV uninfected (N=15)***	***P value***
Haemoglobin, g/dL	9.7 ± 2.0	12.7 ± 1.7	<0.001
Creatinine, µmol/L	62.2 ± 16.9	88.9 ± 32.7	0.01
Sputum gene Xpert, n (%)	0	0	–
TB culture in PE, n (%)	10 (28.6)	5 (33.3)	0.57
TB culture Other, n (%)	1 (2.9)	0 (0)	–
AFB positive in PE, n (%)	0 (0)	2 (13.3)	–
AFB positive in another site, n (%)	1 (2.9)	0 (0)	–
PE ADA, mmol	73.3 ± 23.3	98.9 ± 57.2	0.08
PE protein, IU/L	64.3 ± 9.6	57.4 ± 7.9	0.04
PE LDH, IU/L	2726.3 (974.7-4321.8)	1623.5 (443.6-2410.9)	0.42
Serum protein, IU/L	80.2 ± 9.1	77.6 ± 6.6	0.36
Serum LDH, IU/L	817.4 (410.4-1214.6)	536.6 (243.8-799.6)	0.05
Positive Light's criteria, n (%)	34 (97.1)	15 (100.0)	0.92

Continuous data are mean ± SD unless otherwise indicated
ADA, adenosine deaminase; AFB, acid fast bacilli; LDH, lactate dehydrogenase; PE, pericardial effusion; TB, tuberculosis

Table 8. Cardiovascular magnetic resonance findings

	HIV infected (N=35)	***HIV uninfected (N=37)***	***P value***
LVEDV, mL	143.7 ± 27.5	142.6 ± 26.3	0.90
LVESV, mL	43.34 ± 22.4	36.5 ± 7.4	0.29
LVSV, mL	100.4 ± 23.4	108.3 ± 22.4	0.31
LVEF, %	63.86 ± 18.8	57.54 ± 22.1	0.33
LVMI, g/m^2	58.3 ± 14.3	56.7 ± 30.7	0.82
LA size, cm	2.7 ± 0.5	2.8 ± 0.7	0.40
Presence of LGE, n (%)	25 (71.4)	8 (21.6)	<0.001
Pericardial LGE, n (%)	11 (31.4)	8 (21.6)	0.11
Myocardial T2 SI ratio, %	1.70 ± 0.21	1.49 ± 0.20	0.19
Pericardial thickness, cm	0.5 ± 0.2	0.7 ± 0.3	0.16
Pericardial effusion, n (%)	24 (68.6)	19 (51.4)	0.19

Continuous data are mean ± SD unless otherwise indicated
LA, left atrium; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass indexed to body surface area; LGE, late gadolinium enhancement; SI, signal intensity

Finally, while global LV systolic function was preserved overall in patients with TBPC in this study, there was also great variability in LVEF observed. We undertook Cox proportional hazard univariate regression analysis to investigate the determinants of LV function in this group of patients. Determinants of LV systolic function in TBPC included heart rate, LV size, E/A ratio, pericardial LGE and pericardial thickness (all $p<0.01$) – Table 9.

Table 9. Univariate regression analysis for predictors of LV function in TBPC

Co-variates	***Pearson correlation (R)***	***P value***
Heart rate	-0,464	0.003
LVIDd	-0,711	<0.001
E/A	-0,572	<0.001
Myocardial LGE	-0,239	0.22
Pericardial LGE	-0,645	<0.001
Pericardial thickness	-0,699	<0.001

Discussion

In this study, we used CMR to assess the myocardial phenotype of TBPC patients and we have found evidence of increased myocardial fibrosis in patients with HIV. Further, there was increased pericardial thickness with associated pericardial enhancement on LGE CMR, likely indicating pericardial fibrosis. Forty nine percent of study subjects were co-infected with HIV, with a median CD4 count of 165 mm^3 and only 17% of these on ART. Of note, HIV infected TBPC patients were younger, had lower serum haemoglobin and were more likely to have NYHA class III and IV symptoms. Determinants of LV systolic function in TBPC on univariate analysis included heart rate, LV size, E/A ratio, pericardial LGE and pericardial thickness. These results have implications for the management of TBPC patients with HIV co-infection: the presence of increased focal myocardial fibrosis in patients infected with HIV may explain some of the higher mortality in this group of patients. In the future, it will be important to investigate therapeutic strategies that may improve prognosis of TBPC patients with dual infection.

A previous CMR study on 90 treated HIV infected patients found that asymptomatic HIV infected persons had 47% higher median myocardial lipid content and 74% higher median plasma triglycerides. Further, focal mid-wall myocardial fibrosis was found in 76% of HIV infected persons compared to only 13% on HIV uninfected controls. These myocardial changes in HIV infected persons were associated with impairments in both systolic and diastolic strain and strain rates[25] Moreover, these findings have been confirmed by a more recent publication.[26]In this study, we found that 71% of HIV infected participants had focal

myocardial fibrosis on LGE CMR compared to only 22% of HIV uninfected TBPC patients. While we hadhypothesised that patients co-infected with tuberculosis and HIV would have greater myocardial fibrosis, we are unable to assess the contribution of tuberculosis in driving myocardial fibrosis, as the frequency of fibrotic lesions can be explained by the HIV infection alone. The presence of myocardial fibrosis in patients with HIV infection may indicate prior myocardial inflammation/myocarditis.[25] In the future, a study comparing HIV patients with and without TBPC will be important for addressing the issue of the contribution of tuberculosis.

The vast majority of patients studied had small (sub-centimeter) pericardial effusions, in keeping with tuberculous ECP. While these effusions were more common in those with HIV-infection, this difference did not reach statistical significance. Also, there was no difference in the size of the pericardial effusions when comparing HIV infected and uninfected patients. ECP is a clinical syndrome in which compressive pericardial fluid and a constricting visceral pericardium occur simultaneously.[27]

The inflammatory process seen intuberculouseffusive pericarditis is distinct from that seen in patients with ECP.[28]Previous publications have reported that tuberculousECP is associated with higher levels of pericardial IL-10 and IFN-γ when compared to effusive non-constrictive disease.[28] Similarly, the fibrotic and regulatory cytokine TGF-β is significantly elevated in the serum of tuberculous ECP patients. These findings led to the hypothesis that the immunopathology of tuberculous ECP is largely driven by a pathological cross-regulatory and fibrotic response which abrogates the protective IFN-γ response, with consequent structural changes in the visceral pericardium which are manifested by constrictive physiology. No association has be found between IL-10 and TGF-β and CD4 count in HIV

infected persons,[28]suggesting that we should witness the same degree of visceral and parietal inflammation andfibrosis in both HIV infected and uninfected persons. Indeed, there was no difference in degree of pericardial fibrosis detected by CMR in both HIV infected and uninfected persons in this study

Dyspnea was much more frequently present in HIV-infected persons in our study. Prior studies have also reported that HIV infected TBPC patients tend to present with greater degrees of dyspnea,[22,23]whichmay likely be related to greater myocardial involvement. However, breathlessness in this group of patients may indicate pulmonary tuberculosis, other opportunistic infections, diastolic dysfunction and heart failure from non-tuberculous related factors.

In this study, we were unable to demonstrate active myocardial inflammation in patients. While the myocardial STIR SI ratio was higher in patients with HIV infection, this failed to reach statistical significance. Further, the levels of CK-MB and cardiac Troponin T, when measured, were not elevated. However, nodular tuberculous myocarditis detected on CMR that resolved following anti-tuberculous therapy has been described previously.[19]

Determinants of LV systolic function in TBPC included heart rate, LV size, E/A ratio, pericardial LGE and pericardial thickness. It has been shown that in patients with HIV associated cardiomyopathy the presence LV systolic dysfunction is associated with a high mortality.[29]Interestingly, the presence of myocardial LGE was not associated with LV function in this study. The presence of myocardial LGE has been shown to portend a poor prognosis in many different clinical contexts.[30-33]Similarly, there is a high mortality associated with co-existence of HIV infection andtuberculous pericarditis. The overall

mortality rate at 6 months is 26%; 40% in patients with clinical HIV disease and 17% in those without.[5]Predictors of mortality in HIV-associated TBPC included a proven non-tuberculous diagnosis, presence of clinical features of HIV infection, pulmonary tuberculosis (hence a greater burden of disease), and increasing age. There was also a trend towards an increase in mortality in patients with haemodynamic instability.[4]

This study had several limitations. First, no patients without TBPC were included for comparison. Second, the vast majority of patients did not have serum biomarkers for CK-MB or cardiac troponins for assessment of acute myocardial injury. Third, no parametric mapping was performed in this cohort of patients. However, despite these limitations, in the largest CMR study of TBPC to date, we show that HIV infection is associated with increased myocardial fibrosis in TBPC.

Conclusions

We utilised amultiparametric CMR approach to investigate the myocardial phenotype of TBPC patients. We observed evidence of increased myocardial fibrosis in patients with HIV. Also, there was increased pericardial thickness with associated pericardial enhancement on LGE CMR. Moreover, HIV infected TBPC patients were younger, had lower serum haemoglobin and were more likely to have NYHA class III and IV symptoms. Determinants of LV systolic function in TBPC on univariate analysis included heart rate, LV size, E/A ratio, pericardial LGE and pericardial thickness.

We hypothesise that myocardial inflammation in HIV and tuberculous infection is the cause of increased myocardial fibrosis in our study participants. We were unable to assess causation and the direct contribution of HIV and tuberculous infections to this myocardial fibrotic process in this cross-sectional study. In the future, it will be important to assess the prognostic significance of these findings and to investigate therapeutic strategies that may improve prognosis of TBPC patients with HIVco-infection.

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