

# Systolic function evaluated with cardiovascular magnetic resonance imaging in HIV-infected patients



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**Background:** Of all areas worldwide, sub-Saharan Africa is worst affected by the HIV and/or AIDS epidemic. Cardiovascular manifestations are very common and are a powerful contributor to mortality, but often go undetected. Cardiovascular magnetic resonance (CMR) is the most reliable method of assessing cardiac function and morphology and, with this in mind, we initiated a cross-sectional study comparing CMR-determined morphological and functional parameters in asymptomatic HIV-infected patients who were not yet on treatment and early in the disease, with HIV-uninfected control patients.

**Objectives:** To ascertain whether there were any morphological abnormalities or systolic functional impairments on CMR in untreated asymptomatic HIV-infected patients, compared with HIV-uninfected control individuals.

**Methods:** The CMR studies were performed using a 1.5-T whole-body clinical magnetic resonance 16-channel scanner (Achieva, Philips Medical Systems, Best, The Netherlands), using a cardiac five-element phased-array receiver coil (SENSE coil). Functional assessment was performed on 36 HIV-infected patients and the findings compared with 35 HIV-uninfected control patients who were matched for age and sex.

**Results:** There was no significant difference in systolic function between the HIV-uninfected and the HIV-infected patients. The left ventricular end diastolic mass (LVEDM) was slightly higher in the HIV-infected group, but this was statistically insignificant.

**Conclusion:** No significant differences were found regarding the CMR systolic functional analysis and morphological parameters between the HIV-infected and the healthy volunteers.

## Introduction

Sub-Saharan Africa has the highest worldwide incidence of HIV and/or AIDS, with approximately 6.5 million South Africans infected; 69% of all adults and 90% of all children who are infected live in this region.<sup>1,2</sup>

Cardiovascular manifestations in HIV are very common<sup>3,4,5,6,7,8</sup> but often go undetected owing to symptoms being attributed to other causes such as pulmonary tuberculosis and neurological manifestations.

In the period prior to antiretroviral therapy (ART), the prognosis is poor once the cardiovascular system is affected, which is related in part to the late stage of the disease as well as the fact that certain cardiac complications are in themselves a prominent cause of death.<sup>9</sup>

In developed countries, coronary artery disease is the most common manifestation, mainly owing to accelerated atherosclerosis in patients on ART treatment.<sup>10</sup> Amongst HIV survivors in Botswana, there is a high prevalence of atherosclerotic cardiovascular disease (CVD) in younger patients, which conceivably can lead to an increase in mortality owing to premature CVD in these populations.<sup>11</sup>

In sub-Saharan Africa, however, pericardial tuberculosis and its sequelae, myocarditis and cardiomyopathy still comprise the predominant CVD presentations.<sup>12</sup>

CMR is a highly reliable modality used to assess myocardial morphology and function;<sup>13</sup> however, the majority of, if not all, CMR studies in HIV-infected patients have been performed on patients already receiving ART therapy.<sup>14,15,16</sup>

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Consequently, the objective of the present study was to assess the frequency and type of cardiovascular manifestations on CMR in patients with HIV infection who were not yet on treatment with ART, versus a control group who were HIV-uninfected and with no known overt CVD.

## Methods

### Study population

Suitable patients ( $N = 36$ ) were selected at the HIV and/or AIDS Clinic at the Steve Biko Academic Complex, Department of Health Sciences, University of Pretoria. The HIV-infected patients were at least 18 years old, class two and three according to the World Health Organization (WHO) criteria for HIV, and were not on ART. None of the HIV-infected patients had any symptoms that could have been attributed to HIV-related cardiac failure or cardiac involvement. The control group ( $N = 35$ ) included healthy volunteers from Steve Biko Hospital (health workers). The healthy volunteers were screened for HIV infection before they were enrolled in the study. The groups were matched for age, sex and ethnicity (Table 1).

The HIV-infected patients underwent a clinical examination at the clinic, and any clinical cardiac findings were documented.

A resting standard 12-lead ECG, echocardiography and chest radiograph were done. NT-proBNP levels (as a measure of atrial and ventricular distention), plasma HIV viraemia load (copies/ml) and mean CD4+ cell count (cells/ $\mu$ L) were obtained. Body surface area (BSA) was calculated for all patients. Glomerular filtration rate was determined according to the Cockcroft-Gault formula on all patients (including the healthy volunteers), prior to CMR, and those with impaired renal function (glomerular filtration rate  $<60$  mL/min) were withdrawn.

Other exclusion criteria for the HIV-infected patients included drug abusers, patients suffering from claustrophobia, patients with signs of active pulmonary tuberculosis on chest radiograph, and other identifiable causes of cardiac failure, e.g. valve lesions or congenital heart disease.

### Design and procedure

The study was a cross-sectional study.

CMR studies were performed using a 1.5-T whole-body clinical magnetic resonance 16-channel scanner (Achieva, Philips Medical Systems, Best, The Netherlands), using a cardiac five-element phased-array receiver coil (SENSE coil). Heart rate, blood pressure and oxygen saturation were monitored noninvasively during the examination. The two groups of patients underwent a CMR scan using the same parameters. Functional analysis was performed, and all the functional parameters including ejection fraction (EF), end-systolic and end diastolic volumes (ESV, EDV), stroke volume (SV) as well as left ventricular (LV) mass were obtained.

The CMR procedure included the following sequences:

### Scout images

Axial, coronal and sagittal scans (20 per plane) were done to localise and plan the rest of the study. Balanced turbo field echo sequences (BTfEs), of 10 mm slice thickness, were used for the scout images.

### Functional analysis sequences

Functional imaging of the left ventricle was performed in two long-axis (two- and four-chamber view) orientations and in a contiguous short-axis orientation to cover the left ventricle from the base to the apex (8 mm slices with a 2 mm inter-slice gap). The acquisition was performed in end-expiration hold.

### Analysis

Two experienced operators performed the visual image analysis. The readers were blinded to each other and the interpretation was performed on separate computers, utilising the same software (Circle Cardiovascular Imaging Inc.), but in different locations. If there was a discrepancy in the findings between the two interpreters, a third (blinded) opinion was sought and the majority opinion regarded as the final result.

The long-axis views were used to visualise and confirm possible areas of hypokinesia assessed via the short-axis views. The short-axis images were evaluated with computer-aided analysis packages for planimetry of endocardial and epicardial borders at end diastole and end systole (Figures 1 and 2). Papillary muscles were excluded in the LV mass analysis (selectable option).

TABLE 1: Clinical data.

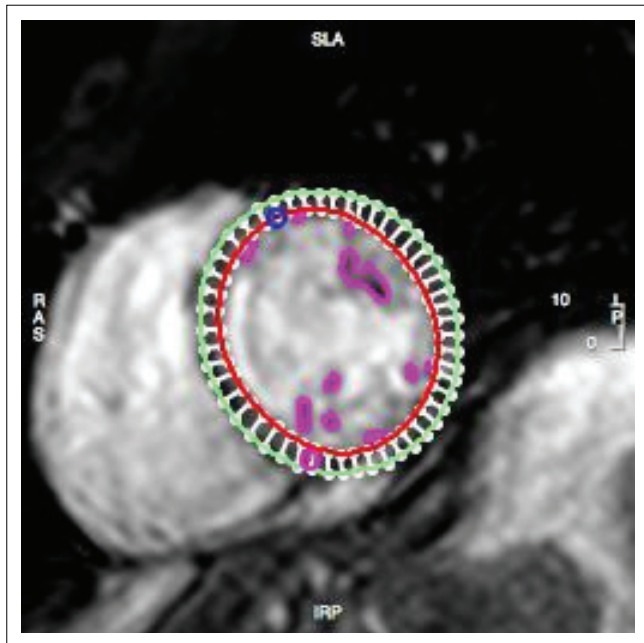
Variables	HIV-infected†			HIV-uninfected‡			p-value
	Mean $\pm$ SD	n	%	Mean $\pm$ SD	n	%	
Age (years)	36.0 $\pm$ 9.66	-	-	36.1 $\pm$ 10.75	-	-	0.990
Weight (kg)	67.7 $\pm$ 17.06	-	-	67.7 $\pm$ 16.51	-	-	0.998
BSA (m <sup>2</sup> )	1.74 $\pm$ 0.213	-	-	1.72 $\pm$ 0.220	-	-	0.786
Male	-	9	25	-	9	26	1.000
Female	-	27	75	-	26	74	1.000

BSA, body surface area.

†,  $n = 36$ ; ‡,  $n = 35$ .

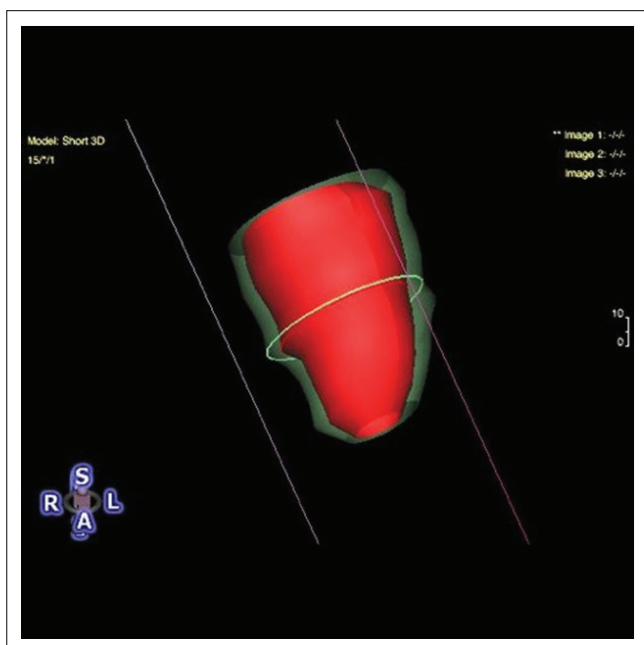
The presence of incidental pericardial effusions (>4 mm in diameter) or pericardial thickening (>1.7 mm in diameter) was documented if present on the four-chamber or short-axis cine sequences.

Computer-aided analysis included left ventricular ejection fraction (LVEF) as a percentage; left ventricular end-systolic volume (LVESV) in mL; left ventricular end diastolic volume (LVEDV) in mL; left ventricular stroke volume (LVSV) in mL; and LV mass in grams/m<sup>2</sup>.



Source: Scholtz and Partners Radiologists.

**FIGURE 1:** Short-axis views were utilised to perform the functional analysis with dedicated software.



Source: Scholtz and Partners Radiologists.

**FIGURE 2:** Three-dimensional image indicating the level of the short-axis image obtained.

## Ethical considerations

Approval was obtained from the Ethics Committee of the Faculty of Health Sciences, University of Pretoria.

All participants (HIV-infected and control) gave informed consent for participation in the study, which also included consent for intravenous gadolinium contrast injection. The consent form addressed and explained all the possible discomforts during the scan as well as the risks involved with gadolinium, including the rare possibility of nephrogenic systemic sclerosis. The patients and controls were also asked to complete a screening form to address and confirm the absence of any detrimental metal implants or devices.

Each patient was given a number; patient clinical information was not provided to the radiographers performing the scans. Medical personnel not involved in the study recruited the control patients, and the control patients were slotted in (on an *ad hoc* basis) in between other groups. The readers were blinded to the clinical data. The readers were not present during the scan. A radiologist not involved in the study administered the contrast.

## Results and statistical analysis

The major focus of the present study was the comparison of functional and structural abnormalities on CMR in untreated patients who were HIV-infected with HIV-uninfected patients. The clinical data are listed in Table 1 and the CMR functional analysis in Table 2.

### Statistical considerations

Mean values were compared by two-sided Student *t* tests, with *p* values as indicated. Normality of the underlying distributions could not be verified for all the variables. In all cases, the non-significance could be confirmed by the nonparametric Wilcoxon rank sum test. Percentages were compared by Fisher's exact test. *P* values were all non-significant. According to the statistical analysis tests, a sample size of at least 33 participants per group would have been adequate to detect a significant difference in functional analysis parameters between the groups.

### Clinical results

In respect of age, weight, BSA and gender ratio, no significant differences were found between the HIV-infected and HIV-

**TABLE 2:** Cardiovascular magnetic resonance functional analysis.

Variables	HIV-infected† (Mean ± SD)	HIV-uninfected‡ (Mean ± SD)	<i>p</i> -value
LVEF, %	59.3 ± 8.73	59.4 ± 7.84	0.951
LVESV, mL	42.8 ± 12.87	44.8 ± 11.74	0.492
LVEDV, mL	105.2 ± 24.73	110.3 ± 18.06	0.326
LVSV, mL	62.5 ± 18.25	65.6 ± 13.91	0.433
LVEDM, g	102.8 ± 25.39	94.3 ± 21.07	0.129
LVESM, g	107.8 ± 30.56	104.8 ± 20.65	0.631

LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end diastolic volume; LVSV, left ventricular stroke volume; LVEDM, left ventricular end diastolic mass; LVESM, left ventricular end-systolic mass.

†, *n* = 36; ‡, *n* = 35.

uninfected patients. The mean viraemia load of the HIV-infected patients was 137 465.42 copies/mL, and the mean CD4 count 276.94 cells/ $\mu$ L. The mean proBNP count of the HIV-infected patients was 32.41 pg/mL.

### Cardiovascular magnetic resonance results

Regarding all the variables, no significant differences were found in the CMR systolic functional analysis between the HIV-infected and HIV-uninfected patients.

The LV mass (LVEDM) was slightly higher in the HIV-infected group, but this was not statistically significant ( $p = 0.129$ ) (Table 2). Small pericardial effusions (5 mm – 7 mm in diameter) were present in 6 (16.6%) of the 36 HIV-infected patients. None of the patients had significant pericardial thickening.

### Discussion

Echocardiography is readily available and has been utilised in several studies to assess LV function in HIV-infected patients.<sup>17,18,19</sup> Functional abnormalities increase with the level of immunosuppression.<sup>12,20</sup> Both systolic and diastolic dysfunction have been reported at echocardiography in HIV-infected patients.<sup>18,21</sup> Most of the studies originate from developed countries and the majority of patients included were on ART. Systolic dysfunction is usually mild and occurs less frequently than diastolic dysfunction.<sup>18,20</sup>

A study from Nigeria performed on patients yet to receive treatment, also reported on impaired function, of which diastolic dysfunction was more prevalent.<sup>22</sup> Increase in myocardial mass on echocardiography occurs frequently.<sup>18,20,21</sup> The cause is speculative and probably multifactorial, and might represent inflammation.

Very few CMR studies have been performed on HIV-infected patients, and the study numbers are small. The first study by Holloway et al. included 90 patients on ART where the presence of mild systolic but marked diastolic dysfunction as seen on echocardiography in previous studies, was reported.<sup>14</sup> The subsequent study by Thiara et al. confirmed their findings.<sup>16</sup> Two recent studies reported higher native T1 values (969 v. 956 ms in controls) in HIV-infected patients (probably caused by inflammation), as well as the presence of oedema. This was probably responsible for the increase in myocardial mass seen on CMR.<sup>15,23</sup> All the studies included patients already on ART treatment, except for the study by Ntusi et al. which included a small subgroup of patients not yet on treatment.<sup>15</sup> There were no statistical differences in the findings between the patients on ART and the untreated group in the latter study.<sup>15</sup>

The study population in the present study included asymptomatic patients not yet on treatment and not yet severely immune compromised. The EF, EDV, ESV and SV with CMR analysis did not differ between the two groups. This point has not previously been assessed with CMR in a similar setting.

Myocardial mass was higher in the HIV-infected group, as seen with echocardiography,<sup>20</sup> although this was not statistically significant. Increased myocardial mass was also observed on CMR by Ntusi et al.,<sup>15</sup> where it was also associated with mild impairment of LV systolic function. The majority of the patients in their study were, however, already on ART.

Small asymptomatic pericardial effusions are a common occurrence in HIV-infected patients and have been documented in many previous echocardiography and CMR studies.

Cardiac function can be assessed with CMR, which is now regarded as the gold standard.<sup>13</sup> CMR is not yet readily available in sub-Saharan Africa. South Africa specifically has the largest antiretroviral programme in the world. Approximately the equivalent of \$US1 billion is spent by the South African government on the prevention and treatment of HIV infection. By making CMR readily available, especially in rural areas, the devastating impact of the disease on its young and active inhabitants will be highly beneficial.

### Limitation of the study

The study numbers are small and patients on ART were not included. Larger studies are needed and more patient groups should be studied, including patients on treatment, and patients with clinical cardiovascular manifestations. It is also necessary to compare patients at different stages in the natural history of the disease.

### Conclusion

No significant differences were found regarding the CMR systolic functional analysis between the HIV-infected and the healthy volunteers. The LVEDM was slightly higher in the HIV-infected group but this was not statistically significant. CMR is regarded as the gold standard for evaluating cardiac function. Up till now, echocardiography has been the main diagnostic tool used to evaluate cardiac function in sub-Saharan Africa. CMR can potentially play an important role in the future.

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#### Competing interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

#### Authors' contributions

L.S. was the project leader. L.S. and A.D.P. performed the functional analysis. L.S. and S.A. were responsible for experimental and project design. A.Sw. performed the scans. A.St., A.K. and A.M. sourced the patients. A.St. and S.A. made conceptual contributions.

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