Subclinical cardiovascular remodelling in HIV-infection: A multimodal case study of 2 serodiscordant, monozygotic twins

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ABSTRACT

Cardiovascular abnormalities are increasingly recognised among people newly diagnosed with HIV, but subclinical pathology may be challenging to diagnose. We present a case study of subtle cardiovascular changes in identical twins, one without HIV-infection and the other recently diagnosed with HIV (serodiscordant). We hypothesise that cardiovascular parameters would be similar between the twins, unless non-genetic (environmental) factors are at play. These differences likely represent occult pathology secondary to the effects of early HIV-infection.

A 25-year-old female incidentally diagnosed with HIV, and her HIV-uninfected identical twin, living with her since birth, underwent comprehensive cardiovascular assessments. The HIV-positive twin exhibited a globular left ventricle (LV), larger LV volumes, decreased LV strain, peak atrial longitudinal strain (PALS) and higher native T1 and T2 mapping values compared to her sister. Cardiac biomarkers high sensitivity cardiac troponin T and N-terminal proBNP, as well as the novel markers of fibrosis and remodelling, galectin-3 and soluble-ST2, were higher in the HIV-infected twin. Given the twins' shared environment and genetic makeup, these differences likely stem from HIV-infection.

Our study supports previous findings and suggests potential screening markers for HIV-associated cardiovascular disease, including PALS. Further research is warranted to explore PALS' utility in this context.

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INTRODUCTION

The link between human immunodeficiency virus (HIV) infection and cardiovascular dysfunction and mortality is well established.[1,2] With the advent of modern antiretroviral treatment (ART), the profile of cardiovascular disease has largely shifted to atherosclerotic cardiovascular disease in high income countries, but this has not been consistently demonstrated in low- and middle-income countries. In these regions, HIV-associated cardiomyopathy still contributes significantly to the burden of HIV-associated cardiovascular disease,[3-5] with HIV-infection seen to almost double the risk of heart failure.[6] HIV-associated cardiomyopathy remains a poorly understood entity due to numerous contributing factors.[5,7] Of these factors, data on the genetic susceptibility of HIV-associated cardiomyopathy in individuals is especially sparse.[8-10]

Cardiovascular research from both high- and low- to middle-income countries has demonstrated the presence of subclinical structural, functional, and biochemical abnormalities in newly diagnosed people living with HIV (PLWH), before the influence of ART.[11-16] However, some controversy remains regarding the finding of systolic dysfunction in asymptomatic PLWH, as this finding has not been consistently observed in contemporary studies.[17] ART may improve subclinical HIV-related alterations in cardiovascular structure and biochemical signals of cardiac disease[16,18] and cardiovascular magnetic resonance imaging (CMR) research has demonstrated improvements

in LV tissue characteristics after the initiation of ART.[19] There are limited prospective studies that track cardiovascular changes after the initiation of ART, and comparisons are usually made between mixed groups of treated and untreated individuals. This heterogeneity may explain the conflicting results, as subclinical abnormalities may be subtle, and observations between matched control groups may be masked by unknown genetic or environmental factors. Many knowledge gaps remain on early myocardial disease in asymptomatic PLWH, and further research is needed to adequately characterise these functional, structural and tissue characterisation abnormalities to better inform research in the ART-era and aid in establishing evidence-based screening and treatment strategies.

Multimodal cardiovascular assessment combines several modalities, employing each of their unique strengths in evaluating various aspects of the cardiovascular system. CMR is the non-invasive gold standard for volumetric examination of the heart and boasts excellent inter- and intra-observer variability.[20,21] Echocardiography with Doppler is a well-validated tool to interrogate diastolic function.[22] Speckle tracking echocardiography (STE) and CMR feature tracking are modalities that may be used to analyse myocardial deformation.[23] STE, however, has the distinct advantage of almost 2 decades of research and its clinical use is supported by treatment guidelines.[24] Peak atrial longitudinal strain (PALS) of the left atrium (LA) is increasingly used to assess atrial reservoir function and mirrors elevation in LA filling pressures,[25] serving as a sensitive tool to assess early cardiac dysfunction. Relatively few studies on this topic have been carried out, but there is emerging evidence to suggest its utility in the diagnosis of subclinical HIV-associated cardiovascular disease.[26,27] Biochemical cardiac markers are integral to the diagnosis and management of cardiovascular conditions. High sensitivity cardiac troponin T (hs-cTnT) and N-terminal proBNP (NT-proBNP) are well established markers that provide information on cardiac injury and myocardial stretch respectively. Various novel cardiac markers, including soluble ST-2 (sST-2) and galectin-3 are associated with specific pathophysiological processes per se, rather than the sequalae of disease. sST-2 is involved in cardiac remodelling, hypertrophy and fibrosis,[28] whereas galectin-3 may be directly involved in the process of ventricular remodelling through tissue repair and fibrosis.[29]

In this article we describe known and novel multimodal cardiovascular findings in the rare scenario of HIV-serodiscordance (1 twin with HIV and the other without) in identical female twins. As monozygotic twins have identical genetic makeup and cardiac heritability has been shown to be high,[30-33] the influence of environmental factors can be evaluated in the absence of genetic confounders. We hypothesised that a difference in cardiovascular parameters would not be demonstrable between the twins, unless non-genetic (environmental) factors were influencing the cardiovascular system. Secondly, we hypothesised that such a difference would represent occult pathology secondary to the direct or indirect effect of early HIV-infection, before the initiation of ART.

METHODS

Study design

This case study was nested within a larger prospective cohort study in the Western Cape, South Africa evaluating newly diagnosed PLWH without known cardiovascular disease.[13] The study was approved by the Stellenbosch Human Research Ethics Committee (Ref: S19/07/137) and all volunteers provided written informed consent for data collection and publication.

Clinical information

A 25-year-old, asymptomatic, African female (twin 1) incidentally tested positive for HIV at a local non-profit organisation's public service and was referred to her local clinic for ART. Her HIV-status was serologically confirmed prior to enrolment in the study, and her identical twin sister volunteered as a HIV-uninfected control (twin 2). Twin 1's last confirmed negative HIV test was 14 months prior. The clinical history and contact tracing estimate her time from HIV-seroconversion to enrolment as 7 months. The twins have shared a household in a low-income neighbourhood since their uncomplicated births. They have both excelled academically, participated in organised sport, and have shared similar lifestyles in terms of physical activity and diet. The twins give a history of equal levels of fitness over the years, frequently walking and exercising together. Both twins have attained a tertiary level qualification. They have never smoked or used illicit drugs and have negligible alcohol intake. There is no significant family history of cardiovascular disease, no comorbidities, no history of COVID-19, or any past illness requiring hospitalisation. The clinical examination was unremarkable, other than the finding of palpable, small axillary and cervical lymph nodes in twin 1. The twins share almost identical physical features. Twin 1 was not overtly wasted but could be described as leaner than her sister. Twin 2 was marginally taller than her sister, although this is not readily apparent without a side-by-side comparison.

Data collection

Detailed description of data collection and methodology has been published previously.[12,13,34] In short, a comprehensive cardiovascular evaluation including anthropometric, biochemical, immunological, virological, pulse wave velocity, and electrocardiogram (ECG) investigations were performed on both twins. Fasting blood for a full lipogram, blood glucose, creatinine, HIV-viral load, CD4 count, hs-cTnT and NT-proBNP was collected and analysed by the on-site National Health Laboratory Service (ISO 15189 accredited laboratory).[35] Additional laboratory work on novel cardiac biomarkers, soluble ST-2 and galectin-3, was performed by the Stellenbosch University Immunology Research Group (ISO 15189 accredited laboratory). Serum concentrations of soluble ST-2 and galectin-3 were determined using multiplexed immunometric assays (Human magnetic Luminex screening assay, R&D Systems, Minneapolis, United States of America). Glomerular filtration rate was estimated using the CKD-EPI equation.[36]

Cardiovascular magnetic resonance

Both CMR studies were performed on a 1.5T magnetic resonance scanning system (Magnetom Avanto, Siemens Healthcare, Germany) with commercially available cardiac sequences as described previously.[12,13] Images included cine imaging for LV function and morphology, as well as native T1, T2, extracellular volume (ECV) mapping and late gadolinium enhancement imaging for myocardial tissue characterisation. The studies were post-processed and analysed by 2 independent observers blinded to the clinical information, using CVI[42] (version 5.11.2, Circle Cardiovascular Imaging, Calgary, Alberta, Canada).[12,13] Quantitative mapping values are reported as the mean basal values.

Echocardiography

Structural and functional 2D echocardiographic studies were acquired using a 2.5 mHz 4Cv probe on a Vivid E95 unit (GE Medical Systems, Norway. Software: EchoPAC PC, version 204, GE Healthcare, United Kingdom). Images were acquired in the left lateral decubitus position by a cardiac physiologist who was blinded to the clinical information. Echocardiographic parameters were acquired using standardised methodology.[37-40] The frame rate and image gain were continuously adjusted to optimise image quality and the cardiac cycle with the best image quality, and free from artefact, was selected for analysis.

Speckle tracking echocardiography derived ventricular strain

Endocardial contours were manually traced at end systole and a concentric region of interest, including the LV myocardial wall, was automatically traced by the EchoPAC software. The myocardial tracking was manually verified and where necessary the region of interest width was adjusted to optimise tracking. Peak systolic longitudinal strain was calculated by averaging the peak systolic values of the 16 LV segments,[41] derived from the apical 2-, 4-, and 3-chamber views.

Speckle tracking echocardiography derived atrial strain

To assess the atrial reservoir function, PALS was obtained using dedicated apical 2- and 4-chamber views to ensure visualisation of the LA throughout the cardiac cycle.[42] The LA endocardial border was contoured in both views, starting at the annulus and tracing along the atrial wall, crossing the pulmonary vein orifices and the LA appendage, stopping at the opposite mitral annulus. Accurate bi-plane tracking of the atrial endocardial border during the cardiac cycle was manually verified and adjusted on the EchoPAC software when necessary.

RESULTS

Clinical data

The twins were well matched in terms of anthropometry, blood pressure, and biochemistry (see Table I). Although twin

TABLE I: Clinical data.

Parameter	Twin 1 HIV-infected	Twin 2 HIV-uninfected
Weight (kg)	64	70
Height (cm)	167	169
Body mass index (kg/m^2)	23	25
Waist circumference (cm)	77	80
Systolic blood pressure (mmHg)	96	98
Diastolic blood pressure (mmHg)	78	68
6-minute walk test distance (m)	623	746
Biochemistry		
Creatinine (µmol/l)	66	65
eGFR (ml/min/1.73m^2)	111	114
Fasting glucose (mmol/l)	4.8	4.9
Fasting blood lipids		
Total cholesterol (mmol/l)	5.12	4.43
HDL cholesterol (mmol/l)	1.62	1.5
LDL cholesterol (mmol/l)	3.35	2.79
Triglycerides (mmol/l)	0.32	0.3
Virological and immunological markers		
WHO clinical stage	1	-
HIV viral load (copies/ml)	4096	-
HIV viral load (log copies/ml)	3.61	-
CD4 count (cells/µl)	513	673
CD8 count (cells/µl)	941	770

eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, LDL: low-density lipoprotein, WHO: World Health Organisation.

I had no cardiac symptoms, her sister outperformed her in the 6-minute walk test and walked almost 20% further during the assessment.

Electrocardiogram and heart rate

Both twins were in sinus rhythm, with normal heart rates of 60 and 66 beats per minute, respectively. Both sisters had non-specific T-wave inversion of standard lead III, with otherwise normal ECGs.

Cardiac morphology

For both cases, the cardiac morphology measured within normal CMR reference ranges,[43] but differed when compared to one another (see Table II). The most prominent difference between the twins' cardiac morphology was the globular geometry of twin 1's LV. This globular LV geometry was most appreciable in the three-chamber view and verified by the quantitative CMR measurements (Figure 1, Table II). Both the sphericity index and the midventricular LV end-diastolic dimension of twin 1 was higher than twin 2, confirming the observation of a more globular LV in twin 1. Furthermore, the LV end-diastolic volume was higher in twin 1 compared with twin 2. The other cardiac chambers of twin 1 demonstrated a similar trend of being larger than her (slightly taller) twin sister. The LA, right atrium and right ventricle were all larger in twin 1. A sliver of pericardial fluid was present in both twins, respectively measuring 4mm and 2mm at the base of the heart.

Systolic function

Visually, the systolic function of the ventricles in both twins were within normal range, although side-by-side CMR evaluation placed the LV ejection fraction (EF) of twin 1 about 5% lower than twin 2. This finding was confirmed with a blinded, quantitative CMR analysis that showed a 2% difference between twin 1 and twin 2. A notable difference was also present in the GLS of twin 1, which measured 3% lower than her sister.

Diastolic function

The diastolic function of both the twins was normal with the E:E' measuring <8 respectively (see Table II). Twin 1's transmitral inflow velocity and the E:E' were noted to be marginally higher than her sister.

Atrial reservoir function

Atrial strain curves are shown in Figure 2. The PALS of the LA was 56% lower in twin 1 compared with her sister and her atrial reservoir function is decreased for a female of her age (2.5th percentile is 29%).[44]

TABLE II: Cardiac parameters.

Parameter	Twin 1 HIV-infected	Twin 2 HIV-uninfected
Diastology of the LV		
E (cm/s)	114	50
E' septal (cm/s)	16	22
E' lateral (cm/s)	18	14
Averaged E' (cm/s)	17	18
E: E'	6.7	2.8
Speckle tracking echocardiography		
GLS (%)	-18	-21
PALS of the LA (%)	24	55
Cardiovascular magnetic resonance		
LA area (cm^2)	22	20
LA volume (ml)	68	58
RA area (cm^2)	20	20
RA volume (ml)	74	68
Basal LVEDD (mm)	50	47
LVEDD at midventricle (mm)	55	43
Sphericity index	0.56	0.48
LV EDV (ml)	146	138
LV mass (g/m^2)	57	55
LVEF (%)	68	70
RV EDV (ml)	153	140
RVEF (%)	62	62
Septal native T1 (ms) Mean basal native T1 (ms)	1 020 1 002	995 992
Mean basal T2 (ms)	48	47
Basal T2 myocardial: skeletal muscle ratio	1.4	1.4
Mean basal ECV (%)	23	23
LGE of myocardium or atria	Absent	Absent
Cardiac biomarkers		
hs-cTnT (ng/l)	5	<3
NT-proBNP (ng/l)	84	60
Galectin-3 (ng/ml)	8.6	5.5
sST-2 (ng/ml)	23.8	9.3
Aortic stiffness		
Carotid-femoral pulse wave velocity (m/s)	4.6	4.4

MV: mitral valve, GLS: global longitudinal strain, BLS: basal longitudinal strain, PALS: peak atrial longitudinal strain, LA: left atrium, RA: right atrium, LV: left ventricular, EDD: end-diastolic dimension, EDV: end-diastolic volume, EF: ejection fraction, RV: right ventricle, ECV: extracellular volume, LGE: late gadolinium enhancement, hs-cTnT: high sensitivity cardiac troponin T, NT-proBNP: N-terminal pro B-type natriuretic peptide, sST-2: soluble ST2. Normal local reference ranges for myocardial mapping: Native T1: 950-1040 ms, T2: 44-52 ms

Multiparametric mapping and late gadolinium enhancement

The native T1 and T2 mapping, ECV and the T2 myocardial to skeletal muscle ratio were comparable between the sisters and were within the normal reference ranges (see Table II). How-

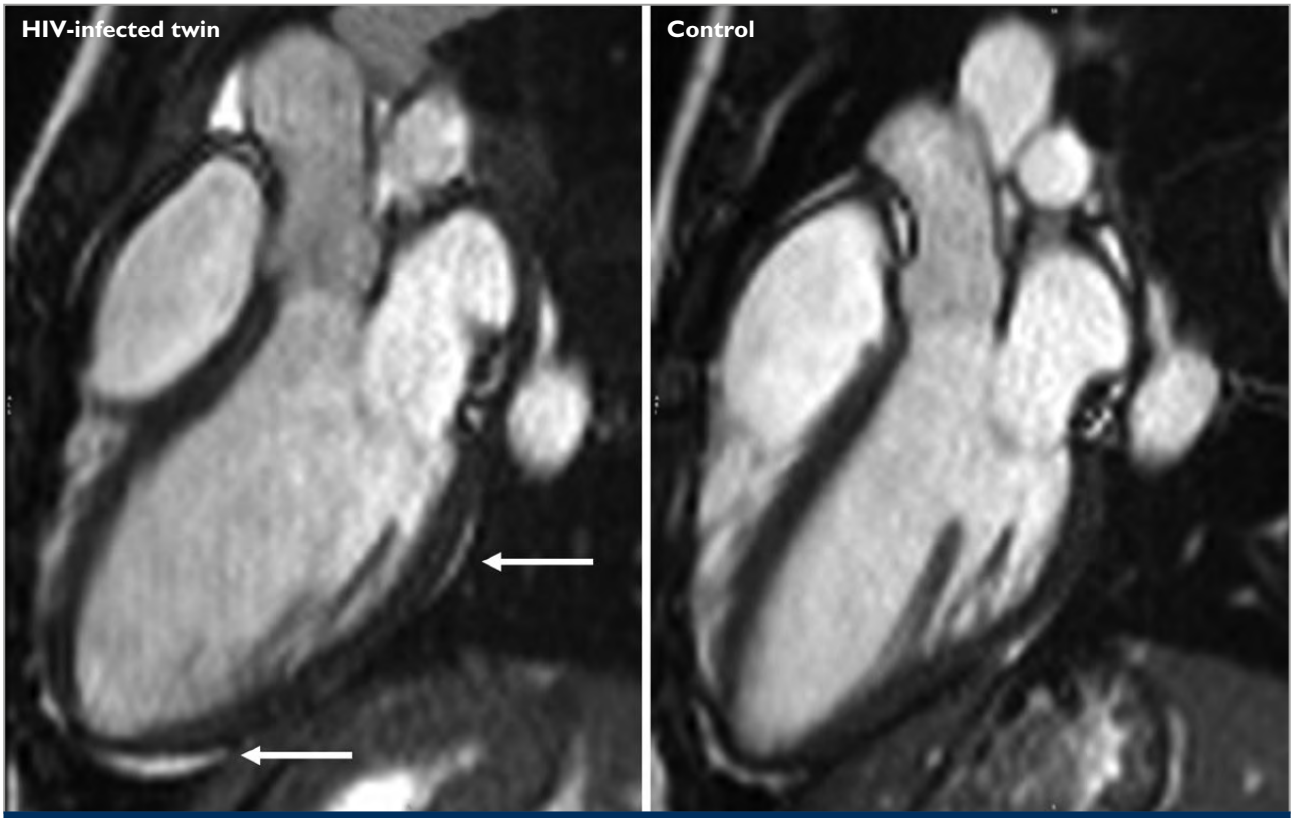

FIGURE 1: Cardiovascular magnetic resonance imaging (balanced steady state free precession image), end-diastole freeze frame of an HIV-infected female (left) and her HIV-uninfected, identical twin sister (right). The left ventricle of the HIV-infected twin appears globular and remodelled compared with her sister, with midventricular end-diastolic diameters of 50 and 47mm respectively. Note the small pericardial effusion in the HIV-infected twin (white arrows).

ever, both the native T1 and T2 were higher in twin 1. No late gadolinium enhancement of the myocardium or atrial walls were present in either twin.

Biomarkers

All measured cardiac biomarkers were higher in twin 1 than in twin 2 (see Table II). hs-cTnT was undetectable in twin 2, whereas it was detectable at normal levels in twin 1. Notably, s-ST2 was 2.6 times higher in twin 1 compared with her sister. The high sensitivity C-reactive protein in twin 1 and twin 2 measured 1.6mg/l and 9.7mg/l respectively.

DISCUSSION

The multimodal cardiovascular data from this set of identical twins supports the hypothesis that the hearts of the serodiscordant twins are different. Given that the twins have an identical genome and live in the same environment, this also supports the hypothesis that these differences suggest subclinical pathology and likely represent manifestations of HIV-infection or its secondary effects. Furthermore, we describe the novel finding of unexplained, early atrial dysfunction in an otherwise healthy, HIV-infected patient before the initiation of ART: A finding that should be explored further in larger cohorts as a potentially sensitive marker of early cardiovascular alteration.

In prior work from our research group, we demonstrated that at population level, there are subtle morphological, functional, and tissue characterisation abnormalities present at the time of HIV diagnosis, before the initiation of ART.[12,13] CMR and biochemical studies emanating from both high and low- to middle-income countries have made similar observations.[11,14,15] In our twin case study, we observed cardiovascular differences that bear a striking resemblance to what was observed in our larger research cohort.[12,13] Notably, the subtle difference in LVEF of 2% in the twins mirrors a difference of 3% in our larger cohort. These findings are comparable to research from other groups. Menacho, et. al and Ntusi, et al. demonstrated a 3% and 4% difference respectively, in the LVEF of PLWH compared to controls.[14,15] This further increases the likelihood that the observed differences in the twins are primarily due to HIV rather than a chance occurrence or measurement error. Although most parameters fall within normal reference ranges and the

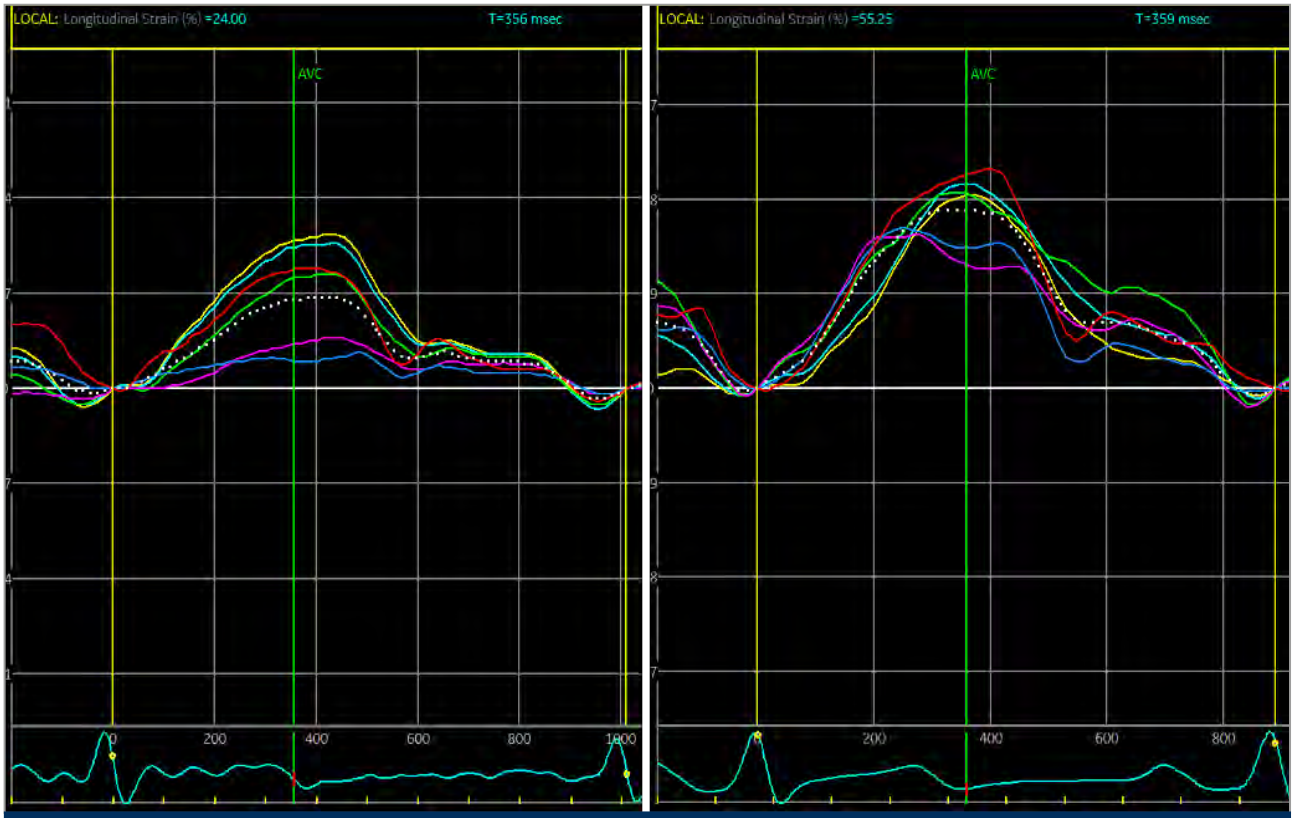

FIGURE 2: Bi-plane peak atrial longitudinal strain (PALS) of the left atrium (LA) demonstrating decreased atrial reservoir function in a 25-year-old HIV-infected female (left). Her HIV-uninfected, identical twin sister's normal PALS of the LA is shown for comparison (right). These findings suggest HIV-related atrial abnormalities and may form part of an HIV-related atriopathy.
AVC: aortic valve closure.

differences are small, it should be noted that these blinded measurements all tended toward abnormality in the HIV-infected twin. The exception was the abnormal PALS measurement that will be discussed later. By using an HIV-uninfected, genetically identical control, we were able to demonstrate subtle cardiovascular pathology in an HIV-infected individual. Demonstrating this would otherwise be extremely challenging, if not impossible, when pathology is only starting to manifest. This descriptive work contributes to our understanding of HIV's early effect on the cardiovascular system, as occult pathology may later manifest as symptomatic heart disease if these underlying pathophysiological mechanisms are not adequately addressed.

Our study's observations are consistent with the view that multiple pathophysiological processes work in synergy to initiate and maintain a chronic state of myocardial inflammation[7] that may be improved, but not completely halted, by ART.[13] These chronic pathological processes likely lead to the cardiac remodelling, fibrosis and disproportionate risk of cardiovascular disease seen in PLWH.[45] The level of systemic inflammation as measured by the high sensitivity C-reactive protein in twin 1 was not elevated in this case study and suggests that systemic inflammation and inflammation at the tissue level may be discrepant.

Strategies to prevent these complications in the ART era are largely understudied. The use of statin therapy has shown promise in preventing HIV-related myocardial infarctions, stroke and peripheral artery disease.[46] A limitation of this trial is that myocardial disease and heart failure were not specifically studied as outcomes and, when evaluating the individual components of major adverse cardiovascular events in this landmark study, no benefit was evident for death from any cardiovascular cause. This highlights the need for additional preventative research in this understudied group of patients.

Nature vs. Nurture: Determinants of cardiac morphology and function

Our participants' hearts demonstrated clear morphological differences. Whether these differences are due to genetic influences on cardiac morphology or due to the HIV-infection and /

or its secondary effects, must be determined. Since our participants are identical twins, we argue that their cardiac morphology should not differ considerably due to genetic influences, and we discuss key findings in the literature to support this. Heritability is the degree (usually reported as a percentage) to which a specific personal trait may be explained by an individual's genetics. Echocardiographic research suggests that the heritability of cardiac morphology is high.[31] Adams, et al. showed high cardiac similarity (predominantly chamber dimensions) between twins (monozygotic and dizygotic), as well as siblings when compared to random subjects. Furthermore, their data show that familial influences, which include common environmental and genetic factors, are important determinants of cardiac size. A cardiovascular study on a large twin cohort observed that LV mass has a significant genetic basis.[47] Contemporary research utilising CMR substantially exceeds the heritability estimates of cardiac structures in monozygotic twins compared to echocardiography, and provides additional evidence of a strong genetic basis for cardiac morphology.[30] High heritability of structural and functional cardiovascular parameters has been demonstrated across 3 South African generations.[33] This provides good evidence that genetics have a significant influence on cardiovascular structure and function in the African context too. Lastly, it has been shown that longitudinal strain has increased heritability in persons with African ancestry, compared to Caucasians.[32] Available data on twins and siblings support the notion that the structure and function of our study's twins should be almost identical, especially considering that they have shared the same environment since birth. However, this was not what was observed in our study. Given that, without exception, our quantitative values consistently trend toward abnormality, the likelihood that these differences are due to measurement error or chance is low. Notably our study employed different modalities and diagnostic techniques that demonstrated the same tendency of subtle abnormality in the HIV-infected twin. This supports the contention that the differences identified are not due to chance or measurement error and are rather, related to the only apparent difference between our twins: their discordant HIV status.

Ventricular dysfunction and remodelling in early HIV-infection

Our dataset suggests that the difference in the twin's LV size and geometry may be due to subclinical cardiac remodelling from HIV-infection or its secondary effects. Using CMR, we demonstrated larger LV dimensions and volumes in twin 1, findings that are corroborated by our biochemical observation of increased NT-proBNP, indicative of myocardial stretch.[29] Although the novel biomarkers sST-2 and galectin-3 are less studied compared to NT-proBNP, increases in these markers are associated with the processes of LV hypertrophy, fibrosis, and remodelling.[28,29] sST-2 has been shown to be useful in predicting cardiac dysfunction, even in otherwise healthy persons,[48] and its use to predict future heart failure in the HIV milieu warrants further study. Importantly, the sST-2 measurement of twin 1 was more than double that of twin 2. This biochemical evidence is in keeping with the imaging findings of an underlying process of remodelling and fibrosis, as sST-2 is believed to reflect cardiovascular stress and fibrosis with the ability to predict cardiovascular outcomes in heart failure.[28]

Employing aortic stiffness as a surrogate marker for risk, it has been shown that cardiovascular risk is higher in asymptomatic, HIV-infected persons compared to age- and sex-matched controls.[34] This difference was observed between twin 1 and twin 2 as well, although the difference was subtle at 0.2m/s.

The underlying cause of the cardiac remodelling in twin 1 is thought to be due to the direct or indirect cause of HIV-infection. Unfortunately, the pathophysiology of HIV-associated cardiovascular disease remains incompletely understood with numerous possible aetiologies.[7] As twin 1 was yet to be placed on ART at the time of study, these findings provide evidence of early cardiac remodelling in the absence of ART; an aetiological consideration frequently explored in contemporary literature. Chronic cardiovascular inflammation (before and despite ART) is thought to play an integral role in the development of a variety of HIV-associated cardiovascular diseases.[6,7,14,49,50] Mirroring the observations from our greater cohort, we measured a higher LV mass, native T1 and T2 in twin 1 compared to twin 2,[13] as well as higher levels of hs-cTnT in twin 1. These findings are in keeping with underlying myocardial oedema with / without concurrent myocardial fibrosis. One should be careful not to overcall pathology based on these subtle findings in the twins, but the clustering of our observations across different modalities is in keeping with the current inflammatory hypothesis of HIV, and in this case, likely represents myocardial inflammation in the HIV-infected twin. We hypothesise that HIV-related inflammation leads to low-grade myocardial injury and oedema, and manifests as structural and functional myocardial changes over time that are detectable with imaging and cardiac biomarkers. The long-term implication of these morphological and functional changes at the time of HIV diagnosis is not known. If underlying inflammation is closely associated with myocardial injury and remodelling, the persistence of inflammation, despite ART,[13,14] could lead to cumulative myocardial dysfunction and ultimately, symptomatic cardiac disease. This plausibly explains the excess cardiovascular

risk that is seen in PLWH, despite modern ART. Prospective research evaluating the cardiac outcomes of HIV-infected patients with subclinical cardiac remodelling is required to better understand the true clinical implication of these findings. This may ultimately lead to improvements in our ability to detect early manifestations of cardiac disease in PLWH using a combination of imaging and / or biochemical modalities.

HIV-associated atriopathy

We demonstrated that twin 1's LA was larger compared to her sister, although still within the normal range. However, we found distinct differences in twin 1's PALS of the LA, falling outside accepted reference ranges. The role of the LA in the modulation of ventricular filling and cardiac output is frequently overlooked. Pathology of the LA in HIV-infection has not been well researched, but there is evidence to suggest that the LA is not excluded from the detrimental effects of HIV, as seen with almost all other components of the cardiovascular system.[51] LA reservoir function is determined by the inherent stiffness of the atrium and the descent of the cardiac base.[52] Given the presence of ventricular function well within the normal range and normal diastolic function, we considered raised atrial stiffness in twin 1 as an explanation for our observations. The decrease in LA reservoir function in twin 1 may represent an early HIV-associated atriopathy. There are alternative explanations for this dysfunction, but given the presence of subclinical fibrosis in the ventricles of PLWH,[13,14] it is reasonable to speculate that the abnormal reservoir function is due to stiffening of the atrium from fibrosis. Although the native T1 of twin 1 was marginally higher than her sister, we do not have compelling evidence of myocardial fibrosis in the twins. Without comparing the PALS to her HIV-uninfected sister, the PALS measurement in twin 1 was already in the abnormal range. Since LA function is frequently employed by clinicians as a sensitive marker for early cardiac disease, the use of atrial strain may prove useful to screen for early HIV-associated cardiovascular dysfunction and merits dedicated future research.

LIMITATIONS

Despite the rare opportunity to compare a set of serodiscordant, monozygotic twins that are well matched and otherwise healthy, it remains possible that unknown environmental factors may have confounded our observations. Although twin 1 was an above average historian, the calculated 7-month duration of HIV-infection is not known with absolute certainty. The possibility remains that the duration may be as long as 14 months. However, examination, clinical staging, and immunological findings correlate with the clinical history and are in keeping with early HIV-infection. Our findings are thought-provoking and support the current thinking of HIV-associated cardiovascular disease. However, our study remains a descriptive case study of subtle findings in 2 (albeit well matched) subjects and should not be interpreted as conclusive, but rather as hypothesis generating to guide future research avenues.

CONCLUSIONS

The morphological, functional, and biochemical cardiovascular differences in our set of identical twins fall outside anticipated genetic variation and likely represent subclinical cardiovascular dysfunction and remodelling secondary to HIV-infection. These observations, in a genetically matched pair, mirror observations from matched, population-based studies and supports the thinking that the cardiovascular system is affected early during HIV-infection, and is most likely secondary to cardiovascular inflammation. Furthermore, atrial strain may be a useful parameter to detect early cardiac dysfunction in this setting and warrants further investigation. More research is required to evaluate the mid- to long-term significance of subclinical cardiac remodelling and dysfunction in PLWH.

Conflict of interest: none declared.

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