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Abnormal myocardial function is related to myocardial steatosis and diffuse myocardial fibrosis in HIV

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Abstract

Background: Impaired cardiac function persists in the era of effective HIV therapy, though the etiology is unclear. We used magnetic resonance imaging (MRI) to measure intramyocardial lipid and fibrosis as possible contributors to HIV-associated myocardial dysfunction.

Methods: Cross-sectional study of 95 HIV-infected and 30 matched-healthy adults, without known cardiovascular disease (CVD) was completed. Intramyocardial lipid, myocardial fibrosis, and cardiac function measured by strain were quantified by MRI.

Results: Systolic function was significantly decreased in HIV-infected subjects compared to controls (radial strain 21.7±8.6% vs 30.5±14.2%, p=0.004). Intramyocardial lipid and fibrosis were both increased in HIV compared to controls ($p \leq 0.04$ for both) and correlated with degree of myocardial dysfunction measured by strain parameters. Intramyocardial lipid correlated positively with antiretroviral therapy duration and visceral adiposity. Further, impaired myocardial function was strongly correlated with increased monocyte chemoattractant protein-1 levels (r=0.396, p=0.0002) and lipopolysaccharide binding protein (r=0.25, p=0.02).

Conclusions: HIV-infected adults have reduced myocardial function compared to controls in the absence of known CVD. Decreased cardiac function was associated with abnormal myocardial tissue composition characterized by increased lipid and diffuse myocardial fibrosis. Metabolic alterations related to antiretroviral therapy and chronic inflammation may be important targets for optimizing long-term cardiovascular health in HIV.

In the era of widespread use of antiretroviral therapy for HIV infection, reports of higher than expected rates of systolic and diastolic dysfunction persist [1-5]. A recent meta-analysis of studies evaluating cardiac dysfunction in HIV in the context of antiretroviral therapy identified left ventricular (LV) systolic dysfunction in 8% and diastolic dysfunction in as many as 43% of HIV-infected adults [1]. While the long-term clinical implications of subclinical cardiac abnormalities is not clear, Moyers and colleagues [6] showed that significantly diminished LV function (e.g. ejection fraction < 40%) was a strong predictor of sudden cardiac death in a large cohort of HIV-infected patients. The etiology of impaired myocardial function in HIV is not yet fully understood, but studies have implicated traditional risk factors such as age, hypertension and smoking [1, 4] as well as antiretroviral therapy [7] and direct effects of HIV [5, 8].

Prior investigation has demonstrated significant abnormalities of lipid deposition in various tissue compartments in HIV [9-14], and myocardial lipid deposition may also be increased. Advances in magnetic resonance spectroscopy (MRS) now permit reliable non-invasive quantification of intramyocardial fat content [15]. Myocardial steatosis is abnormal and likely represents subclinical myocardial injury that may ultimately lead to myocardial dysfunction [16-20]. Magnetic resonance tagging techniques also represent a valid and sensitive method to assess myocardial contraction through myocardial strain measurements [21]. For example, tagged MRI measurements can identify subclinical regional LV dysfunction (impaired strain) that corresponds to coronary atherosclerosis in adults without known cardiovascular disease [22].

We hypothesized that abnormal myocardial lipid accumulation and myocardial fibrosis in HIV may be related to impairment in cardiac function. Therefore, we examined intramyocardial lipid content using MRS in a cohort of HIV-infected adults compared to healthy controls and we evaluated the relationships between measures of myocardial steatosis, fibrosis, and myocardial strain, as well as biomarkers of immune activation.

Methods

Subjects

We prospectively evaluated 95 HIV-infected adults and 30 age-, sex-, and race-matched controls from 4/2010 to 5/2013 at the National Institutes of Health (NIH) Clinical Research Center in Bethesda, MD. Subjects were recruited through self-referral and in response to local advertisements. Participants were excluded if they had a known history of cardiovascular disease, a contraindication to MRI, or estimated glomerular filtration rate (eGFR) <60 cc/min/1.73m^2. There were no restrictions regarding antiretroviral (ARV) medication use or CD4 count. Controls were documented HIV-negative and were required to be healthy with no known significant medical conditions including cardiovascular disease. Targeted recruitment of control subjects was performed to match the relative age (+/- 5 years), sex and racial distribution HIV-infected group in approximately a three to one ratio. Written informed consent was obtained from each participant, and the protocol was approved by the institutional review board of the National Institute of the Allergy and Infectious Diseases of the NIH.

A medical history, physical exam, and laboratory tests were obtained from each participant, including detailed review of ARV exposures and cardiovascular disease risk factors. Diagnosis of chronic HCV infection and diabetes were based on patient report and verified by medical records when available. Fasting lipid panel, glucose, insulin, homeostatic model of insulin resistance (HOMA-IR), CD4 T-cell count, HIV viral load, as well as serologic biomarkers of inflammation, coagulation, immune activation (e.g. C-reactive protein [CRP], D-dimer, and pro-brain natriuretic peptide [pro-BNP], monocyte chemoattractant protein-1 [MCP-1], lipopolysaccharide binding protein [LBP]) were determined. Subjects also completed standard echocardiography.

Cardiac MRI/MRS

All studies were performed on a 3.0-T MR scanner (Verio; Siemens, Erlangen, Germany) with a 32-channel phased-array torso coil (In Vivo, Orlando, FL) and combined with posterior coil elements. In order to quantify intramyocardial triglyceride content, each participant had a myocardial ^{1}H-MR spectroscopy (MRS) (Figure 1). A 6-8 ml voxel was positioned in the interventricular septum. MRS was performed with ECG gated PRESS, TR/TE=1R-R/30 ms with the navigator across the liver lung interface to

reduce the effect of breathing. One spectrum was recorded with water suppression (32 averages), and another spectrum (eight averages) was recorded without water suppression. The same sequence was used for liver fat measurement with the MRS voxel placed in the right hepatic lobe. Eight averages of water suppressed and eight averages of no water-suppressed spectrum were acquired with breath holding. Fat content was quantified with Amares/MRUI and related to water in unsuppressed spectrum and expressed as percentage fat relative to water signal.

Myocardial strain was derived from grid tagged cine MR images in the axial plane with temporal resolution of 35 msec. Strain images were analyzed using HARP (Diagnosoft, v.4.3.1, Morrisville, NC)[23]. By convention, greater circumferential strain is more negative (greater shortening with contraction), while greater radial strain is more positive (more thickening with contraction). Therefore impairment in circumferential strain is less negative (less shortening) and impairment in radial strain is less positive. The distribution of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were quantified by a single-shot fast spin echo sequence (slice thickness=10mm). Three transverse images were acquired at the level of the fifth lumbar vertebrae during one breath hold. VAT and SAT were identified by selecting the region of interest and thresholding the pixel signal intensity using QMASS (QMass 7.2, Medis, The Netherlands).

Gadopentetate dimeglumine (0·15 mmol/kg, Berlex, Bayer Healthcare, NJ) was administered to assess myocardial scar at 15 minutes after contrast administration using the late gadolinium enhancement method [24]. Myocardial T1 mapping were obtained by modified Look-Locker inversion recovery (MOLLI) sequence [25]. Single-slice T1 mapping was performed before and at two time points between 10 and 25 minutes after contrast injection. The MOLLI sequence acquired a set of 8 source images in the mid-ventricle with one breath-hold (11 heartbeats), allowing the reconstruction of one parametric T1 map[26]. A region of interest was manually drawn on the core of myocardium. Fibrosis index scores were evaluated by the extracellular volume fraction, ECV=partition coefficient×(1-hematocrit), where partition coefficient was determined by the slope of the linear relationship of ($1/T_{1myo}$ vs. $1/T_{1blood}$) at pre and post-contrast time points.

Statistical Analysis

Group comparisons were performed using Student's t-tests or chi-square statistics as appropriate. Non-normally distributed variables (CRP, D-dimer, intramyocardial lipid content, pro-BNP, LBP, MCP-1, TIMP-1 and triglyceride level) were log transformed to approximate a normal distribution, are presented as median and interquartile range (IQR), and group differences tested using a Wilcoxon test. Two-sided p-values of $p<0.05$ were used to determine statistical significance. Univariate linear regression analyses were calculated to identify variables associated with intramyocardial lipid content both in the entire study population and within HIV-infected subjects only. We evaluated the relationship between years of ARV exposure and years of subclasses of ARVs (NNRTI and PI). The study was not sufficiently large to evaluate individual ARV agents. Multivariate regressions models were constructed to include all variables identified as significant in univariate regression, as well as important potential confounders (e.g. smoking pack-years, age, use of lipid lowering therapy). Similar analyses were performed for myocardial fibrosis and cardiac strain parameters. Major findings were retested in separate sub-analyses that excluded subjects with HCV, diabetes, and those not on ARV therapy. Statistical analyses were completed using SAS JMP® version 11.0.

Results

The study groups were similar with respect to age, sex, and race (Table 1). The majority of HIV-infected subjects were receiving ARV therapy, and 84.2% had HIV viral loads below the limit of detection (<50 copies/ml). One subject not an ARV therapy was a known elite controller, all others not on ARV therapy (n=6) had detectable HIV virus. HIV-infected subjects were more likely to have ever smoked and had greater mean smoking pack-years. More HIV-infected subjects were receiving lipid lowering therapy than controls (p=0.06) and of the subjects receiving lipid lowering therapy, 84% were receiving a statin. Metabolic parameters and biomarkers of inflammation and immune activation are presented in Table 2. The HIV-infected group had an increased fasting glucose compared to controls, but the groups were similar with respect to insulin, HOMA-IR, and free fatty acids. LDL cholesterol was lower in the HIV-infected subjects, but there were no statistical differences in total or HDL cholesterol or triglyceride levels between the groups. Median D-dimer values were higher in the control group, but in both

groups the upper quartile was within the normal range for the assay (< 0.50 ug/mL FEU). MCP-1 and TIMP-1 were higher in the HIV group, but there was no difference in LBP between the groups.

HIV-infected individuals had normal ejection fraction. However, there was evidence of subclinical systolic dysfunction compared to control subjects. Systolic radial strain and strain rate, as well as epicardial-endocardial circumferential strain were impaired compared to controls (Table 3). In a multivariate regression including age, sex, body mass index (BMI), lipid lower therapy use,and smoking pack-years, HIV status (p=0.004) was the only variable independently associated with decreased radial strain. In sensitivity analyses excluding HCV-infected subjects, those with diabetes or those not on ARV therapy, HIV status remained independently associated with impaired radial strain. Impaired radial strain rate and epicardial-endocardial circumferential strain were associated with greater intramyocardial lipid (r=0.19, p=0.04; r=0.20, p=0.03) and fibrosis index (r=0.26, p=0.007; r=0.22, p=0.03), respectively. Duration of ARV exposure did not correlate with measures of cardiac strain.

Intramyocardial lipid content was significantly higher in HIV-infected subjects compared to controls (Table 3). Intramyocardial lipid was positively associated with age (r=0.22, p=0.01), fasting glucose level (r=0.21, p=0.02), triglyceride levels (r=0.19, p=0.04), and VAT volume (r=0.37, p<0.001). Intramyocardial lipid did not correlate with CD4 count, nadir CD4, HIV viral burden, CRP, D-dimer, or pro-BNP, MCP-1, or LBP levels. In a multivariate analysis, including age, sex, smoking pack-years, diabetes, glucose, triglycerides, lipid lowering therapy use, and VAT volume, HIV status remained an independent predictor of intramyocardial lipid (p=0.03) as did VAT volume (p=0.0006) and female sex (p=0.02). These observations did not change in sub-analyses that excluded subjects with HCV infection or those not on ARV therapy.

Duration of ARV exposure was positively correlated with intramyocardial lipid (r=0.27, p=0.007). No association between exposure to specific subclasses of ARVs (i.e. NNRTI or PI) and intramyocardial lipid was found. VAT volume was also correlated with years of ARVs (r=0.31, p=0.004). In a multivariate regression, VAT (p=0.02) and female sex (p=0.02) were associated with intramyocardial lipid, but years of ARV exposure was not significant (p=0.2). We failed to identify a difference in

intramyocardial lipid content between HIV-infected patients with diabetes (n=9) and those without (n=86) (1.69 ± 1.13% vs. 1.42 ± 1.23%, respectively, p=0.5). Similarly, within the HIV cohort, there was no difference detected in intramyocardial lipid content based on HCV status, history of illicit drug use, or current use of lipid lowering therapy.

Focal myocardial scar (identified by late gadolinium enhancement) was infrequent and similar rates of focal scar were present in the HIV versus the control groups (HIV-infected 8.6% versus controls 7.7%, p=0.8). In all cases, myocardial scar volume was <5% of total myocardial mass. However, HIV-infected subjects had significantly greater indices of diffuse myocardial fibrosis (i.e., greater extracellular volume index) compared to controls as measured by MRI T1 mapping (Table 3). A multivariate regression including HIV-status, and adjusting for age, gender, BMI, heart rate, systolic blood pressure, HDL and LDL cholesterol, lipid lowering therapy use, as well as hematocrit showed independent associations between myocardial fibrosis index scores and HIV status (p=0.004), female sex (p=0.002) and systolic blood pressure (p=0.03). Again, these finding persisted when subjects with HCV, diabetes or those not on ARV therapy were excluded. There was a positive correlation between fibrosis index and intramyocardial lipid content (r=0.29, p=0.005) among subjects with HIV. However, there was no association between fibrosis index and nadir CD4, current CD4 count, years of ARVs, HIV viral load, or the measured biomarkers of inflammation and immune activation.

Within the HIV-infected cohort, higher levels of pro-BNP and MCP-1 were correlated with decreased radial strain (pro-BNP r=-0.28, p<0.01, MCP-1 r=-0.43, p<0.0001) as was increased LBP levels (r=-0.25, p=0.02). Each correlation remained statistically significant in subsequent sensitivity analyses in which subjects with diabetes, HCV infection or those not on ARV therapy were excluded. However, the correlations between pro-BNP, MCP-1 and LBP with radial strain were not observed within the control group, but this may have been limited by the smaller sample size of this group.

Discussion

To investigate the potential relationship between subclinical cardiac dysfunction and myocardial lipid and fibrosis, this study evaluated subjects with a broad range of exposure to HIV and its therapies, but without clinical cardiovascular disease. Despite

normal ejection fraction, we identified significantly reduced systolic function (27% relative reduction in radial strain), greater intramyocardial lipid content (by 38%), and evidence of diffuse myocardial fibrosis (by 8%) in HIV-infected individuals compared to age, sex, and race-matched controls. Impaired myocardial function as measured by strain parameters was associated with increased myocardial lipid and fibrosis in this cohort.

One brief report and one cohort study have used MRI/MRS to examine subjects with HIV infection receiving antiretroviral therapy [27, 28]. In the U.K. cohort, subjects had more overt cardiac disease than those in the current study (e.g. 76% of the U.K. HIV cohort had overt, focal myocardial scar on MRI vs. only 8% in the current study). Focal myocardial scar represents macroscopic replacement of myocardium by collagen; the most common cause of focal scar is myocardial infarction but other conditions (e.g. myocarditis, hypertension, diabetes) are also associated with focal scar. Although our U.S. HIV cohort had very little focal myocardial scar, our cohort did have evidence of expanded extracellular volume (ECV) index that is associated with diffuse myocardial fibrosis. Diffuse myocardial fibrosis may represent a sequelae of subclinical myocarditis and, in the general population, is a histologic finding in the failing heart associated with adverse cardiac outcomes [29, 30]. ECV remained increased in HIV compared to controls after controlling for variables known to increase fibrosis index, such as age and lower hematocrit. Further, myocardial fibrosis index was positively correlated with intramyocardial lipid content but not with duration of ARV exposure, HIV viremia, or inflammatory markers in the HIV subjects. Our findings suggest cardiac fibrosis may be secondary to downstream metabolic effects of HIV infection. Similar to the U.K. cohort, we found that the relationship between HIV and increased cardiac steatosis persisted when adjusted for potential confounders, such as smoking.

Myocardial strain was lower in HIV-infected subjects compared to control subjects. Holloway et al.[27] proposed their observed cardiac dysfunction in HIV-infected subjects was due to cardiac steatosis and fibrosis, but did not report a correlation between myocardial strain and these parameters. We, however, observed overall correlations between cardiac steatosis and fibrosis with depressed cardiac strain in subjects with a minor degree of focal scar that did not differ from age and gender matched controls (8-9%). Our findings strongly suggest that diffuse, rather than focal

myocardial injury, may be the sequelae of HIV infection and myocardial steatosis.

The relationship between visceral abdominal fat volume and myocardial lipid content has been well-established in obese populations [16, 31]. HIV infection is associated with increased central adiposity which conveys a two-fold increased risk in 5-year mortality [9], but the present study is among the first to characterize the relationship between visceral adipose tissue (VAT) and intramyocardial steatosis in HIV-infected individuals. VAT, in part due to side effects of ARV exposure, was the strongest independent predictor of intramyocardial lipid. This suggests that the altered metabolic activity of the visceral fat compartment may be a driving force of observed myocardial effects. Studies of non-HIV-infected obese populations have shown that increased intramyocardial triglyceride content, which correlates with VAT, is inversely associated with stroke volume [16]. Therefore, visceral adiposity in HIV-infected individuals may increase the risk for clinical cardiac dysfunction through cardiac steatosis.

Monocyte chemoattractant protein-1 (MCP-1) is a chemokine important in monocyte and macrophage migration and is a marker of chronic inflammation and immune activation. In patients with chronic heart failure, elevated MCP-1 levels are associated with decreased left ventricular ejection fraction and, in one study, higher MCP-1 levels predicted subsequent cardiac events [32]. We found that increased MCP-1 levels were strongly associated with degree of impairment in cardiac strain. Lipopolysaccharide binding protein, a marker of chronic inflammation and an acute phase protein made in response to lipopolysaccharide (LPS), was also associated with impaired cardiac strain in the HIV-infected cohort. In a case-control study, Sandler and colleagues [33] found sCD14, a marker of LPS mediated monocyte activation, though not associated with cardiovascular events, was a predictor of mortality in HIV. Therapeutic interventions targeted at attenuating immune activation in chronic HIV infection are under active investigation. Our data support this as an approach that may modify or reduce end organ injury that accumulates through this process.

Previously uncharacterized differences related to sex in both cardiac steatosis and cardiac fibrosis indices were observed. Female sex was an independent predictor of intramyocardial lipid content in both HIV and controls. Earlier data in HIV-infected populations suggest that women may be more susceptible than their male counterparts to

the metabolic effects of ARVs [34]. In the general population, female sex independently predicts higher myocardial fatty acid esterification and lower percent fatty acid oxidation in the left ventricle of the heart [35], suggesting cardiomyocytes may have an increased fatty acid deposition-to-utilization ratio in females. Therefore, HIV-infected women on ARVs may be particularly susceptible to abnormal cardiac lipid deposition. As seen in large population studies[30], female sex was independently associated with greater myocardial fibrosis indices compared to males.

The cross-sectional design of the present study limits the interpretation of observed associations and cannot establish causality. HIV-infected and control subjects were allowed to self-refer which may have introduced bias to the sample selection. Subjects with known cardiovascular disease, though, were excluded and therefore the abnormalities identified in cardiac steatosis and function are subclinical in nature. Prospective longitudinal studies evaluating these characteristics in patients initiating ARVs, as well as studies with clinical cardiovascular disease endpoints are needed to fully appreciate the etiology and significance of cardiac steatosis, fibrosis, and impaired cardiac strain in HIV. Females were relatively underrepresented in the study population. Further studies focusing on cardiovascular disease in women are needed to better examine the relationship between HIV infection and cardiac steatosis.

Our study identified increased subclinical cardiac dysfunction in association with cardiac steatosis and fibrosis in HIV-infected adults. Given the known increased risk of cardiovascular disease in persons living with HIV [36], it is important to identify risk factors and create targeted strategies to prevent progression of global cardiac dysfunction. We demonstrate that increased visceral adipose tissue is a strong independent predictor of myocardial steatosis, and as such, reducing visceral adiposity should be a target for strategies of lifestyle modification and cardiovascular risk reduction. Further, impaired cardiac strain tracked with markers of chronic inflammation and immune activation, which may serve as targets for the development of therapeutic strategies to optimize long-term cardiovascular health in persons living with HIV.

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Conflicts of Interest:

The authors have no real or apparent conflicts of interest to report regarding the research presented.

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Table 1: Demographic and Clinical Characteristics

Values are mean ± standard deviation unless otherwise indicated

	HIV (n=95)	**Control (n=30)**	**p-value**
Age, years	49±10	46±8	---
Sex, n (%)			
Male	71 (75)	22 (73)	---
Female	24 (25)	8 (27)	
Race, n (%)			
White	27 (28)	8 (27)	---
Black	55 (58)	18 (60)	
Hispanic	9 (10)	4 (13)	
Mixed Race	1 (1)	0 (0)	
Asian	3 (3)	0 (0)	
BMI (kg/m^2)	28.0±5.4	29.8±4.3	0.07
Current Smoker, n (%)	18 (19)	2 (7)	0.08
Ever Smoked, n (%)	**62 (65)**	**10 (33)**	**0.002**
Smoking Pack years	**11.3±22.3**	**1.6±3.7**	**0.0001**
Diabetes, n (%)	9 (10)	0 (0)	0.09
Hepatitis C, n (%)	**18 (19)**	**0 (0)**	**0.01**
Framingham Risk Score (%)	4.5±4.9	3.4±3.2	0.16
Systolic blood pressure (mmHg)	127±13	123±13	0.13
Diastolic blood pressure (mmHg)	79±9	76±10	0.12
Current Lipid Lowering Therapy, n (%)	33 (34.7)	5 (16.7)	0.06
Duration HIV diagnosis, years	14±8	---	---
Current ARV use, n (%)	88 (93)	---	---
Duration of ARV use, years	9±6	---	---
Current CD4 T-cells, cells/μL	**615±276**	**904±349**	**0.0002**
Nadir CD4 T-cells, cells/μL	235±182	---	---
Undetectable HIV Viral Load (<50 copies/mL), n (%)	80 (84.2)	---	---

Table 2: Metabolic and Inflammation Biomarkers

	HIV (n=95)	**Control (n=30)**	**p-value**
Fasting Glucose (mg/dL)	**97±18**	**92±8**	**0.03**
Fasting Insulin (µIU/mL)	9.9±8.3	9.2±5.5	0.6
HOMA-IR	2.6±2.8	2.1±1.4	0.3
Free Fatty Acids (uEq/L)	0.47±0.21	0.47±0.20	0.99
Total Cholesterol (mg/dL)	168±30	181±40	0.11
HDL cholesterol (mg/dL)	47±15	45±13	0.6
LDL cholesterol (mg/dL)	**94±29**	**112±34**	**0.01**
Triglycerides (mg/dL), median (IQR)	117 (86, 173)	91 (62, 188)	0.13
D-Dimer (ug/mL FEU), median (IQR)	**0.26 (0.22, 0.37)**	**0.38 (0.23, 0.48)**	**0.03**
CRP (mg/L), median (IQR)	1.76 (0.78, 4.06)	2.06 (0.79, 4.46)	0.7
Pro-BNP (pg/mL), median (IQR)	29 (11, 54)	17 (13, 44)	0.19
MCP-1 (pg/mL), median (IQR)	**394 (294, 779)**	**260 (195, 395)**	**0.0001**
LBP (ng/mL), median (IQR)	413 (282, 534)	358 (227, 548)	0.5
TIMP-1 (ng/mL), median (IQR)	**11.6 (8.2, 15.0)**	**8.8 (6.9, 12.1)**	**0.046**

HDL= High density lipoprotein, HDL=Low density lipoprotein, FEU= fibrinogen equivalent units**,** CRP=C reactive protein, Pro-BNP=pro-brain natriuretic peptide, MCP-1= monocyte chemoattractant protein-1, TIMP-1=Tissue inhibitor of metalloproteinase-1
Values are mean ± standard deviation unless otherwise indicated

Table 3: Myocardial Measurements and Regional Adipose Measurements

	HIV (n=95)	**Control (n=30)**	**p-value**
Intramyocardial Lipid Content (%) Median (IQR)	**1.14 (0.55, 1.85**	**0.58 (0.36, 1.58)**	**0.04**
Intrahepatic Lipid Content (%)	7.0±10.4	10.5±14.9	0.23
Subcutaneous Abdominal Fat (mL)	622±375	650±281	0.68
Visceral Abdominal Fat (mL)	499±228	467±151	0.41
Myocardial Extracellular Volume Index	**0.28±0.04**	**0.26±0.03**	**0.02**
Ejection Fraction (%)	62±6	63±4	0.4
Systolic Circumferential Strain (%)	-15.8±2.7	-16.4±2.5	0.31
Systolic Circumferential Strain Rate	-93.9±18.9	-100.4±23.7	0.23
Systolic Radial Strain (%)	**21.7±8.6**	**30.5±14.2**	**0.004**
Systolic Radial Strain Rate	**99.7±41.0**	**121.3±49.6**	**0.048**
Systolic Epicardial-Endocardial Circumferential Strain (%)	**7.0±2.5**	**8.5±2.8**	**0.02**

Values are mean ± standard deviation unless otherwise indicated

Figure Legends

Figure 1. Representative MRS of the interventricular septum with good spectra results (a) triacylglycerol (TG) peaks, (b) fat peak with water signal suppressed, and (c) water signal unsuppressed