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ORIGINAL PAPER

Intra-thoracic adiposity is associated with impaired contractile function in patients with coronary artery disease: a cardiovascular magnetic resonance imaging study

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Abstract

The influence of visceral adiposity on left ventricular remodeling following coronary artery disease (CAD)-related events has not been examined to date. Using magnetic resonance imaging (MRI) we explored intra-thoracic fat volume (ITFV) and strain-based markers of adverse remodeling in patients with CAD. Forty-seven patients with known CAD (25 with prior MI, 22 without prior MI) were studied. ITFV was quantified using previously validated imaging techniques. Myocardial strain was derived from cine MRI using a validated 3D feature-tracking (FT) software. Segmental LGE quantification was performed and was used to incrementally constrain strain analyses to non-infarcted (i.e. remote) segments. Remote myocardial strain was compared to the non-MI control cohort and was explored for associations with ITFV. Mean age was 57 ± 13 years with a mean BMI of 30.0 ± 6.2 kg/m^2 (range 20.3–38.4 kg/m^2). Patients with versus without prior MI had similar demographics and BMI (29.4 ± 4.4 vs. 30.4 ± 7.9 kg/m^2, $p = 0.62$). Patients with prior MI had lower mean peak strain than non-MI patients ($p = 0.02$), consistent with remote tissue contractile dysfunction. Inverse associations were identified between ITFV and mean peak strain in both the MI group (circumferential: r = 0.43, $p = 0.03$; radial: − 0.41, $p = 0.04$; minimum principal: r = 0.41, $p = 0.04$; maximum principal: r = − 0.43, $p = 0.03$) and non-MI group (circumferential: r = 0.42, $p = 0.05$; minimum principal: r = 0.45, $p = 0.03$). In those with prior MI higher ITFV was associated with a greater reduction in remote tissue strain. ITFV is associated with contractile dysfunction in patients with CAD. This association is prominent in the post-MI setting suggesting relevant influence on remote tissue health following ischemic injury. Expanded study of intra-thoracic adiposity as a modulator of myocardial health in patients with CAD is warranted.

Keywords Intra-thoracic fat volume · ITFV · Strain · Late gadolinium enhancement · Adiposity · Adaptive remodeling

Abbreviations

BMI	Body mass index
BSA	Body surface area
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CMR	Cardiac magnetic resonance
HDL	High density lipoproteins
ICC	Intra-class correlation
ITFV	Intra-thoracic fat volume
GFR	Glomerular filtration rate
LDL	Low density lipoproteins
LGE	Late gadolinium enhancement
LV	Left ventricle
LVEDV	Left ventricular end-diastolic volume
LVEDVI	Left ventricular end-diastolic volume index
LVEF	Left ventricular ejection fraction
LVM	Left ventricular mass
LVMI	Left ventricular mass index
LVESVI	Left ventricular end-systolic volume index
MI	Myocardial infarction
MRI	Magnetic resonance imaging
PCI	Percutaneous coronary intervention

Anna Todd and Alessandro Satriano contributed equally to this study.

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Introduction

Adiposity is a recognized contributor to the pathogenesis of coronary artery disease (CAD) [1, 2] with increased central distribution strongly associated with CAD-related mortality [3]. However, anthropometric measures of adiposity, such as BMI and waist circumference (WC), do not accurately reflect regional visceral adipose tissue stores [4, 5]. This adipose tissue sub-type is uniquely associated with free fatty acid (FFA) and pro-inflammatory adipokines production that may act locally or systemically to invoke vascular endothelial injury [6]. This has led to expanded interest in the study of adipose stores in a variety of visceral compartments, one being the intra-thoracic cavity.

To date, intra-thoracic fat volume (ITFV), measured by multi-detector computed tomography (MDCT) or magnetic resonance imaging (MRI), has been associated with the development of coronary artery disease (CAD) [7], coronary artery calcification [8], and myocardial infarction (MI) [9]. However, whether this tissue extends metabolic influence to the ventricular myocardium in patients with established CAD, a vulnerable patient population, has not been explored. To date, the Framingham Heart Study has identified both anthropometric markers and CT-based measures of intra-thoracic fat to be correlated with LV mass and chamber dilation in healthy subjects [10], findings that expanded on existing literature suggesting obesity to have detrimental impact on myocardial health [11–14]. More recently, 3D speckle tracking echocardiography has revealed sub-clinical reductions in myocardial strain in non-CAD patient populations in association with increasing thoracic visceral adipose stores [15]. However, the influence of intra-thoracic fat in patients with established CAD has not been explored.

In this MRI-based study we combined tomographic fat imaging, 3D myocardial strain analysis, and late gadolinium enhancement (LGE) imaging to investigate the relationship between ITFV and non-infarcted myocardium contractile health in patients with CAD. This analysis was performed for subjects both with and without evidence of prior MI, allowing exploration across both clinical settings.

Methods

Study population

We studied 47 consecutive subjects with known CAD referred for cardiovascular magnetic resonance (CMR). Patients were required to have 1 or more of the following criteria for CAD; obstructive CAD ($\geq 70\%$ in ≥ 1 major epicardial vessel) confirmed by invasive coronary angiography, prior revascularization, or prior myocardial infarction (> 6 months prior to CMR). Any patient reporting any chest discomfort within the past 3 months was required to have negative first-pass stress perfusion CMR imaging for the exclusion of concurrent ischemia. All patients were stratified by presence of prior MI based on the presence or absence of ischemic (sub-endocardial based) injury by LGE imaging.

Patients were excluded if they were unwilling to sign informed consent or had a Glomerular Filtration Rate (GFR) ≤ 30 ml/min/1.73 m^2, as per FDA recommendations regarding contrast administration [16] or any standard contraindications to MRI.

The project was approved by the Institution's Research Ethics Board and all subjects provided written informed consent prior to being enrolled.

Cardiac magnetic resonance imaging protocol

All patients underwent a standardized CMR imaging protocol using a 3.0 T MRI scanner (Siemens, Erlangen, Germany), as previously described.[8] Routine cine imaging was acquired using a standard steady-state free precession (SSFP) pulse sequence in sequential short and 2, 3 and 4 chamber long axis images. These images were performed during repeated, end-expiratory breath holds of 10 to 15 s. Typical scan parameters were as follows: Echo Time (TE) 1.3 ms, Repetition Time (TR) 2.6 ms, 10° Flip angle, Slice thickness 6 mm, gap 4 mm, and 256 × 205 matrix, iPAT 2, temporal resolution 28–38 ms.

Intra-thoracic fat imaging was performed using a black-blood Half-Fourier Acquisition Single-Shot Turbo-spin Echo (HASTE) pulse sequence during shallow breathing in the sagittal orientation, inclusive of both humeral heads. Typical imaging parameters as: slice thickness 8 mm, gap 2 mm, matrix 256 × 155, FOV 400–450 × 350–400 mm, TE 50 ms, TR 600 ms, iPAT 2. Standard imaging time was 25–30 s, by acquiring a single image slice per cardiac cycle, as per the patient heart rate.

Late gadolinium enhancement (LGE) imaging was performed to identify the presence of prior ischemic injury and was acquired using a standard segmented inversion-recovery gradient echo pulse sequence 10–15 min following intravenous Gadolinium contrast agent administration (0.1–0.2 mmol/kg, Gadovist®, Bayer, Inc). This was performed in imaging planes identical to cine images. Typical imaging parameters were: trigger pulse: 2, segments 13–21, iPAT 2, 256 × 205 matrix; 3.9/800 ms TE/TR; 20 degree flip angle, slice thickness = 6 mm; gap = 4 mm. Inversion time

was optimized to null normal myocardium, as previously described [17].

Image analysis protocol

All images were blindly analyzed in random order by experienced CMR readers. For visually-coded findings 2 readers (one with 10 years clinical experience, one with 2 years clinical experience) scored findings by consensus opinion. Objective quantitative analyses were performed by trained core laboratory personnel with ≥ 2 years' experience. Chamber volumes, global functional parameters, segmental LGE scar burden and ITFV quantification were performed using commercially available software: cvi[42] (Circle Cardiovascular Imaging Inc., Calgary, Canada). 3D myocardial strain analysis was performed using validated 3D feature tracking based software [18–20].

Sequential short axis cine images underwent semi-automated contouring of the endocardial and epicardial borders in both end-diastole and end-systole to obtain LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LV ejection fraction and diastolic LV mass (LVM). The papillary muscles were included as part of the LV mass. All volume and mass measurements were indexed to body surface area (BSA) using Mosteller's formula.

Sequential short axis LGE images underwent signal threshold-based quantification using the Signal Threshold versus Reference Mean (STRM) technique and a ≥ 5SD threshold, as previously described [21]. All segments with ≥ 10% signal enhancement by volume were considered to have significant ischemic injury and were censored from remote tissue strain analysis.

ITFV was quantified from sequential sagittal HASTE images, as previously described and validated [9]. This provided volumetric measures of ITFV using a signal threshold approach, defining fat as tissue with signal ≥ 10 standard deviations (SD) above the mean reference signal of paravertebral muscle, as shown in Fig. 1. Total ITFV was calculated as the sum of all segmented tissue on sequential slices multiplied by the total slice thickness, and was reported as absolute volume (mL) as well as indexed (mL/kg/m^2) to body mass index (BMI).

Three-dimensional strain analysis was performed from co-registered multi-planar 2D cine SSFP images using validated 3D feature-tracking software [20]. Long-axis images underwent manual tracing of the epicardial and endocardial borders on a single end-diastolic phase, generating a 3D mesh model that was deformed throughout the cardiac cycle using a feature tracking based algorithm. Lagrangian strain was calculated for conventional reference axes (longitudinal, circumferential and radial) and principal strain, an axis-independent measure of strain, incrementally calculated, as has been previously described [18, 19]. All strain analyses were reported using the standard AHA 16-segment model.

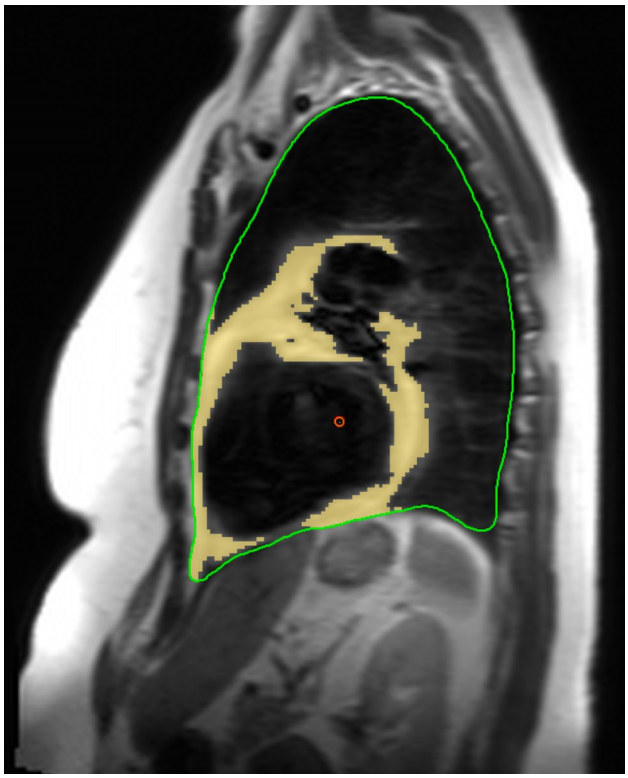

Fig. 1 Intra-Thoracic Fat Volume Evaluation. Example of free-breathing imaging using the HASTE pulse sequence with signal-threshold based measurement of adipose tissue. The green line represents the outer limits of the analyzed thoracic region (parietal thoracic border). The segmented fat signal is shown in yellow

Intra- and inter-observer reproducibility

Reproducibility testing of 3D strain was assessed by two independent and blinded observers for 10 randomly selected subjects. Our group has previously described reproducibility analysis for the described ITFV quantification techniques [9].

Statistical analysis

Continuous variables were presented as mean ± standard deviation; categorical values were presented as frequencies and percentages. In a sub-study comparison of patients with and without prior-MI, continuous variables were compared between the group with prior MI, and without prior MI using 2-tailed independent samples t-test for normally distributed variables. Categorical variables were compared using a Chi-squared or Fischer exact test, as appropriate. The linear association of two continuous variables was assessed

by a Pearson correlation coefficient. To account for the potentially confounding effects of diabetes and hypertension, we performed a sensitivity analysis, excluding patients with a history of hypertension (n = 24), and subsequently, those with type 2 diabetes (n = 11). Collinearity between LGE extent and ITFV was assessed by means of Basley collinearity diagnostics. Multivariable linear regression analysis was performed to evaluate for an independent association between strain and ITFV, including both LGE and ITFV, both before and after indexing ITFV for BMI. Demographic and clinical parameters (including volumetric data, strain, and laboratory findings) were compared to the baseline cohort by independent t-test.

For all comparisons, a p value less than 0.05 was considered significant. Statistical analysis was performed on SPSS software for Mac (Version 22, SPSS Inc., Chicago, IL, USA).

Results

Study population

Clinical patient characteristics and CMR characteristics are shown in Table 1. The mean age of the study population was 57 ± 13 years with a mean BMI of 30.0 ± 6.2 kg/m^2 (range 20.3–38.4 kg/m^2). Twenty-five patients (53%) had LGE evidence of prior MI, having no significant differences across baseline clinical characteristics versus those without prior MI. Specifically, they were of similar age (58 ± 13 versus 56 ± 13 years, $p = 0.766$), and had similar BMI, both with respect to range (22.0–38.4 kg/m^2 vs. 20.3–38.4 kg/m^2) and mean values (29.4 ± 4.4 vs. 30.4 ± 7.9 kg/m^2, $p = 0.621$). There were no observable differences in comorbidities or lipid profiles between the two sub-groups (Table 1).

Table 1 Clinical and cardiac magnetic resonance based patient characteristics

Parameters	All subjects (n = 47)	With MI (n = 25)	Without MI (n = 22)	p value
Clinical characteristics				
Age (years)	57 ± 13	57.6 ± 13.3	56.4 ± 13.0	0.77
Female, n (%)	10 (21%)	4 (16%)	6 (28%)	0.48
Height (m)	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	0.27
Weight (kg)	89.5 ± 16.2	80.5 ± 7.4	84.0 ± 9.2	0.64
BMI (kg/m^2)	30.0 ± 6.2	29.4 ± 4.4	30.4 ± 7.9	0.62
ITFV (ml)	866.4 ± 434.5	958.0 ± 454.5	762.3 ± 395.0	0.12
ITFV indexed (ml/kg/m^2)	28.7 ± 13.1	32.0 ± 14.2	24.8 ± 10.9	0.06
Comorbidities				
Hypertension, n(%)	24 (51%)	12 (48%)	12 (55%)	0.65
Diabetes, n (%)	11 (23%)	4 (16%)	7 (32%)	0.30
Hyperlipidemia, n (%)	29 (62%)	14 (56%)	15 (68%)	0.39
Smoker, n (%)	17 (36%)	8 (32%)	9 (41%)	0.53
Prior revascularization, n (%)	18 (38%)	12 (48%)	6 (27%)	0.23
Blood profile				
Total cholesterol (mmol/L)	4.2 ± 0.9	4.2 ± 0.9	4.2 ± 1.0	0.66
Triglycerides (mmol/L)	1.6 ± 1.0	1.7 ± 1.2	1.6 ± 0.5	0.88
HDL (mmol/L)	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.4	0.90
LDL (mmol/L)	2.5 ± 0.9	2.6 ± 0.9	2.3 ± 1.0	0.52
Total cholesterol:HDL ratio	4.7 ± 1.9	4.9 ± 2.3	4.3 ± 0.9	0.36
CMR characteristics				
LVEF (%)	49 ± 20	39 ± 17	60 ± 18	**0.001**
LVEDVI (ml/m^2)	64.8 ± 27.2	75.0 ± 25.6	53.3 ± 24.6	**< 0.0001**
LVESVI (m/m^2)	36.4 ± 23.5	47.6 ± 22.0	23.7 ± 18.3	**< 0.0001**
LVMI (g/m^2)	56.6 ± 19.3	59.0 ± 16.7	53.9 ± 22.1	0.16
LA size (mm)	39.8 ± 10.4	42.4 ± 11.9	37.0 ± 8.0	0.08
Ischemic LGE, n (%)	25 (53%)	25 (100%)	0	–
Total LGE burden (% LV mass at > 2SD)	12.3 ± 14.2	17.9 ± 14.1	5.8 ± 11.6	**< 0.01**

Bold values in table corresponds to the p-values lower than 0.05

BMI Body mass index, *CABG* coronary artery bypass graft, *HDL* high density lipoproteins, *ITFV* intra-thoracic fat volume, *LDL* low density lipoproteins, *LGE* late gadolinium enhancement, *LVEDVI* left ventricular end-diastolic volume index, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass index, *LVESVI* left ventricular end-systolic volume index, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *SD* standard deviation

The mean LVEF of the overall study population was 49.0 ± 20.2% with a mean LVEDVI of 64.8 ± 27.2 ml/m^2 and LVMI of 56.6 ± 19.3 g/m^2. As anticipated, patients with prior MI showed a higher LVEDVI and LVESVI with lower LVEF (39 ± 17% vs. 60 ± 18%, $p = 0.001$) (Table 1).

Typical scan times were 50–60 min. Respective typical image post-processing times were:15 min for strain analysis, 20 min for ITFV quantification, 10 min for LV function and mass evaluation and 10 min for LGE quantification.

Intra-thoracic fat volume

ITFV quantification was successfully performed in all study subjects. Non-indexed ITFV values ranged widely across the study population from 186.2 to 1900.1 ml with BMI-indexed ITFV values ranging from 8.1 to 50.3 ml/kg/m^2 (mean 28.7 ± 13.1 ml/kg/m^2). ITFV was associated with BMI by linear regression analysis (r = 0.47, $p = 0.001$).

Patients with MI showed a non-significant trend towards elevation in indexed ITFV versus those without prior MI (32.0 ± 14.2 vs. 24.8 ± 10.9 ml/kg/m^2; $p = 0.056$, respectively).

3D myocardial strain

Three-dimensional strain analysis was successfully performed in all subjects, the results being summarized in Table 2. The mean peak segmental strain of remote myocardium (non-infarcted segments) in patients with prior MI was significantly lower than the same measures from patients without prior MI when analyzed using circumferential, longitudinal, and minimal principal directions of deformation, consistent with remote contractile impairment. An example of myocardial strain analysis performed for one of the subjects is provided in Fig. 2.

Associations between ITFV and myocardial strain

Linear regression analysis was performed to examine for associations between ITFV and myocardial strain in both CAD cohorts. These analyses consistently demonstrated elevations in ITFV to be associated with a reduction in peak strain amplitudes.

Among all subjects ITFV was inversely associated with a reduction in peak myocardial strain in the circumferential (r = 0.482, $p = 0.001$), longitudinal (r = 0.432, $p = 0.002$), radial (r = − 0.387, $p = 0.007$), minimum principal (r = 0.477, $p = 0.001$), and maximum principal (r = − 0.456, $p = 0.001$) directions (Table 3). Importantly, these relationships were not observed when comparing strain values to the anthropometric measure of BMI. Figure 3 illustrates that incremental reductions in peak strain were observed with increasing values of ITFV across the population.

Non-strain based measures of global LV remodeling were also studied and similarly showed associations with ITFV. Following adjustment for total infarct size, an inherent confounder for global measures of remodeling, ITFV demonstrated significant associations with the following markers: LVEDVI (r = 0.49, $p < 0.0001$), LVESVI (r = 0.55, $p < 0.0001$), LVEF (− 0.45, $p = 0.002$), LVMI (r = 0.55, $p < 0.0001$), and LA size (r = 0.41, $p = 0.005$). Again, anthropometric measures of adiposity, such as BMI, failed to show any association with markers of LV remodeling (Table 3).

Sensitivity analysis was performed to account for the potential confounding effects of hypertension and diabetes. Both after excluding patients with diabetes mellitus (n = 11) and after excluding patients with hypertension (n = 24), correlation between strain and ITFVI remained significant. This was found with the sole exception of longitudinal strain, that lost significance after hypertensive patients were excluded.

Finally, we evaluated for independent association of ITFV following adjustment for LGE burden. Following confirmation of no collinearity between ITFV and LGE, a multilinear regression was performed inclusive of both variables (Supplemental Table S1). This identified that indexed ITFV is independently associated with LV strain, following adjustment for LGE.

Table 2 3D strain characteristics of non-infarcted myocardium

Parameters	All subjects (n = 47)	MI (n = 25)	No MI (n = 22)	*p* value
Peak circumferential strain (%)	− 9.9 ± 3.8	− 8.6 ± 3.9	− 11.1 ± 3.2	**0.02**
Peak longitudinal strain (%)	− 8.9 ± 3.3	− 7.7 ± 3.3	− 9.9 ± 3.0	**0.02**
Peak radial strain (%)	22.6 ± 13.0	19.0 ± 12.2	25.3 ± 13.3	0.10
Peak minimum principal strain (%)	− 13.6 ± 4.1	− 12.1 ± 4.3	− 14.9 ± 3.6	**0.02**
Peak maximum principal strain (%)	34.4 ± 16.8	29.5 ± 16.3	37.8 ± 16.6	0.09

Bold values in table corresponds to the *p*-values lower than 0.05

All values expressed as mean ± standard deviation. *p* value described for t-test between MI and No MI subgroups

MI myocardial infarction

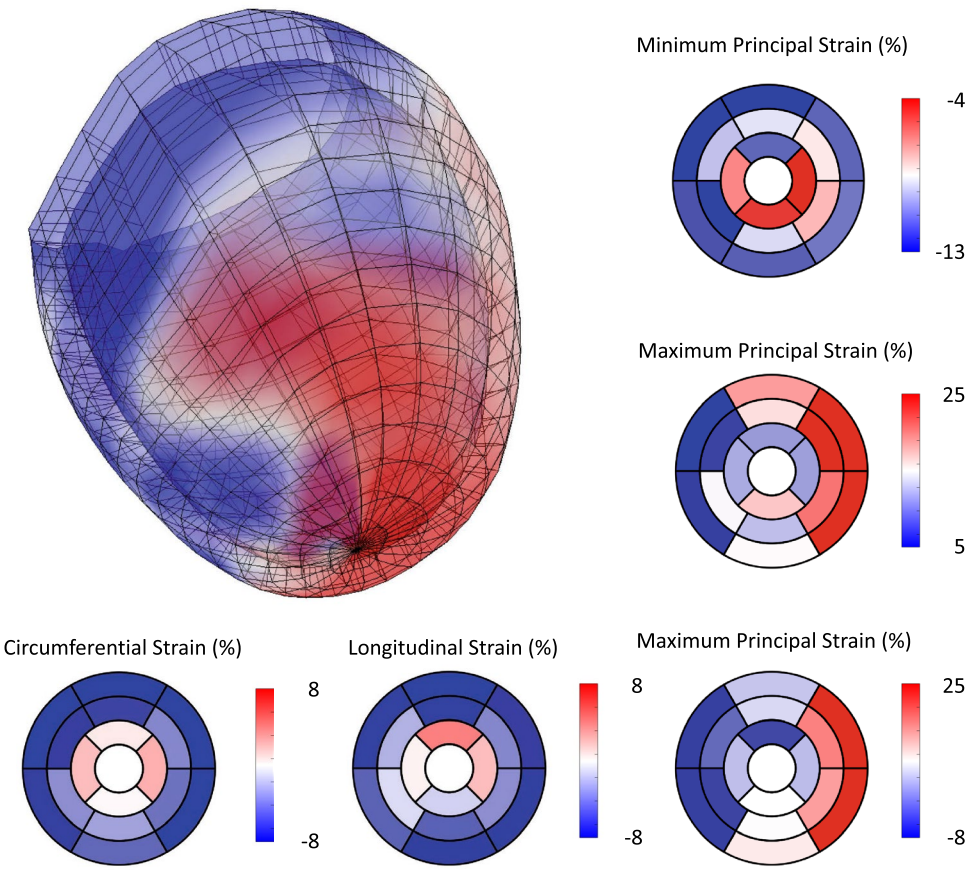

Fig. 2 Example of 3D myocardial strain analysis. The displayed colour map represents minimum principal strain at peak systole. Surrounding segmental bullseye maps are provided to show respective segmental values for minimum principal, maximum principal, radial, longitudinal, and circumferential strain

Sub-group analyses—patients with versus without prior MI

Univariable regression analyses were performed for subjects with and without prior MI. This demonstrated maintained significance for associations between ITFV and strain measures for both patients with prior MI (circumferential: $r = 0.43$, $p = 0.03$; radial: -0.41, $p = 0.04$; minimum principal: $r = 0.41$, $p = 0.04$; maximum principal: $r = -0.43$, $p = 0.03$) and patients without prior MI (circumferential: $r = 0.42$, $p = 0.05$; minimum principal: $r = 0.45$, $p = 0.03$), as reported in Table 4.

Mean strain values for patients with low (below median value of 31.7 mL/kg/m^2) versus high (above median value) ITFV are shown in Fig. 4 for the prior-MI and no-MI cohorts (Fig. 4). Greater differences in strain measures were observed between these cohorts at higher ITFV values, consistent with a stronger influence of ITFV on contractile dysfunction in the post-MI setting.

Reproducibility analysis

Intra-observer reproducibility analysis for 3D strain measurements was good for all strain measures, providing ICC values between 0.83 and 0.98 ($p < 0.001$ for all directions). Of all strain analyses, maximal and minimal principal strain provided the highest reproducibility (ICC 0.92 and 0.98, respectively). Inter-observer reproducibility was similarly robust, providing ICC values ranging from 0.83 to 0.97, again, highest for maximum and minimum principal strain.

Discussion

This study identifies important associations between ITFV and strain-based measures of contractile dysfunction in patients with established CAD. Our findings support an adverse influence of ITFV on myocardial performance, particularly following myocardial infarction. In the latter patients high burden of ITFV was associated with the greatest reduction in remote myocardial strain, raising important considerations for therapeutic targets surrounding visceral adiposity and its influence in the post-MI setting.

ITFV is an established and reproducible imaging marker, to date studied primarily for its relationship with coronary artery disease. In the Multi-Ethnic Study of Atherosclerosis (MESA), ITFV measured by non-contrast CT imaging was found to be strongly associated with the Coronary Artery

Table 3 Bivariate correlation of LV parameters and measures of adiposity

Parameters	ITFV indexed to BMI		BMI (kg/m^2)	
	r	*p*	r	*p*
Strain characteristics				
Peak circumferential strain (%)	0.48	**0.001**	0.14	0.37
Peak longitudinal strain (%)	0.43	**< 0.01**	0.06	0.68
Peak radial strain (%)	−0.39	**< 0.01**	−0.27	0.07
Peak minimum principal strain (%)	0.48	**0.001**	0.13	0.38
Peak maximum principal strain (%)	−0.46	**0.001**	−0.29	0.05
CMR characteristics				
LVEF (%)	−0.45	**< 0.01**	−0.06	0.67
LVEDVI (mL/m)	0.49	**< 0.0001**	0.25	0.10
LVESVI (mL/m)	0.55	**< 0.0001**	0.12	0.41
LVMI (g/m$^{2.7}$)	0.55	**< 0.0001**	0.39	**0.01**
LV thickness (mm)	0.18	0.24	0.23	0.12
LV mass:volume ratio	−0.19	0.20	0.07	0.65
LA size (mm)	0.41	**0.005**	0.25	0.10
Blood profile				
Total cholesterol (mmol/L)	0.02	0.93	0.01	0.96
Triglycerides (mmol/L)	0.01	0.98	0.50	**0.01**
HDL (mmol/L)	0.09	0.67	0.06	0.77
LDL (mmol/L)	0.10	0.65	0.18	0.40
Total cholesterol:HDL ratio	0.001	0.996	0.37	0.07

Bold values in table corresponds to the *p*-values lower than 0.05

BMI Body mass index, *HDL* high density lipoproteins, *ITFV* intra-thoracic fat volume, *LA* left atrium, *LDL* low density lipoproteins, *LGE* late gadolinium enhancement, *LV* left ventricle, *LVEDVI* left ventricular end-diastolic volume index, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass index; *LVESVI* left ventricular end-systolic volume index

Calcification (CAC) score quantified by MDCT imaging [8]. Other population-based studies have supported associations between intra-thoracic or pericardial fat burden and incident CAD diagnosis over prolonged periods of clinical follow-up [22, 23]. While CT-based techniques are effective, MRI is also well suited to studying fat distribution. Chen, et al. used an MRI-based techniques to quantify ITFV in patients referred for CAD and found this marker to be associated with severity of CAD as measured by the Duke Jeopardy score at invasive angiography [7]. MRI-based measures of ITFV have also been established to be elevated in patients with metabolic syndrome, incrementally so among those with prior myocardial infarction by LGE imaging [9]. Overall, an established body of evidence supports associations between increased volume of intra-thoracic fat and the development of CAD.

The exploration of visceral adiposity and LV remodeling have, to date, focused on volumetric markers of mass, volume and function in otherwise healthy adolescents or adults. Using MDCT, the Framingham Heart study evaluated both pericardial fat volume and total intra-thoracic fat volume and demonstrated associations with CMR-based LV mass, LV EDV, and LA size [10]. However, these relationships were similarly observed for BMI leading them to conclude that the systemic influences of obesity may outweigh those unique to visceral fat stores [10]. More recently, 3D speckle tracking echocardiography has been used to explore sub-clinical alterations in contractile performance in healthy subjects versus visceral adiposity. In a study by Ng, et al. [15] 130 patients with no CAD by contrast-enhanced cardiac CT had epicardial adipose tissue volume measured and were additionally studied using 3D speckle tracking echocardiography. Significant reductions in radial, circumferential and longitudinal strain were identified with increasing burden of epicardial fat volume. However, similar to our findings, the anthropometric measure of BMI was not associated with alterations in strain. Incremental to this study, ours provides evidence that this relationship extends to patients with CAD, and may adversely influence LV remodeling following acute MI.

Several plausible mechanisms exist for influences of excess intra-thoracic adipose tissue and reduced myocardial health. Recognized as an active endocrine organ, expansion of adipose tissue is thought to promote metabolic, biochemical and hemodynamic pathways recognized to adversely influence LV contractile function [6, 24]. Metabolically, an elevated FFA flux from visceral fat can lead to lipid deposition in non-adipose tissues, [25] a condition termed myocardial steatosis when seen in the heart and postulated to lead to impairments in systolic function [26]. As elevations in FFA levels and cellular FA oxidation increase oxygen consumption, adiposity may lead to reduction in cardiac efficiency [25, 27, 28].

Our observation that ITFV has a significant effect on myocardial health following ischemic injury is of clinical importance. Despite substantive knowledge surrounding myocardial healing and remodeling, [29, 30] few therapeutic interventions have been shown to mitigate this phenomenon that is strongly associated with major cardiovascular events [31]. ITFV is a modifiable target, one that lends itself to dietary, exercise-mediated and pharmacologic interventions. Supporting such a paradigm, pre-clinical studies in mice have demonstrated dynamic alterations in CMR-derived 2D myocardial strain while introducing dietary modifications to alter obesity severity [32]. With a contemporary capacity to clinically investigate post-MI remodeling in human subjects through currently described techniques and incrementally through the use of tissue mapping (T1 and T2 mapping) [33], the community is

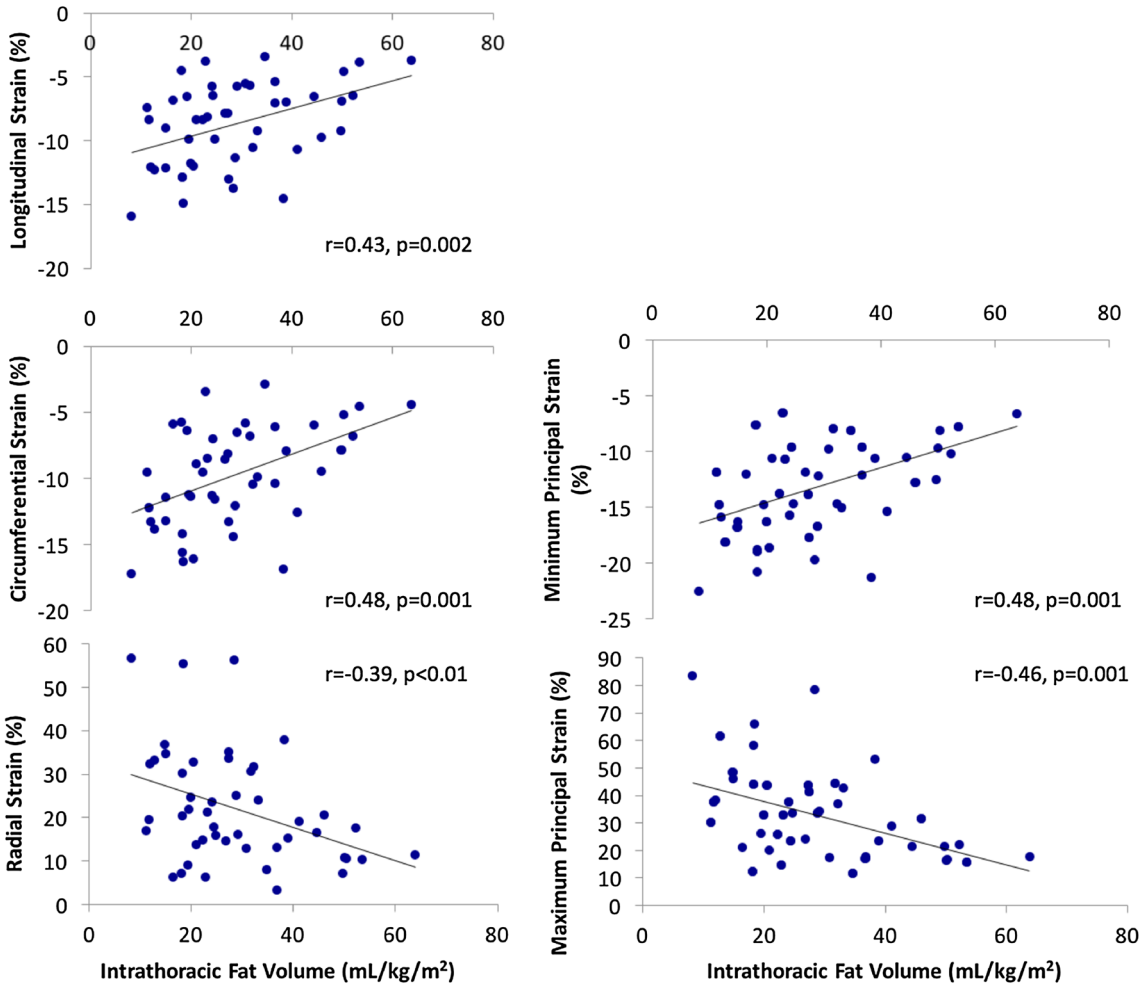

Fig. 3 Strain versus ITFV. Linear regression analysis of strain versus ITFV, in radial circumferential, longitudinal, minimum principal and maximum principal directions. *ITFV* intra-thoracic fat volume

well poised to investigate the influence of visceral adiposity on LV remodeling.

Study limitations

As a single center study, these findings require validation in larger, multi-center setting. Our limited sample size prevented meaningful adjustment for relevant demographic covariates beyond total infarct volume. To address this, we repeated analyses in the absence of patients with documented diabetes and hypertension, two covariates felt to be most influential. This showed maintained associations between ITFV and non-infarct territory strain. While associations between the measures of intra-thoracic adiposity and reduced myocardial strain were identified, such findings do not demonstrate causality. Accordingly, whether intra-thoracic fat is an arbitrator or simply a surrogate marker of adverse remodeling becomes an important area for future research. We did not evaluate the sub-components of ITFV (pericardial versus epicardial) as the described "single shot" MR imaging technique does not provide sufficient spatial and temporal resolution to reliably distinguish these two fat layers. Whether such compartments provide unique weighting to the described findings is therefore not explored. Stress perfusion imaging to exclude significant myocardial ischemia was only routinely performed for patients reporting chest discomfort. Therefore, contributions of silent ischemia to observed reductions in strain values in non-infarcted myocardium cannot be excluded.

Finally, estimations of remote tissue extra-cellular volume (ECV) fraction were not possible as T1 mapping was not included as part of this study protocol. Future work comparing remote tissue strain to ECV estimations are therefore of priority.

Table 4 Bivariate correlation of LV parameters and strain with ITFV

Parameters	Patients with prior MI (n = 25)		Patients without prior MI (n = 22)	
	r	*p*	r	*p*
Strain characteristics of non-infarcted myocardium				
Mean circumferential strain (%)	0.43	**0.03**	0.42	**0.05**
Mean longitudinal strain (%)	0.38	0.07	0.38	0.08
Mean radial strain (%)	−0.41	**0.04**	−0.26	0.25
Minimum principal strain (%)	0.41	**0.04**	0.45	**0.03**
Maximum principal strain (%)	−0.43	**0.03**	−0.40	0.07
CMR characteristics				
Thickness (mm)	0.12	0.57	0.33	0.14
LVEF (%)	−0.46	**0.02**	−0.27	0.23
LEDVI (mL/m)	0.48	**0.01**	0.34	0.13
LESVI (mL/m)	0.59	< **0.01**	0.34	0.12
LVMI (g/m)	0.33	0.11	0.45	**0.04**
LA size (mm)	0.42	< **0.05**	0.23	0.29
M:V ratio	−0.28	0.18	0.05	0.84

Bold values in table corresponds to the *p*-values lower than 0.05

ITFV Intra thoracic fat volume, *LA* left atrium, *LVEDVI* left ventricular end-diastolic volume index, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass index, *LVESVI* left ventricular end-systolic volume index, *M:V* mass to volume, *MI* myocardial infarction

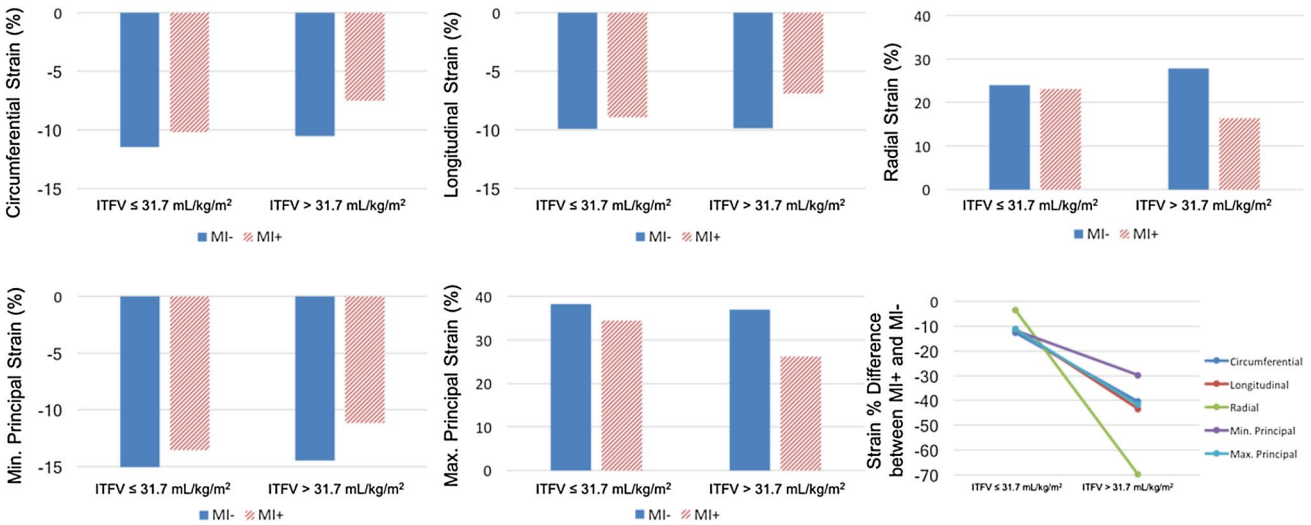

Fig. 4 Mean remote strain value in patients with low ITFV (below median value of 31.7 mL/kg/m^2) and high ITFV (above median value of 31.7 mL/kg/m^2) in circumferential, longitudinal radial, minimum principal and maximum principal directions. The bottom right corner provides the percentage difference in mean remote strain in the group with prior MI with respect to the group without prior MI, for patients with low and high ITFV. *ITFV*, Intra-Thoracic Fat Volume; *MI*, Myocardial Infarction; *MI-*, patients without prior MI; *MI+*, patients with prior MI

Conclusion

This study identifies that contractile performance of non-injured myocardium is inversely associated with intra-thoracic fat volume in patients with CAD, a relationship that is most prominent in the post-MI setting. Overall, these findings support intra-thoracic adiposity to be a meaningful contributor to contractile dysfunction in patients with CAD and a meaningful target for future investigations aimed at

risk stratification and novel therapeutic interventions in this population.

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Compliance with Ethical Standards

Conflict of interest Dr. Anna Todd has no conflict of interest. Dr. Alessandro Satriano declares that he has no conflict of interest. Ms. Kate Fenwick declares that she has no conflict of interest. Dr. Naeem Merchant declares that he has no conflict of interest. Dr. Carmen P. Lydell declares that she has no conflict of interest. Dr. Andrew G. Howarth receives consulting fees from Amgen. Dr. Matthias G. Friedrich is Chief Medical Officer of Circle Cardiovascular Inc. Dr. Todd J. Anderson declares that he has no conflict of interest. Dr. Nowell M. Fine receives consulting fees from Novartis and Pfizer. Dr. James A. White received salary support from the Heart and Stroke Foundation during this study, received research grants from Circle Cardiovascular Inc., and is a shareholder of Cohesic Inc.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Research involved in human or animal rights This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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