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Ultra-high sensitivity cardiac troponin-I concentration and left ventricular structure and function in women with ischemia and no obstructive coronary artery disease

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Abstract

Aims: Women are disproportionally impacted by ischemia and no obstructive coronary artery disease (INOCA), and such women are at increased risk of developing heart failure with preserved

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Declaration of Helsinki

This study complies with the Declaration of Helsinki, ethics committee approved the research protocol and informed consent has been obtained from the subjects (or their legally authorized representative).

Declaration of competing interest

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ejection fraction (HFpEF), however the mechanisms linking these conditions remain poorly understood. The aim of this study was to determine whether ultra-high sensitivity cardiac troponin I (u-hscTnI), an indicator of cardiomyocyte injury, is associated with abnormalities in myocardial perfusion and left ventricular (LV) structure and function in women with INOCA.

Methods: 327 women with INOCA enrolled in the Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction (WISE-CVD) study underwent vasodilator stress cardiac magnetic resonance imaging (CMRI) and u-hscTnI measurements (Simoa HD-1 Analyzer, Quanterix Corporation). Multivariable linear regression was used to evaluate associations between u-hscTnI concentrations and myocardial perfusion (MPRI), LV mass index and feature-tracking derived strain measures of LV function.

Results: u-hscTnI concentrations were quantifiable in 100% of the cohort and ranged from 0.004 to 79.6 pg/mL. In adjusted models, u-hscTnI was associated with LV mass index (+2.03; 95% CI 1.17, 2.89; $p < 0.01$) and early diastolic radial strain rate (SR) (+0.13; 95% CI 0.01, 0.25; $p = 0.03$), early diastolic circumferential SR (−0.04; 95% CI −0.08, 0.002; $p = 0.06$) and early diastolic longitudinal SR (−0.03; 95% CI −0.07, 0.002; p = 0.06). u-hscTnI was not associated with MPRI ($p = 0.39$) in adjusted models.

Conclusion: Together, these findings support cardiomyocyte injury as a putative pathway towards adverse LV remodeling and dysfunction; however, further research is needed to define the specific mechanism(s) driving myocellular injury in INOCA.

Keywords

Ischemia and no obstructive coronary artery disease (INOCA); Ultra-high sensitivity cardiac troponin; Cardiomyocyte injury; Left ventricular mass; Diastolic strain; Left ventricular dysfunction

1. Introduction

Women are disproportionally impacted by ischemia and no obstructive coronary artery disease (INOCA), and such women are at increased risk of developing heart failure with preserved ejection fraction (HFpEF) [1–3]. While the specific mechanisms driving HFpEF progression in INOCA remains incompletely understood, several common characteristics shared between INOCA and HFpEF have been identified. For example, coronary microvascular dysfunction (i.e. impaired myocardial perfusion reserve) is prevalent in INOCA and increasingly recognized in HFpEF [4–6]. Likewise, women with INOCA frequently have left ventricular (LV) diastolic dysfunction, often a precursor to development of HFpEF [7–10]. In a recent study, among patients with INOCA, those with impaired myocardial perfusion reserve had the highest cardiac troponin-I (cTnI) and worse diastolic function [11]. These observations have led to the hypothesis that in INOCA microvascular dysfunction leads to ischemia-mediated cardiomyocyte injury with resultant adverse remodeling and subclinical LV dysfunction, precursors of HFpEF.

High sensitivity (Hs)-cTn assays that detect low concentrations of circulating cardiac troponins are increasingly used [12,13]. Higher concentrations of circulating cardiac troponin using these hs-cTn assays is associated with higher LV mass, LV diastolic

dysfunction, and higher risk of adverse cardiovascular outcomes including heart failure in the general population [14–17] and in patients with cardiovascular disease [18–20]. The latest generation of cardiac troponin assays, the u-hscTnI, has the highest analytical sensitivity of all commercial assays and can detect even lower concentrations of troponin [21–23].

In a large cohort of well-phenotyped women with INOCA enrolled in the Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction (WISE-CVD) study we examined the relationship of cardiomyocyte injury and measures of myocardial perfusion and LV structure and function.

2. Methods

2.1. Study design

The cohort consisted of women enrolled in the National Heart, Lung, and Blood Institute (NHLBI)-sponsored WISE-CVD multicenter prospective study (NCT00832702) as previously described [8,24]. In brief, women with suspected signs and symptoms of ischemia and no evidence of obstructive coronary artery disease (CAD) (defined as <50% stenosis) on clinically indicated invasive angiography were recruited from January 2009 to August 2015. The WISE-CVD study prespecified the collection of biomarkers such as u-hscTnI to test the hypothesis in this study. The protocol was approved by the IRBs at Cedars-Sinai Medical Center, Los Angeles, CA and University of Florida, Gainesville, FL; and all participants provided written informed consent.

Invasive angiography was performed at time of enrollment and films were analyzed by the core laboratory to quantitatively assess the extent and severity of CAD. Each coronary artery was classified as no CAD (<20% stenosis), no obstructive CAD (20–50% stenosis), obstructive CAD (≥50%), and "not analyzable." Additionally, coronary severity score was calculated based on stenosis severity weighted by proximal location using previously published methods [25]. In a subset of patients in this cohort, invasive coronary functional angiography was performed [8,24].

2.2. Cardiac magnetic resonance imaging (CMRI)

Vasodilatory stress and rest CMRI were performed on 1.5 Tesla scanners (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany) in the supine position with electrocardiogram (ECG)-gating. Subjects were asked to hold all their cardiac medications 24–48 h prior to CMRI. A highly standardized protocol was used as previously described, with adenosine as the primary vasodilator [8,24]. Blood pressures and heart rate were recorded at rest and during vasodilatory stress test. Adenosine stress adequacy was confirmed by advanced cardiac imaging cardiologist as part of the core laboratory process and included the presence of appropriate heart rate response, evidence of splenic switch-off sign on CMRI and measuring caffeine levels.

Epicardial and endocardial borders of short-axis cine images were manually traced to derive LV volumes used to generate volume-time curves and LV mass. Volume-time curves were used to determine peak LV filling rate (PFR), and time to PFR using post-processing

software. CAAS MRV 3.4 (PIE Medical Imaging) software was used for analysis of LV mass and volume [8,24].

Myocardial feature tracking of cine images was performed using dedicated software (Circle CVI42 version 5.3.0, Calgary, AB, Canada) to assess LV systolic and diastolic function, as previously described [10,26]. Briefly, a single experienced observer manually traced the LV endocardial and epicardial borders at end-diastole from short-axis images spanning the LV from base-to-apex, and horizontal and vertical long axis images). Previously published normal strain values using the same technique, analysis software version, and imaging core laboratory include: longitudinal systolic strain rate (SR) −1.00 ± 0.21, early longitudinal diastolic SR 1.13 ± 0.32, late longitudinal diastolic SR 0.69 ± 0.26, circumferential systolic SR −1.08 ± 0.20, early circumferential diastolic SR 1.38 ± 0.37, late circumferential diastolic SR 0.56 ± 0.21 [26]. Intra-observer reliability in corelab for measuring early circumferential diastolic SR, early radial diastolic SR, early longitudinal diastolic SR reported as a coefficient of variation, was 7.6%, 7.3%, and 11.4%, respectively.

LV cavity contours were manually adjusted to include the region of maximal signal intensity within the cavity and to exclude papillary muscle, including frame by frame adjustment of contours in the case of motion. Blood pool and linear dark rim artifact at the LV cavity/endocardial border were excluded. Myocardial perfusion reserve index (MPRI) was calculated as stress relative upslope divided by rest relative upslope. Stress relative upslope was defined as the ratio of the maximum upslope of the first-pass myocardial perfusion time-intensity curve and rest relative upslope as the maximum upslope of the first-pass LV cavity time-intensity curve. An American Heart Association 16-segment model was used (true apex not imaged) where the average of 16 segments was used to calculate MPRI [24]. CAAS MRV 3.4 (PIE Medical Imaging) software was used for analysis of the MPRI [8,24]. As per prior report, a MPRI threshold of <1.84 was used as a surrogate for microvascular dysfunction [27].

2.3. Ultra-high sensitivity cardiac troponin-I assay

Blood for cTn assay were obtained at time adenosine stress CMRI prior to receiving stress agent. The u-hscTnI assay (LLOQ 0.38 pg/mL, ULOQ 15,736.55 pg/mL, LLOD 0.0046 pg/mL) was performed on the Simoa HD-1 Analyzer (Quanterix Corporation, Lexington, MA). Each cTnI kit (TnI kit, Cat#100133 Quanterix) contained eight calibrators, two controls, sample diluent, bead, detector, streptavidin beta galactosidase, and fluorogenic β-galactosidase substrate resorufin reagents [22]. For all the samples: 120 μl of plasma, which is sufficient for duplicate analysis, was centrifuged for 8 min at 12,000 ×g and then diluted four-fold with quanterix troponin kit dilution buffer. A total of 400 μl of the diluted sample was loaded into each well and assay run finished according to the manufacture's protocol. There were 96 wells per plate and a standard curve and other quality controls were run with each plate. Each sample was run twice and the concentration was calculated based on the average enzyme per bead. The u-hscTnI concentrations were determined based on 8-point standard curves run for each plate. Any sample with the percent coefficient of variation (%CV) higher than 20% was repeated with appropriate calibrators and controls.

Women with u-hscTnI concentrations >50 pg/mL, considered to be outliers, were not excluded from the analysis; because for all cases, the measurements in duplicate samples had %CV <20% and the values were within the linear range of the standard curves run on each plate. Also, there were no known deviations from protocol for collection of u-hscTnI plasma, or evidence of alternative diagnosis that could explain the elevation (i.e. anemia, myocarditis, LV hypertrophy).

2.4. Statistical analyses

Of the 374 women enrolled in WISE-CVD, women were excluded for missing/uninterpretable MPRI, tissue tracking myocardial strain data, and/or u-hscTnI assay results, and for >30% CV which is the threshold for the laboratory assay utilized resulting in 327 participants in this analysis.

Variables were summarized using mean ± SD, median (range), or count (percent) for categorical variables. The distribution of u-hscTnI was not normally distributed, therefore correlations between u-hscTnI and CMRI measures of LV structure and function were assessed using Spearman rank correlations. A Holm-Bonferroni multiple testing correction was applied and adjusted *p*-values are reported in Table 2 [28].

Primary outcomes of interest included MPRI and measures of subclinical adverse LV remodeling and diastolic dysfunction: LV mass index, and early diastolic circumferential, radial and longitudinal SR. Secondary outcome measures included blood pressure, hypertension, LV volumes, peak left ventricular filling rate normalized to end-diastolic volume (PFR/EDV), time to PFR, late diastolic circumferential, radial and longitudinal SRs, and systolic function (LV ejection fraction, circumferential, radial and longitudinal strain). Analysis with Bonferroni correction was completed to account for multiple comparisons. Wilcoxon Rank sum test was used to compare u-hscTnI between subjects with MPRI <1.84 and MPRI ≥1.84.

Multivariable linear regression was used to test the association of u-hscTnI on: LV mass index, diastolic and systolic strain measures, MPRI and hypertension. The model examining LV mass index as the outcome was adjusted for significant clinical covariates a priori including age, body mass index, and hypertension. Models for diastolic and systolic strain measures, were adjusted for age, body mass index, hypertension and LV mass index. Additional models were created that examined the association with diastolic and systolic strain measures adjusted for systolic blood pressure instead of history of hypertension. The model examining MPRI as the outcome was adjusted for age, body mass index, LV mass index, and history of hypertension. The model examining hypertension as the outcome was adjusted for age, body mass index, and LV mass index. Given the non-normal distribution of u-hscTnI, each model was ran on log transformed u-hscTnI values.

In addition, in secondary analysis the subset of patients that had invasive coronary functional angiography and found to have at least one abnormal physiologic pathway indicative of microvascular dysfunction $N = 158$ were analyzed. Abnormal physiologic pathway was defined as coronary flow reserve <2.32, left anterior descending artery diameter change in response to acetylcholine ≤0%, coronary blood flow in response to acetylcholine ≤50%,

or left anterior descending artery diameter change in response to nitroglycerin ≤20%. Multivariable linear regression was used to test the association of u-hscTnI on diastolic and systolic strain measures adjusted for significant clinical covariates a priori including age, body mass index, LV mass index and history of hypertension in the subset of women with microvascular dysfunction.

A p-value of <0.05 was considered statistically significant. SAS was used for all analyses.

3. Results

u-hscTnI were quantified in all 327 women, ranging from 0.004 to 79.6 pg/mL, mean 1.69 pg/mL, median 0.75 pg/mL. Participant characteristics are presented in Table 1. By design, participants were all women, 55 ± 11 years of age, with the majority being post-menopausal (73.1%). History of hypertension was present in 40.1% and 42.1% reported smoking (ever smoker). The medium coronary severity score was 10 (3.8–22.8) in this cohort with no obstructive CAD.

3.1. Associations of u-hscTnI concentrations with measures of left ventricular structure and function

Fig. 1 illustrates longitudinal, radial and circumferential strain rate profiles throughout the cardiac cycle in a representative subject with low u-hscTnI concentration and a normal strain rate pattern, and a representative subject with high u-hscTnI concentration and abnormal strain rate pattern consistent with diastolic dysfunction. Summary data are also presented (panel c), showing that INOCA women in the highest tertile of u-hscTnI concentration had the worst early diastolic longitudinal SR, early diastolic circumferential SR and early diastolic radial SR (Kruskal-Wallis $p < 0.01$ for all).

As detailed in Table 2, u-hscTnI concentration was moderately related with systolic and diastolic blood pressure, LV mass index, PFR/EDV and measures of diastolic and systolic strain which remained significant after Holm-Bonferroni multiple testing correction. In addition, there was an increase of 2.22 in LV mass index per unit increase in multivariable linear regression model adjusted for age, body mass index, and hypertension (Table 3). u-hscTnI was not significantly associated with history of hypertension or MPRI in adjusted models. Further, u-hscTnI was significantly associated with early diastolic radial SR, radial systolic SR, radial peak systolic strain, and circumferential peak systolic strain, with a strong trend in the association with early diastolic circumferential SR and early diastolic longitudinal SR. Results were similar in model adjusting for SBP in place of hypertension history (Supplemental Table 1).

A total of 307 participants were evaluated for LGE similar to the overall cohort [29]. Among these 24 participants (7.8%) had evidence of LGE with 16 demonstrating typical scar pattern in a vascular territory, 7 had atypical scar pattern characterized as patchy epicardial pattern, and 1 was uninterpretable. The mean total LGE scar size was 5.47 ± 3.43 g.

3.2. u-hscTnI concentrations and microvascular dysfunction

u-hscTnI concentration was negatively correlated with MPRI (Table 2). A trend was observed towards higher mean concentration of u-hscTnI in those with MPRI <1.84 versus MPRI ≥1.84 (u-hscTnI 1.73 ± 3.13 pg/mL vs. 1.67 ± 6.68 pg/mL, $p = 0.07$). In multivariable linear regression models adjusted for age, body mass index, LV mass index, and hypertension history, u-hscTnI no longer remained significantly associated with MPRI ($p = 0.39$).

In secondary subgroup analysis, among patients with an abnormal physiologic pathway based on invasive coronary functional angiography there was a significant association in adjusted models between u-hscTnI and radial peak systolic strain ($p = 0.02$) and circumferential peak systolic strain (p = 0.02) and a strong trend in the association with early diastolic radial SR ($p = 0.08$) and early diastolic longitudinal SR ($p = 0.07$) similar to findings observed in the larger cohort (data not shown).

4. Discussion

The major findings from this investigation were: 1) u-hscTnI was detectable and quantifiable in 100% of participants with INOCA using a novel u-hscTnI assay; 2) higher levels of u-hscTnI were associated with higher LV mass index and measures of systolic and diastolic dysfunction.

That cardiac troponin was detectable in our participants is consistent with several prior observations, including by Omland et al. who found detectable levels in over 97% of 3679 patients with CAD [30]. However, unlike their cohort, where about half of patients had history of percutaneous coronary intervention and a third had coronary-artery bypass grafting, in our cohort none of the patients had obstructive CAD. Other cohorts, evaluating cTn in the general population, including the Dallas Heart Study and the Atherosclerosis Risk in Communities Study, have also reported detectable levels using high sensitivity assays, albeit in much smaller percentages of participants (12.9% and 55% of women, respectively) [14,31]. The ability to quantify cTn in all participants in this cohort with INOCA is a major advantage, particularly as it allows data to be analyzed as a continuous variable, as opposed to a categorical term (i.e. + or −).

In this cohort of women with INOCA there was a significant association between cTnI concentration and LV mass and LV strain abnormalities; both of which are known to predict HF-related hospitalization, CVD-related mortality and aborted cardiac arrest [32–37]. We found not only an association between cTnI concentrations and CMRI measured LV diastolic strain but also LV systolic strain; expanding prior reports showing a strong correlation between hs-cTnI and echocardiographic derived measures of LV diastolic dysfunction [38]. Elevations in cTnI concentrations can be due to a number of biological mechanisms including cardiomyocyte turnover, cardiomyocyte injury with reversible cell leakage and cardiomyocyte injury with cell death [39]. Although concentration alone cannot distinguish between these mechanisms, the correlation between higher levels of cTnI and higher LV mass and measures of LV systolic and diastolic dysfunction suggest cardiomyocyte injury as the underlying mechanism.

We hypothesized that ischemia mediated cardiomyocyte injury would be a primary contributor to circulating measures of cTnI in INOCA, whereby repeat bouts of micro-infarctions and ischemia-mediated myocellular damage results in alterations in LV structure and function that culminates in development of HFpEF. Indeed, Taqueti et al. found that among 201 patients with INOCA, those with impaired myocardial perfusion reserve by positron emission tomography (PET) had the highest cTnI and worse diastolic function [11]. Why we did not observe a similar association between u-hscTnI and CMRI measured MPRI (adjusted models) remains unclear, but may be related to differences in approach (i.e. PET vs. CMRI) and/or INOCA endotype. Indeed, similar to other reports [40,41] Albadri et al. [42] reported u-hscTnI was most closely related to endothelial dysfunction, as measured by functional coronary angiography; whereas, CMRI-measured MPRI more closely reflects non-endothelial dependent microvascular function.

Several investigations have found a relationship between hypertension and circulating cTnI [43–45]. In line with this observation, we observed a significant correlation between circulating cTnI and arterial blood pressure, supporting experimental data demonstrating that mechanical forces, angiotensin II, and osmotic stress trigger cardiomyocyte apoptosis [46]. However, there was no significant association between cTnI concentrations and hypertension and the association between u-hscTnI levels and measures of subclinical adverse LV remodeling and strain remained significant in models that adjusted for blood pressure and hypertension, illustrating the complexity and multiple factors at play that warrant further investigation.

4.1. Limitations

This is one of the first clinical investigations to link u-hscTnI with LV structure and function in women with suspected INOCA. Of course, the cross-sectional design cannot prove direction or causality. While CMRI-derived MPRI is a valuable tool for noninvasive assessment of microvascular dysfunction, it is unable to distinguish the different microvascular dysfunction endotypes (i.e endothelial and non-endothelial dependent pathways). Given the enrollment period of this investigation, CMRI T1 and extracellular volume (ECV) measurements were not performed in this cohort, limiting our overall understanding of the extent of adverse ventricular remodeling in this patient cohort.

The u-hscTnI assay used in the present investigation is precise, accurate and reproducible; however, only a single sample was used, raising the possibility of variability over time. While this is a limitation, it is also consistent with other biomarker studies [40,47]. Drawbacks associated with cTn assays includes false-positive troponin results due to interferences such as icterus, lipemia, autoantibodies, anticoagulant(s), fibrin clots, hemolysis, alkaline phosphate, immunocomplex formation interference [48,49]. Additionally, heterophilic antibodies as a result of exposure to antigens through transfused blood, vaccinations, exposure to mice, therapeutic use of mouse monoclonal antibodies, autoimmune disease such as and in some cases dietary antigens, can also cause high troponin values or false positive [50]. Furthermore, sample storage conditions may also interfere with measurement of cTn and cause either false-positive or false negative values.

5. Conclusions

In a cohort of women with suspected INOCA, u-hscTnI was quantifiable in 100% of cases using a novel ultra-high sensitivity assay. We found an association between higher u-hscTnI concentrations and higher LV mass and measures of subclinical systolic and diastolic dysfunction, HFpEF precursors. Together, these findings support myocellular injury as a putative pathway towards adverse remodeling and LV dysfunction; however, further research is needed to define the specific mechanism(s) driving myocellular injury in INOCA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

WISE-CVD	Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction
INOCA	Ischemia and no obstructive coronary artery disease
HFpEF	Heart failure with preserved ejection fraction
u-hscTnI	Ultra-high sensitivity cardiac troponin-I
SR	Strain rate

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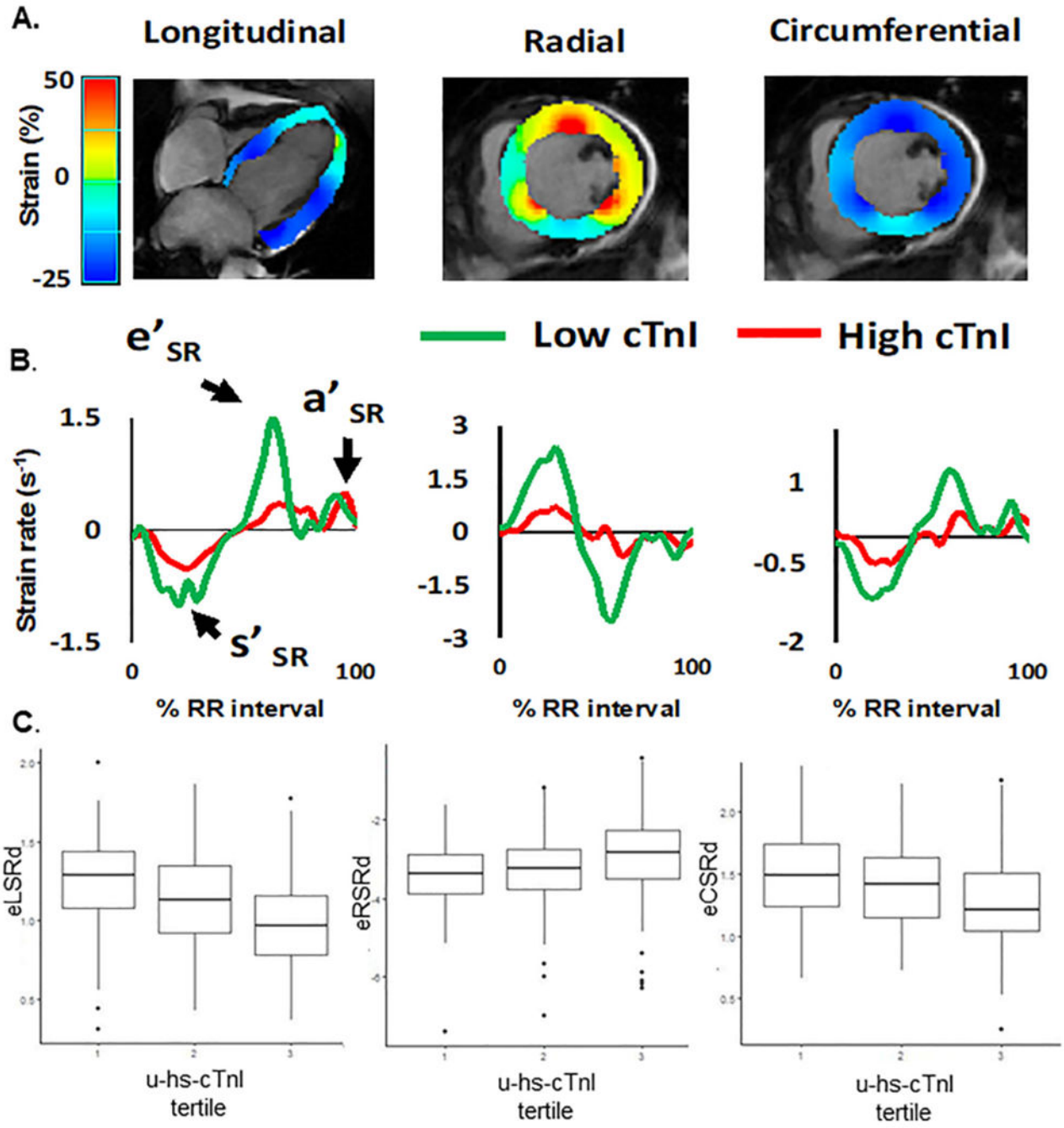

Fig. 1.

Strain rate maps and profiles. A. Longitudinal, radial and circumferential strain maps. B. Typical strain rate profiles across the cardiac cycle in a representative subject with elevated ultra-high sensitive cardiac troponin-I (u-hscTnI, red line, 5.61 pg/mL) and a representative subject with low u-hscTnI (green line, 0.13 pg/dL). Data are reported as a percentage of the cardiac cycle, beginning with systolic contraction (s'_{SR}) and progressing to early and late diastole (e'_{SR} and a'_{SR}, respectively). C. Early longitudinal diastolic strain rate (eLSRd),

early radial diastolic strain rate (eRSRd), and early circumferential diastolic strain rate (eCSRd) by tertiles of u-hscTnI concentration. Kruskal-Wallace p-value < 0.0001 for all.

Central Illustration. Summary of the relation between ultra-high sensitive cardiac troponin-I (u-hscTnI) and left ventricular strain. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

Demographics and clinical characteristics of WISE-CVD cohort at baseline visit.

Demographics & clinical characteristics	***N* = 327**
Age, y, mean ± SD	54.9 ± 10.7
Race/ethnicity, n (%)	
White/Non-Hispanic	248 (76.8%)
Hispanic/Latin	25 (7.7%)
Black/African American	21 (6.5%)
Other	29 (9%)
Hypertension, n (%)	119 (40.1%)
Diabetes mellitus, n (%)	40 (12.7%)
Dyslipidemia, n (%)	48 (18.8%)
Ever smoker, n (%)	136 (42.1%)
Post-menopausal, n (%)	237 (73.1%)
Seattle Angina Questionnaire, median (range)	
Physical limitation	67 (0–100)
Angina stability	48 (0–100)
Angina frequency	64 (0–100)
Treatment satisfaction	69 (0–100)
Disease perception/quality of life	50 (0–100)
Body mass index, kg/m^2, mean ± SD	28.3 ± 6.9
Medications, n (%)	
ACEI/ARB	79 (25.4%)
Beta Blocker	104 (33.2%)
Calcium Channel Blocker	70 (22.4%)
Diuretics	46 (14.6%)
Statin	138 (43.5%)
Nitrates	97 (30.8%)
Coronary artery severity score, median(range)	10 (3.8–22.8)
MPR1<1.84, n (%)	174 (54.6%)

Angiotensin-converting enzyme inhibitors (ACEI); Angiotensin reception blocker (ARB); myocardial perfusion reserve index (MPRI).

Table 2

Correlation between u-hscTnI concentration and hemodynamic measures, left ventricular structure and function, and myocardial perfusion.

CMRI characteristics	Median (range)	Spearman correlation u-hscTnI	*P*-value	Holm adjusted *P*-value
Hemodynamic measures				
Systolic blood pressure (mmHg)	131 (117, 144)	0.27	**<0.01**	**<0.01**
Diastolic blood pressure (mmHg)	63 (35, 111)	0.26	**<0.01**	**<0.01**
Heart rate (bpm)	68 (40, 111)	−0.1	0.09	1.0
LV structure and function				
LV end-diastolic volume index	67 (31, 109)	0.06	0.33	1.0
LV end-systolic volume index	21 (5, 63)	−0.002	0.97	1.0
LV stroke volume (mL)	81(39, 127)	0.01	0.91	1.0
Ejection fraction (%)	69 (39, 89)	0.07	0.2	1.0
LV mass index	51 (34, 88)	0.24	**<0.01**	**<0.01**
LV mass to volume ratio	0.8 (0.5, 1.6)	0.12	**0.04**	0.46
LV diastolic parameters				
PFR (mL/s)	353.3 (133.2, 641.8)	−0.15	**0.01**	0.15
PFR/EDV	2.9 (1.4, 5)	−0.23	**<0.01**	**<0.01**
Time to PFR (msec)	183.7 (79.0, 659.9)	0.08	0.14	1.0
LV strain parameters				
Early diastolic strain rate (s^{-1})				
Radial	−3.2 (−7.4, −0.4)	0.23	**<0.01**	**<0.01**
Circumferential	1.4 (0.3, 2.6)	−0.28	**<0.01**	**<0.01**
Longitudinal	1.1 (0.3, 2)	−0.37	**<0.01**	**<0.01**
Late diastolic strain rate (s^{-1})				
Radial	−0.7 (−2.0, −0.1)	−0.16	**<0.01**	0.07
Circumferential	0.6 (0, 1.3)	0.16	**<0.01**	0.07
Longitudinal	0.7 (0.1, 1.8)	0.13	**0.02**	0.28
Systolic strain rate (s^{-1})				
Radial	2.5 (1.0, 6.1)	−0.05	0.36	1.0
Circumferential	−1.1 (−2.1, −0.6)	0.05	0.37	1.0
Longitudinal	−1.0 (−1.9, −0.4)	0.04	0.43	1.0
Peak systolic strain (%)				
Radial	48.0 (19.1, 48)	0.01	0.85	1.0
Circumferential	−22.8 (−29.2, −10.7)	0.01	0.89	1.0
Longitudinal	−20.8 (−29.9, −7.7)	0.04	0.48	1.0
Myocardial Perfusion				
MPRI	1.8 (0.7, 3.3)	−0.12	**0.03**	0.40

LV, left ventricle; end-diastolic volume (EDV); peak filling rate (PFR); myocardial perfusion reserve index (MPRI).

Table 3

Association of u-hscTnI concentration with left ventricular structure and function measures, myocardial perfusion, and hypertension.

Outcome variables	Estimate*	SE	95% CI		*P*-value
LV mass index[1]	2.03	0.44	1.17	2.89	<0.01
LV strain measures[2]					
Peak systolic strain (%)					
Radial	−1.27	0.58	−2.41	−0.13	**0.03**
Circumferential	0.39	0.17	0.06	0.72	**0.02**
Longitudinal	0.02	0.19	−0.36	0.39	0.93
Systolic strain rate (s^{-1})					
Radial	−0.10	0.05	−0.19	−0.01	**0.03**
Circumferential	0.01	0.01	−0.02	0.03	0.54
Longitudinal	−0.01	0.01	−0.04	0.02	0.49
Early diastolic strain rate (s^{-1})					
Radial	0.13	0.06	0.01	0.25	**0.03**
Circumferential	−0.04	0.02	−0.08	0.002	0.06
Longitudinal	−0.03	0.02	−0.07	0.002	0.06
Late diastolic strain rate (s^{-1})					
Radial	0.01	0.02	−0.03	0.04	0.75
Circumferential	−0.005	0.01	−0.03	0.02	0.71
Longitudinal	0.01	0.02	−0.02	0.04	0.43
Myocardial perfusion reserve index[3]	−0.03	0.03	−0.09	0.03	0.39
Hypertension[4]	0.26	0.15	−0.03	0.55	0.08

*Estimate per unit increase in log (u-hscTnI).

[1]Multivariable regression model adjusted for age, BMI, hypertension.

[2]Multivariable regression model adjusted for age, BMI, hypertension, left ventricular (LV) mass index.

[3]Multivariable regression model adjusted for age, BMI, LV mass index, hypertension.

[4]Multivariable regression model adjusted for age, BMI, LV mass index.