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 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 (β = 2.03; 95% CI 1.17, 2.89; p < 0.01) and early diastolic radial strain rate (SR) (β = 0.13; 95% CI 0.01, 0.25; p = 0.03), early diastolic circumferential SR (β = 0.04; 95% CI −0.08, 0.002; p = 0.06) and early diastolic longitudinal SR (β = 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.

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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1. Introduction

Women are disproportionately 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 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.

2.2. 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 CVI52 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 included: 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/endo-cardial 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 cTnI assay were obtained at time adenosine stress CMRI prior to receiving stress agent. The u-hscTnI assay (LLOQ 0.38 pg/mL, ULOQ 15,756.55 pg/mL, LLOD 0.0046 pg/mL) was performed on the Simoa HD-1 Analyzer (Quanterix Corporation, Lexington, MA). Each cTnI kit (Tnl 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 manufacturer’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/interpretable 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, and hypertension. The model examining LV mass index as the outcome was adjusted for age, body mass index, and hypertension (Table 3). 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 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.

### 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 (%)                  | 248 (76.8%) |
| White/Non-Hispanic                     | 25 (7.7%) |
| Hispanic/Latin                         | 21 (6.5%) |
| Black/African American                  | 136 (42.1%) |
| Other                                  | 20 (9.9%) |
| Hypertension, n (%)                    | 100 (100%) |
| Diabetes mellitus, n (%)               | 100 (100%) |
| Dyslipidemia, n (%)                    | 48 (18.8%) |
| Ever smoker, n (%)                     | 20 (9.9%) |
| Post-menopausal, n (%)                 | 327 (100%) |
| Physical limitation                    | 67 (20%) |
| Angina stability                       | 60 (18%) |
| Treatment satisfaction                 | 67 (21%) |
| Age, y, mean ± SD                      | 54.9 ± 10.7 |
| Race/ethnicity, n (%)                  | 248 (76.8%) |
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| Ever smoker, n (%)                     | 20 (9.9%) |
| Post-menopausal, n (%)                 | 327 (100%) |
| Physical limitation                    | 67 (20%) |
| Angina stability                       | 60 (18%) |
| Treatment satisfaction                 | 67 (21%) |
| Disease perception/quality of life     | 50 (15%) |
| Body mass index, kg/m², mean ± SD      | 28.3 ± 6.9 |
| Medications, n (%)                     | 70 (22.4%) |
| ACEI/ARB                               | 70 (22.4%) |
| Beta Blocker                           | 104 (32.3%) |
| 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) |
| MPRI−1.84, n (%)                       | 174 (54.6%) |

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

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...
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 myocardial 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-hsTnI 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, MPRI (adjusted models) remains unclear, but may be related to differences in approach (i.e. PET vs. CMRI) and/or INOCA endotype. Indeed, MPRI (adjusted models) remains unclear, but may be related to differences in approach (i.e. PET vs. CMRI) and/or INOCA endotype. Indeed, MPRI (adjusted models) remains unclear, but may be related to differences in approach (i.e. PET vs. CMRI) and/or INOCA endotype.
similar to other reports [40, 41] Albadi 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 cTnT [43–45]. In line with this observation, we observed a significant correlation between circulating cTnT 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 cTnT 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 myocardial injury as a putative pathway towards adverse remodeling and LV dysfunction; however, further research is needed to define the specific mechanism(s) driving myocardial injury in INOCA.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2022.100115.

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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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