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Coronary atheroma burden predicts flow reserve in women with ischemia and nonobstructive coronary artery disease☆

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ABSTRACT

Background: Women with signs and symptoms of ischemia and no obstructive coronary artery disease often have coronary microvascular dysfunction (CMD) with reduced coronary flow reserve (CFR), and compensatory coronary remodeling. Angiographic measurements of epicardial coronary anatomy (AMCA) may improve understanding of relations between CFR and atherosclerosis. We investigated AMCA and CFR in women evaluated for CMD.

Methods: Women consecutively enrolled in the Women's Ischemia Syndrome Evaluation CVD Continuation (NCT00832702) were included. All underwent clinically indicated coronary function testing measuring CFR. AMCA included coronary angiographic atheroma burden (AB), percent diameter stenosis (PDS), and tapering reference diameter Z score (RDZ), derived for the left main and left anterior descending coronary epicardial segments.

Results: The 51 women were aged 55.8 ± 10.8 years, with 19(38%) hypertensive, 10(20.4%) hyperlipidemic, 4 (7.8%) diabetic, 13(25.5%) prior smokers, and mean CFR 3.0 ± 0.8. Both average and maximal AB negatively correlated with CFR ($r = -0.30$ and -0.31, with $p = 0.04$ for both), as did average and maximal PDS ($r = -0.38$ and -0.41 with $p = 0.009$ and $p = 0.005$) while average RDZ was directly related ($r = 0.37$, $p = 0.01$). Multiple linear regression analyses revealed that both average PDS (Units of CFR −0.03 95% CI: −0.06, −0.002, $p = 0.023$) and maximal PDS (−0.04 95% CI −0.07, −0.01, $p = 0.007$) were negatively related to CFR.

Conclusions: Measures of epicardial coronary atheroma burden, size and tapering are related to CFR, suggesting that atherosclerotic anatomical findings may contribute to or be a consequence of CMD, with further work is needed to investigate these measures as treatment targets.

Abbreviations: CMD, coronary microvascular dysfunction; CFR, coronary flow reserve; AMCA, epicardial coronary anatomy; AB, atheroma burden; PDS, percent diameter stenosis; RDZ, reference diameter Z score; INOCA, ischemia and no coronary artery disease; CSS, coronary severity score; MACE, major adverse cardiovascular events; IVUS, intra-vascular ultrasound.

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1. Introduction

Women with signs and symptoms of ischemia and no evidence of obstructive coronary artery disease (INOCA) have an increased risk of major adverse cardiovascular events (MACE) [1], related to the presence of coronary microvascular dysfunction (CMD) on invasive coronary function testing [2] and non-obstructive epicardial atherosclerosis on coronary angiography [3]. We have previously demonstrated that coronary severity score (CSS), a measure of epicardial atherosclerotic extent and severity, predicts MACE in this population [3]. Furthermore, we have demonstrated that coronary intra-vascular ultrasound (IVUS) measured atheroma burden is related to compensatory remodeling [4], with a recent report suggested an association between invasive coronary evidence of CMD and plaque burden detected by IVUS [5]. Given existing knowledge of atherosclerotic plaque, understanding relations between epicardial plaque burden and CMD may identify treatment targets for this population.

Angiographic measurements of coronary anatomy (AMCA) for atheroma burden and tapering are developed and validated using IVUS [6,7]. Derived from pooled population-based studies examining coronary artery dimensions [6,8,9], AMCA are sensitive in detecting anomalies in coronary angiograms that are seemingly normal on visual assessment [10]. Whether these anatomical findings in epicardial coronary arteries are related to CMD in women is unknown, and measurement of AMCA may be useful for potentially considering epicardial atherosclerosis as a treatment target for CMD. We sought to characterize AMCA atheroma burden, size and tapering in women with suspected INOCA relative to invasively determined coronary flow reserve (CFR).

2. Methods

2.1. Study design

A consecutive subgroup of women 18 years or older with suspected INOCA undergoing clinically indicated coronary function testing were included in the ongoing Women's Ischemia Syndrome Evaluation – CVD Continuation Study (NCT02582021) between November 1, 2015 and September 1, 2017. Data is available from the corresponding author upon reasonable request. Baseline data collected included age, body mass index (BMI), cardiovascular risk factors, functional capacity as assessed by the Duke Activity Status Index [11] (DASI) and symptom severity assessed using the Seattle Angina Questionnaire (SAQ) [12]. Exclusion criteria included the presence of obstructive coronary artery disease (CAD) (≥50% stenosis), acute coronary syndrome within the last 3 months, chest pain due to a non-ischemic etiology, need for valve repair or replacement, patients with cardiogenic shock, left ventricular ejection fraction (LVEF) <50%, previous percutaneous coronary intervention or coronary artery bypass grafting, end-stage renal or liver disease, life expectancy < four years, or inability to give informed consent. Women with clinically diagnosed Takostubo syndrome or myocarditis upon review of clinical data were also excluded. All study participants gave written informed consent before undergoing coronary reactivity testing. The study received full approval by the local institutional review board.

2.2. Coronary function testing

Coronary function testing was performed to assess coronary microvascular function using a previously published protocol [13]. Left-ventricular end-diastolic pressure (LVEDP) was measured at the beginning of each procedure. A Doppler flow wire was placed in the left anterior descending (LAD) artery to measure coronary blood flow velocities. Coronary flow reserve (CFR) (Normal>2.32 [2]) in response to intracoronary (IC) adenosine was calculated as the average peak velocity at maximal hyperemia (best CFR obtained following bolus IC adenosine 18 μg, 18 μg and 100 μg, respectively) divided by the average peak velocity at baseline using the Volcano Combomap® Software (Version 1.0). All angiograms and pulsed-wave Doppler flow spectra recordings were analyzed by a core laboratory masked to clinical data (University of Florida, Gainesville) and included measurement of CSS, a previously validated score in this population reflecting extent and severity of atherosclerosis [3].

2.3. Angiographic measurements of coronary anatomy (AMCA)

A separate core laboratory (University of British Columbia, Vancouver), masked to clinical data, measured AMCA as previously published [10]. Measurements were performed using QCA after calibration to catheter size. For each coronary arterial segment, anatomically defined using the Coronary Artery Surgery Study [6], AMCA were derived using the segment proximal diameter, reference diameter, minimal diameter, distal diameter and compared to population-referenced normal reference diameter for the coronary artery segment being analyzed (Fig. 1) [7]. Angiographic atheroma burden index represents the level of focal stenosis in relation to a population-referenced normal reference diameter (abnormal > ±2 standard deviations [SD]). Percent diameter stenosis represents the level of focal stenosis in relation to the segment reference diameter (abnormal lower confidence interval

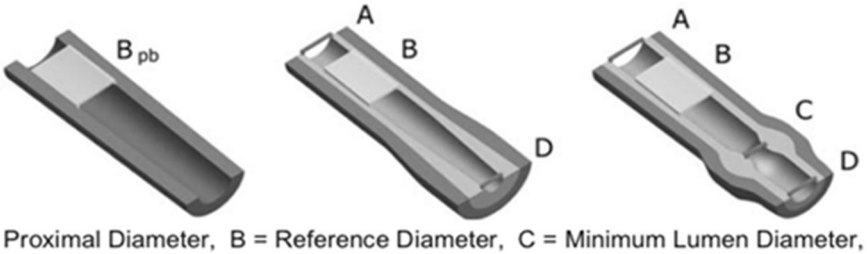

Fig. 1. Schematic representation of a coronary artery segment and calculation of angiographic measurements of coronary anatomy (AMCA).
Pending copyright permission. Mancini GBJ, Ryomoto, A., Kamimura, C., Yeoh, E., Ramanathan, K., Schulzer, M., Hamburger, J., Ricci, D. Redefining the normal angiogram using population-derived ranges for coronary size and shape: validation using intravascular ultrasound and applications in diverse patient cohorts. Int J Cardiovasc Imaging 2007;23:441–53.

Atheroma Burden (AB) = $(B_{pb} - C)/SD\ B_{pb}$

Percent Diameter Stenosis (PDS) = $[1 - (C/B)] \times 100$

Reference Diameter Z-score (RDZ) = $(B - B_{pb})/SD\ B_{pb}$

Antegrade Tapering (AT) = $[1 - (D/B)] \times 100$

Retrograde Tapering (RT) = $[1 - (A/B)] \times 100$

[C.I.] > 30%). Reference diameter Z score compares the reference diameter in the segment in relation to the population-referenced diameter for the segment of the coronary artery being measured (abnormal > ±2 SD). AMCA evaluating coronary artery tapering, the progressive narrowing and thinning of coronary arteries from their origin to their distal extremity, included Antegrade Tapering (AT) and Retrograde Tapering (RT), which were compared to population- referenced AT (AT_{pb}) and RT (RT_{pb}), yielding an Antegrade Tapering Z Score ($ATZ = [AT - AT_{pb}] / SD\ AT_{pb}$) (abnormal > ±2 SD), which evaluates distal tapering with regards to the more proximal artery diameter in a given coronary artery segment, and a Retrograde Tapering Z Score ($RTZ = [RT - RT_{pb}] / SD\ RT_{pb}$) (abnormal > ±2 SD), which assesses proximal tapering with respect to a more distal artery diameter in a given segment (Fig. 1). An average measurement of each AMCA of the left main, proximal, middle and distal LAD was calculated. Absolute averages were used for antegrade tapering and retrograde tapering z-score. Absolute maximal values of antegrade tapering and retrograde tapering z-score, representing greatest abnormal remodeling, were also calculated. Maximal measurements of atheroma burden index and percent diameter stenosis, representing highest burden of atheroma and greatest focal stenosis, and minimal reference diameter z-score, indicative of smaller angiographic reference diameter, possibly due to atherosclerosis and remodeling, were also derived for these same segments.

2.4. Statistical analysis

Continuous variables are presented as mean ± SD and categorical variables as counts and percentages. To assess for correlation between AMCA variables and measures of CMD and functional capacity, Pearson correlation coefficient tests were performed. Assessment for confounding in the association between AMCA and CFR was performed using multiple linear regression to adjust for age, history of hypertension, history of dyslipidemia, smoking history, diabetes, and CSS. Sensitivity and specificity analysis and ROC analysis were used to evaluate whether AMCA could discriminate between women with CFR above and below CFR = 2.32. This CFR threshold was selected as it has been previously associated to adverse outcomes in women with signs and symptoms of ischemia and no obstructive CAD [2]. A significance level = 0.05 was used. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC), and R version 3.5, (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Clinical characteristics and AMCA

Baseline characteristics of the 51 women are presented in Table 1 which demonstrates a cohort of predominantly mid-life women often with multiple cardiovascular risk factors. Women included in the study had relatively minimal atherosclerosis as measured by CSS, which ranged from 5 to 15 and was higher than 5 in only 3 (6%), consistent with the absence of obstructive CAD. Average CFR was 3.0 (±0.8) and was considered abnormal in 9 (19.2%) women. We found a trend for negative weak correlation between higher CSS and lower CFR ($r = -0.28$, $p = 0.059$). Some AMCA measurements directly correlated with CSS (Maximal absolute antegrade tapering z-score $r = 0.29$, $p = 0.04$; maximal absolute retrograde tapering z-score $r = 0.33$, $p = 0.02$).

The AMCA variables are presented in Table 2. When compared to reference control values for population-referenced AMCA [7], the group mean values of atheroma burden index were within reference control range, however maximal atheroma burden index values were higher than population-referenced control values. Group mean percent diameter stenosis was within the reference control range, and maximal percent diameter stenosis values were higher (more adverse) than population-referenced control values. The group mean reference diameter z-score was similar to population-referenced control values, as were mean antegrade tapering z-score and absolute maximal antegrade tapering z-score, however maximal retrograde tapering z-score was higher (more adverse) than expected population-referenced values.

Table 1
Baseline characteristics of women with suspected INOCA undergoing coronary reactivity testing ($n = 51$).

Age (years)	55.8 (±10.8)
Hypertension	19 (38.0%)
Hyperlipidemia	10 (20.4%)
Diabetes	4 (7.8%)
History of smoking	11 (21.6%)
Family history of premature CAD	27 (52.9%)
BMI (kg/m^2)	30.9 (±8.9)
DASI-estimated METS	7.6 (±6.3)
LVEDP (mmHg)	11.3 (±5.7)
CFR	3.0 (±0.81)
CFR < 2.32	9 (19.2%)
Coronary severity score	5.3 (±1.5)

Data is presented as mean (±SD) or n (%) CAD = coronary artery disease, BMI = body mass index, DASI = Duke Activity Status Index, METS = metabolic equivalents, LVEDP = left ventricular end-diastolic pressure, CFR = coronary flow reserve.

Table 2
Population-referenced angiographic measurements of coronary anatomy (AMCA) in women undergoing coronary reactivity testing (n = 51).

AMCA (n = 51)	Mean (±SD)	Expected values [7] (% or SD)
Average AB (SD)	1.43 (±0.50)	±2
Maximal AB (SD)	**2.14 (±0.55)**	±2
Average PDS (%)	24.39 (±8.79)	<30%
Maximal PDS (%)	**37.44 (±9.80)**	<30%
Average RDZ (SD)	−0.17 (±0.97)	±2
Minimal RDZ (SD)	−0.94 (±1.71)	±2
Average ATZ (SD)	0.20 (±0.47)	±2
Absolute maximal ATZ (SD)	1.53 (±0.80)	±2
Average RTZ (SD)	0.99 (±2.29)	±2
Absolute maximal RTZ (SD)	**6.87 (±4.65)**	±2

AMCA = angiographic measurements of coronary anatomy, AB = atheroma burden index, SD = standard deviation, PDS = percent diameter stenosis, RDZ = reference diameter z-score, ATZ = antegrade tapering z-score, RTZ = retrograde tapering z-score.
Bold = AMCA in study population that were different from expected values.

3.2. AMCA relations to CMD

Both the group mean and maximal atheroma burden index showed a weak inverse correlation with CFR ($r = -0.30$ and -0.31, $p = 0.040$ for both, respectively), as did average and maximal percent diameter stenosis ($r = -0.38$, $p = 0.009$ and -0.41, $p = 0.005$, respectively). Average reference diameter z-score also correlated inversely with CFR ($r = -0.37$, $p = 0.010$) (Fig. 2), however average and absolute maximal antegrade tapering z-score nor retrograde tapering z-score did not (data not shown). Both mean and maximal atheroma burden index and percent diameter stenosis were fair discriminators in identifying women with CFR ≤ 2.32. Other AMCA were poor discriminators with regards to this CFR threshold (Fig. 3).

Multiple linear regression models evaluating the AMCA variables for the association with CFR after adjustment for hypertension, diabetes, dyslipidemia, smoking and CSS identified an independent negative association between both average percent diameter stenosis and maximal percent diameter stenosis with CFR, and a positive association between average reference diameter z-score and CFR (Table 3). There was no significant difference in AMCA according to reported statin use at baseline ($p > 0.10$ for all, data not shown). Average atheroma burden

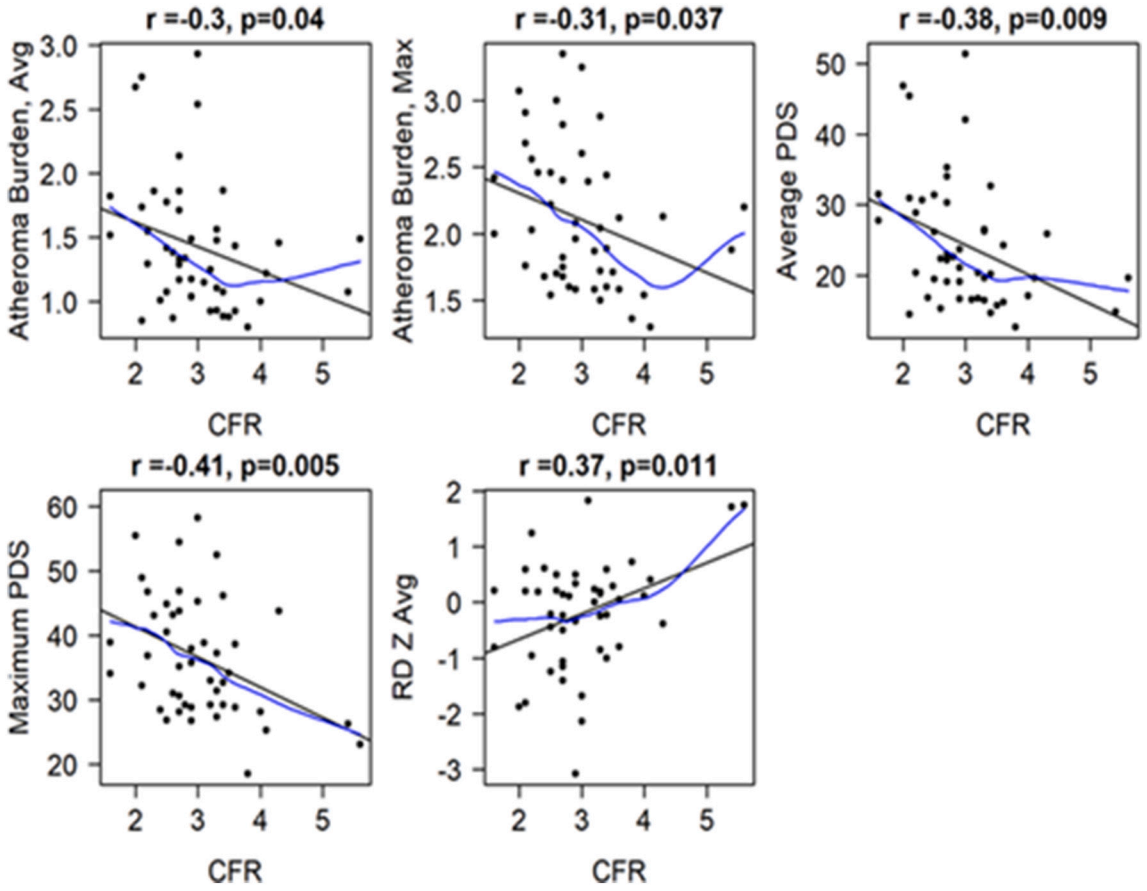

Fig. 2. Correlations between AMCA and CFR.
Abbreviations: PDS = percent diameter stenosis, RDZ = reference diameter z-score, CFR = coronary flow reserve black line is a linear regression and blue line is a LOESS smoother.

index, maximal atheroma burden index, minimal reference diameter z-score, average and maximal absolute antegrade tapering z-score, average and maximal absolute retrograde tapering z-score were not independently associated with CFR.

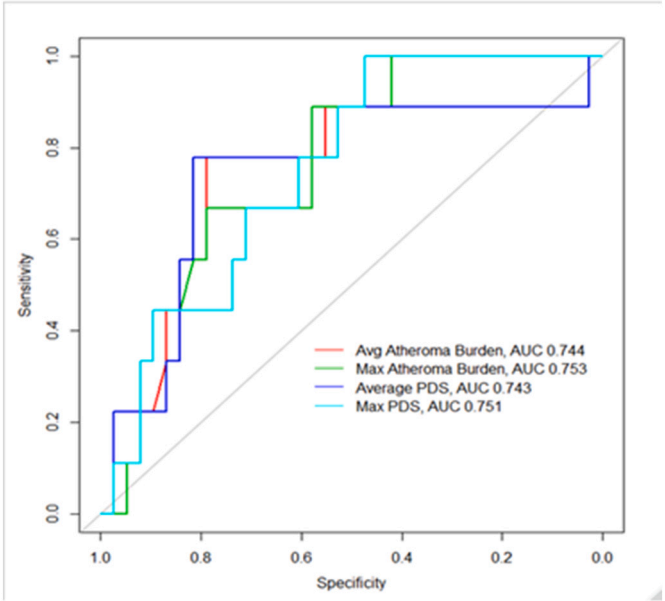

Fig. 3. Area-under-the-curve analysis for AMCA diagnosis of CFR < 2.32.

3.3. AMCA relations to functional status

We have previously demonstrated that lower CFR is related to lower functional capacity in women with suspected CMD [14]. To examine the clinical relevance of the AMCA measures, we evaluated relations to the DASI-estimated functional capacity. Both average and maximal atheroma burden index demonstrated moderate negative correlations

Table 3
Multiple linear regression analysis of AMCA for prediction of coronary flow reserve.

AMCA	Estimates from adjusted model (units of CFR) (95% CI)	*p*-Value from adjusted model[a]
Average AB	−0.45 (−0.96, 0.06)	0.087
Maximal AB	−0.41 (−0.91, 0.09)	0.112
Average PDS	−0.03 (−0.06, −0.002)	**0.023**
Maximal PDS	−0.04 (−0.07, −0.01)	**0.007**
Average RDZ	0.27 (0.02, 0.52)	**0.047**
Minimal RDZ	0.07 (−0.07, 0.21)	0.322
Average ATZ	−0.17 (−0.74, 0.40)	0.559
Absolute maximal ATZ	−0.08 (−0.45, 0.29)	0.671
Average RTZ	−0.009 (−0.13, 0.11)	0.886
Absolute maximal RTZ	0.03 (−0.03, 0.09)	0.298

AMCA = angiographic measurements of coronary anatomy, AB = atheroma burden index, SD = standard deviation, PDS = percent diameter stenosis, RDZ = reference diameter z-score, ATZ = antegrade tapering z-score, RTZ = retrograde tapering z-score.
Bold = $p < 0.05$.
[a] Adjusted for hypertension, dyslipidemia, history of smoking, diabetes, CCS.

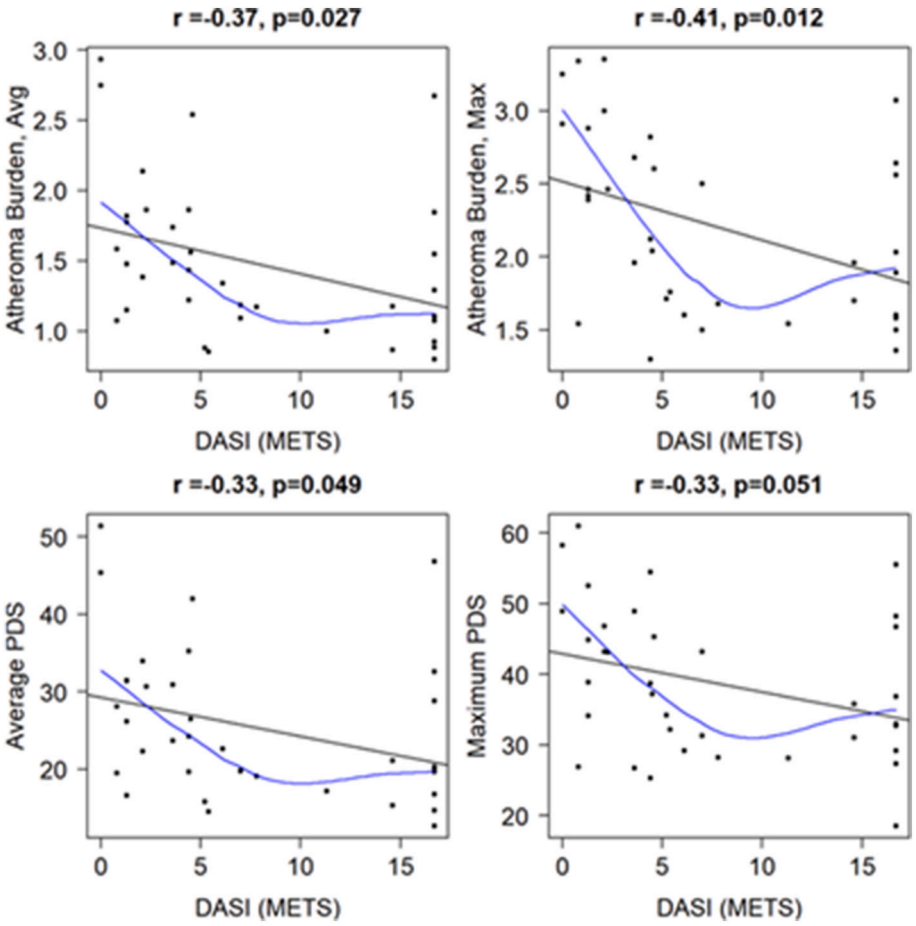

Fig. 4. Correlation between DASI-estimated functional capacity and AMCA.
Abbreviations: AB = atheroma burden index, PDS = percent diameter stenosis, DASI = Duke Activity Status Index, METS = metabolic equivalents.

($r = -0.37$, $p = 0.027$ and -0.41, $p = 0.01$, respectively) with DASI-estimated functional capacity, as was average percent diameter stenosis ($r = -0.33$, $p = 0.049$) and maximal percent diameter stenosis ($r = -0.33$, $p = 0.051$) (Fig. 4). AMCA did not correlate with SAQ scores (not shown).

4. Discussion

Our results demonstrate consistent and multiple relationships between epicardial coronary angiographic measures of atheroma burden, size and tapering with coronary microvascular function, indicative of CMD in women with signs and symptoms of ischemia but no obstructive CAD. Several AMCA variables weakly correlated with lower CFR. Percent diameter stenosis, which represents the level of focal stenosis in the coronary artery, and atheroma burden index and reference diameter z-score, which both assess focal stenosis in relation to population-referenced normal reference diameter, were the AMCA that correlated with CFR, independent of traditional cardiovascular risk factors and plaque burden score. We further found that atheroma burden index and percent diameter stenosis associated with lower CFR are clinically relevant as they relate to worse functional capacity in this population.

Evaluation of coronary atheroma burden, size and tapering using population-referenced AMCA, which correlate with CFR, allow for the detection of clinically relevant non-obstructive coronary atherosclerosis in women without obvious atherosclerotic plaque [6,7]. In the presence of non-focal atherosclerosis, it may be difficult to appreciate whether overall and reference diameters are normal without comparing these to truly normal subjects, or considering the degree of segmental tapering. Previous reports indicate that 73% of women exhibit positive remodeling due to atherosclerosis detectable by IVUS [4], suggesting that coronary atherosclerosis is often missed on conventional angiograms. We have demonstrated previously that a CSS which considers extent and severity of atheroma is of importance in identifying women at increased risk of adverse outcomes [3], suggesting that the MACE observed in this population may be in part related to consequences of epicardial atherosclerosis, such as plaque rupture and acute myocardial infarction. Women in our current cohort, however, had overall low angiographic severity scores [3], and risk stratification using this score in this context may therefore be limited. AMCA, including average percent diameter stenosis, maximal percent diameter stenosis and average reference diameter z-score, which detect the level of focal stenosis in relation to the segment reference diameter and expected population-referenced diameter were associated with lower CFR as evidence of CMD, independent of traditional risk factors and atherosclerosis scores. AMCA may therefore represent a novel method to further discriminate disease phenotype women undergoing invasive coronary angiography for suspected ischemia but without obvious atherosclerotic plaque. Anatomical findings such as AMCA can be evaluated offline after conventional coronary angiography and may represent a feasible surrogate marker of CMD and related risk in women.

Appropriate diagnosis of CMD in the setting of non-obstructive CAD is important due to the elevated risk of adverse events, including myocardial infarction and death, and is facilitated by invasive evidence of CMD, specifically CFR [2,15,16]. Furthermore, lower functional capacity, including when measured using standardized self-administered questionnaires such as DASI, have also been associated with poor outcomes in women [17]. We observed associations between abnormal AMCA and lower DASI-measured functional capacity, further supporting

that these anatomical findings are of clinical relevance and may be prognostically useful. CFR is of particular prognostic importance in the setting of no obstructive CAD, as a CFR < 2.32 was an independent predictor of adverse events including cardiovascular death, myocardial infarction and hospitalization for heart failure in this population at 5 year follow-up [2].

In the current analyses, individual AMCA (atheroma burden index, percent diameter stenosis) as well as combined AMCA, were fair discriminators in identifying women with CFR ≤ 2.32, suggesting that evidence of abnormalities in coronary shape and size may be involved in the development of or at least related to CMD. Traditional cardiovascular risk factors contribute to epicardial atherosclerosis, and are also associated with CMD as measured by CFR, suggesting potential commonality in disease pathways [18]. Anatomic findings on IVUS such as cross-sectional lumen area, and coronary atherosclerotic lesion length, have previously been correlated with CFR in the setting of intermediate coronary artery disease [19]. AlBadri et al. recently reported an association between abnormal hyperemic microvascular resistance, an invasive measure of coronary microvascular function, and plaque burden, as detected by IVUS in 77 patients with angina and no obstructive coronary artery disease [5]. Khuddus et al. found a high degree of atherosclerotic plaque, as shown using IVUS, in a majority women with no obstructive CAD [20], a population in whom CMD is often diagnosed. Nicholls et al. reported that women exhibit different patterns of remodeling, as assessed using IVUS, according to the presence or absence of obstructive CAD, suggesting distinct patterns of atherosclerotic disease. It is possible that epicardial coronary artery remodeling is a result of underlying CMD, which has been identified as a potential precursor of CAD because of its association to adverse cardiac events [21,22]. Alternately, non-obstructive atherosclerotic plaque and remodeling may lead to chronic inflammation and subsequent dysfunction of the microvasculature, as has been previously observed in patients with chronic multisystemic inflammatory disease [23,24]. Existing atherosclerotic plaque may be responsible for embolization of microscopic cholesterol crystals and microspheres downstream into the microvasculature, potentially causing endothelial dysfunction, capillary obstruction, and abnormal vasoreactivity, with subsequent coronary microvascular dysfunction [25,26]. Association of AMCA with low CFR values of previously established prognostic significance adds to the growing body of evidence of an association between CMD and coronary atherosclerosis.

Previous studies have demonstrated that women with CMD as assessed by low CFR may benefit from statin therapy, including fluvastatin and atorvastatin, which improves CFR over time [27–29]. Statin therapy favours atherosclerotic plaque stabilisation, has anti-angiogenic and anti-inflammatory properties and may reduce endothelial dysfunction [29]. Identifying women with abnormal AMCA may help identify women who have occult atherosclerotic disease, and whom therefore may derive benefit from existing therapies.

4.1. Strengths and limitations

Interpretation of these findings are limited by the relatively small sample size included in the analysis, however deployment of these rigorous core lab measurements in this novel population is innovative. Although only 19% of women found to have CFR < 2.32, CFR measured in a single vessel alone likely underestimates the prevalence of coronary microvascular dysfunction and although this does represent a limitation with regards to statistical sample size and associations, our findings potentially underestimate the association. Although our results indicate that these features discriminate low CFR, we acknowledge that our models have relatively poor calibration because of our limited sample size and further studies with larger sample sizes to develop an adequate predictive model are needed. Although AMCA are derived from population-based reference control coronary artery dimensions, the performance of AMCA measurements was conducted by one central core laboratory who also developed this specific measurement technique, and adequate derivation of these measurements by other operators in other centers remains to be validated. Our exclusive focus on women precludes potential relevance to men. Long-term follow-up data for this patient population was not available, limiting findings in relation to overall prognosis.

5. Conclusions

Measures of coronary atheroma burden, size and tapering in women with suspected INOCA undergoing evaluation for CMD with no obstructive coronary artery disease by conventional methods are related to CFR, a strong prognostic predictor of major adverse cardiac events in this population. Anatomical abnormalities in coronary artery shape and size measured in conventional invasive coronary angiography may be a useful predictor of CMD. These findings add to the evidence that anatomical findings appear to be related to CFR, and that feasible evaluation of invasive coronary angiography may be useful for detection of microvascular dysfunction. Further work is needed to investigate epicardial atherosclerosis as a treatment target for CMD.

Declaration of competing interest

Dr. Pacheco has received honoraria from Pfizer and Novartis, and consulting fees from KYE pharmaceuticals. Dr. Bairey Merz reports personal fees from iRhythm, other from Sanofi, other from Abbott Diagnostics, during the conduct of the study. Dr. Pepine reports grants from NIH/NHLBI, during the conduct of the study; grants from NIH/NCATS, grants from BioCardia BC-14-001-02; Mesoblast, Inc. MSB-MPC-CHF001; Ventrix, Inc.; Athersys Inc. AMI MultiStem; Verily Life Sciences LLC-Project Baseline OSMB; Ironwood MSB-MPC-CHF00 DMC, Imbria Pharmaceuticals Inc.; Milestone Pharmaceuticals Inc.; Caladrius Biosciences, Inc.; Gatorade Trust; and McJunkin Family Foundation, outside the submitted work.

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