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Research paper

Coronary lumen volume to myocardial mass ratio in primary microvascular angina

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ABSTRACT

Background: Microvascular angina (MVA) is an incompletely understood clinical entity. Computational analysis of coronary Computed Tomography Angiography (CTA) has shown an association between low coronary lumen volume to myocardial mass (V/M) ratio and lower Fractional Flow Reserve values, independent of plaque measures. We hypothesized that low V/M ratio may be present in patients with MVA.

Methods: A retrospective case-control analysis was performed using patients fulfilling guideline criteria for MVA with controls matched for age, gender, coronary risk factors and atherosclerotic plaque burden. V/M was extracted off site (Heartflow Inc; Redwood City, CA) employing allometric scaling laws that allow the definition of the coronary circulation beyond the epicardium. FFR_{CT} values were calculated in the major epicardial coronary arteries for each group.

Results: A total of 30 patients with MVA and 32 matched controls were included in the study. Mean total coronary lumen volume (2302 mm^3 ± 109 vs 2978 mm^3 ± 134, $p < 0.001$) and mean myocardial mass (90.4 g ± 13.7 vs 100.4 g ± 20.1, $p = 0.029$) were lower in MVA patients compared to controls. Mean V/M ratio was significantly lower in MVA compared to controls (25.6 mm^3/g ± 5.9 vs 30.0 mm^3/g ± 6.5, $p = 0.007$; c-statistic 0.69). V/M ratio did not differ significantly between subclasses of angina severity ($p = 0.747$). No difference in mean nadir FFR_{CT} values was found between MVA and control groups in the LAD (0.86 ± 0.07 vs 0.83 ± 0.07, $p = 0.154$), LCX (0.90 ± 0.05 vs 0.90 ± 0.06, $p = 0.240$) and RCA (0.90 ± 0.04 vs 0.90 ± 0.03, $p = 0.773$) vessels.

Conclusion: Patients with microvascular angina demonstrate a significantly lower coronary CTA-derived coronary volume/myocardial mass ratio than asymptomatic controls.

1. Introduction

Coronary microvascular dysfunction (CMD) is a complex and incompletely understood manifestation of coronary artery disease (CAD). CMD is believed to play an important etiological role in the pathogenesis of myocardial ischemia in the condition known as microvascular angina (MVA) or 'cardiac syndrome X'.[1,2] MVA can occur either independently or in association with other myocardial diseases (primary versus secondary MVA respectively) and is linked to adverse clinical outcomes and increased health expenditure.[3,4]

Diagnosis of primary MVA, as per the 2013 European Society of Cardiology Task Force guidelines, is one of exclusion, wherein

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patients present with typical ischemic chest pain and abnormalities on functional ischemia testing in the absence of fixed or dynamic obstruction of the epicardial coronary arteries on angiography.[2] While the precise mechanisms of chest pain in MVA remain controversial, primary dysfunction of the small coronary arteries (<500 μm in diameter) with impaired coronary flow reserve (CFR) is believed to represent the underlying pathophysiological basis and speaks to an unmet need to investigate novel means of evaluating coronary flow in MVA.[1,5–9]

Notably, the recently reported NXT trial analysis (*HeartFlow analysis of coronary blood flow using CCTA: **NeXt** s**Teps***) proposed the coronary luminal volume to myocardial mass (V/M) ratio as a new coronary CTA-derived quantitative metric of potential imbalance between coronary blood supply and myocardial demand.[10] In this analysis, low V/M ratios were an independent predictor of ischemia and were identified in patients with non-obstructive CAD (stenosis ≤50%) demonstrating vessel-specific ischemia measured by invasive fractional flow reserve (FFR ≤0.80). Based on this observation, we hypothesized that symptomatic patients with MVA may have a lower V/M ratio compared with asymptomatic controls of similar age, sex, baseline risk, and extent of CAD on coronary CTA.

2. Methods

2.1. Study design and population

A retrospective case-control cohort analysis was conducted with approval from the research ethics board at the University of British Columbia under protocol number H16-02460. A MVA cohort of 30 patients was obtained from a single-tertiary referral centre fulfilling guideline criteria for the diagnosis of primary MVA.[2] All MVA patients underwent a coronary CTA examination between June 2010 and October 2016 as part of their routine clinical evaluation to exclude obstructive epicardial CAD after manifesting with typical angina and positive functional ischemia testing (using either exercise treadmill EKG stress testing or stress adenosine perfusion Cardiac MRI). The control cohort was comprised of 32 patients who were asymptomatic from a cardiorespiratory perspective and underwent a coronary CTA examination between October 2015 and December 2016 for the purpose of risk stratification and to guide the intensity of cardiovascular risk factor modification. Control patients were selected to match the MVA cohort in terms of age, sex, BMI, participation in regular exercise defined as at least 20 min three times a week, cardiovascular risk factors and atherosclerotic burden including number of affected plaque segments and absence of adverse plaque characteristics.

2.2. Coronary CTA acquisition

All coronary CTA examinations were performed on CT scanners with ≥64 detector rows and in accordance with optimal Society of Cardiovascular Computed Tomography (SCCT) acquisition guidelines.[11] Patient preparation included administration of oral and/or intravenous β-adrenergic receptor blocker as needed to achieve a target pre-acquisition heart rate of <60 beats per minute. Sublingual nitroglycerin at a dose of at least 0.4 mg by spray was administered to all patients prior to acquisition.

2.3. Coronary CTA plaque analysis

Interpretation of coronary CTA exams was performed in accordance with current SCCT guidelines.[12] The segment involvement score (SIS) was used in all patients to quantify the overall burden of coronary artery plaque. SIS was calculated by summation of the absolute number of coronary artery segments with plaque, irrespective of the degree of luminal stenosis within each segment (scores from 0 to 16). Stenosis severity was visually assessed within each segment as either 0%, 1–24% or 24–49% based on the guideline definition of MVA with the exclusion of obstructive CAD at the 50% threshold. Adverse plaque characteristics were evaluated and included positive remodelling, low attenuation and spotty calcification.[13]

2.4. Coronary artery lumen volume-to-myocardial mass (V/M) ratio and FFR_{CT} calculation

Coronary CTA datasets were sent to HeartFlow (HeartFlow Inc., Redwood City, CA, USA), an external entity that performed FFR-CT and V/M analysis, as described below, in an independent and blinded matter as no information on the patient cohort or coronary CTA was provided. For calculation of V/M, methods recently described were used[10]; Briefly, specialised segmentation methods were used to derive three-dimensional patient-specific anatomic models of the epicardial coronary arteries from the coronary CTA datasets provided (Fig. 1). Branches off the main epicardial coronary arteries identified in the coronary CTA dataset down to a diameter of approximately 1 mm were included by means of allometric scaling laws to determine total arterial lumen volume. The volume of the myocardium extracted from the image data was multiplied by an average value of myocardial tissue density (1.05 g/ml) to calculate the total myocardial mass. Finally, to adjust for variation in the quantity of subtended myocardium, the ratio of the vessel volume to myocardial mass (volume-to-mass or V/M ratio) was calculated by dividing the total luminal volume of the epicardial coronary arterial tree by the total myocardial mass.

Nadir FFR_{CT} values, defined as the lowest FFR_{CT} value within a vessel of interest, were determined for each patient in the major epicardial vessels (LAD, LCX, RCA) with FFR_{CT} computation conducted at HeartFlow in an independent and blinded manner as previously described.[14,15] Briefly, 3D modeling of each patient's aortic root and epicardial arteries was completed from each coronary CTA in early diastole using semi-automated segmentation.

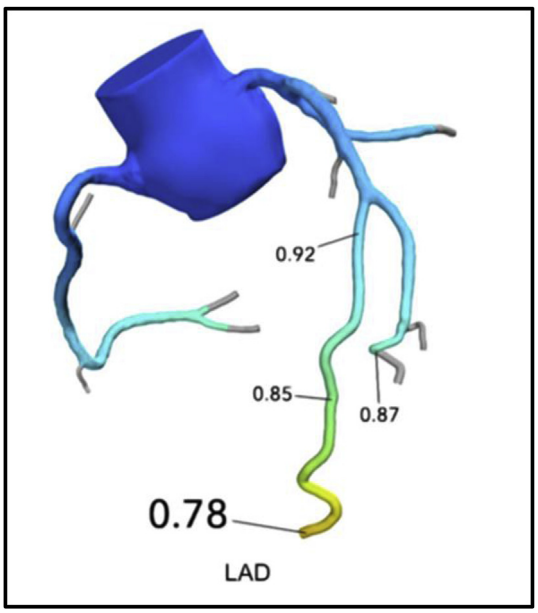

Fig. 1. Modeling of coronary arteries. Three-dimensional patient-specific anatomic model of the epicardial coronary arteries derived from coronary CTA data utilised for derivation of coronary lumen volume and myocardial mass. Numerical FFR_{CT} values are pinpointed along the length of the LAD.

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