

Manuscript Details

Manuscript number	IJC_2017_628
Title	Myocardial Blood Flow Reserve Is Impaired In Patients With Aortic Valve Calcification And Unobstructed Epicardial Coronary Arteries
Article type	Original clinical research study

Abstract

Background: Although calcific aortic valve disease (CAVD) is associated with coronary atherosclerosis, it is not known whether early CAVD is associated with coronary microcirculatory dysfunction (CMD). We sought to investigate the relationship between myocardial blood flow reserve (MBFR) - a measure of CMD, and early CAVD. We also determined whether this relationship was independent of coronary artery disease (CAD) and hs-CRP, a marker of systemic inflammation. Methods: 183 patients with chest pain and unobstructed coronary arteries were studied. Aortic valve calcification score (AVCS), coronary total plaque length (TPL), and coronary calcium score were quantified from multislice CT. MBFR was assessed using vasodilator myocardial contrast echocardiography. Hs-CRP was measured from venous blood using a particle-enhanced immunoassay. Results: Mean(\pm SD) participant age was 59.8(9.6) years. Mean AVCS was 68(258) AU, TPL was 15.6(22.2) mm, and median coronary calcification score was 43.5AU. Mean MBFR was 2.20(0.52). Mean hs-CRP was 2.52(3.86) mg/L. Multivariable linear regression modelling incorporating demographics, coronary plaque characteristics, MBFR, and inflammatory markers, demonstrated that age ($\beta=0.05$, 95%CI:0.02,0.08, $P=0.007$), hs-CRP ($\beta=0.09$, CI:0.02,0.16, $P=0.010$) and diabetes ($\beta=1.03$, CI:0.08,1.98, $P=0.033$), were positively associated with AVCS. MBFR ($\beta=-0.87$, CI:-1.44,-0.30, $P=0.003$), BMI ($\beta=-0.11$, CI:-0.21,-0.01, $P=0.033$), and LDL ($\beta=-0.32$, CI:-0.61,-0.03, $P=0.029$) were negatively associated with AVCS. TPL and coronary calcium score were not independently associated with AVCS when included in the regression model. Conclusion: Coronary microvascular function as determined by measurement of myocardial blood flow reserve is an independent predictor of early CAVD. This effect is independent of the presence of coronary artery disease and also systemic inflammation.

Keywords	Aortic valve calcification score; coronary microvascular dysfunction; calcific aortic valve disease
Taxonomy	Coronary Microvascular Dysfunction, Aortic Valve Disease
Manuscript category	Original clinical research studies, basic science/translational research papers
Manuscript region of origin	Asia Pacific
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Suggested reviewers	Dhrubo Rahkit, Benoy Shah

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Prof Paolo Camici,
Editor-in-Chief,
International Journal of Cardiology,

5th February 2017

Editorial Board, International Journal of Cardiology

Dear Professor Camici,

I am writing to submit our original article entitled, “Myocardial Blood Flow Reserve Is Negatively Associated With Aortic Valve Calcification In Patients With Unobstructed Epicardial Coronary Arteries ” for consideration of publication in International Journal of Cardiology. We assess coronary microvascular function using myocardial contrast echocardiography in patients presenting with chest pain and unobstructed coronary arteries, and find that coronary microvascular dysfunction is positively associated with aortic valve calcification score as measured on multiplanar CT scan. Importantly we found that this relationship is independent of coronary plaque and systemic inflammation. This has not been reported previously.

The paper is not under consideration elsewhere and none of the paper’s contents have been previously published. All authors have read and approved the manuscript. We have fully disclosed of any relationship with industry or potential financial conflict of interest. All authors were involved in the conception and design or analysis and interpretation of data, drafting of the manuscript or revision for important intellectual content. All authors have provided final approval of the manuscript submitted.

Yours sincerely,

Professor Kim Greaves

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Author Agreement Form – International Journal of Cardiology

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This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology*.

We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in the International of Cardiology (citable as: Shewan LG, Rosano GMC, Henein MY, Coats AJS. A statement on ethical standards in publishing scientific articles in the International Journal of Cardiology family of journals. *Int. J. Cardiol.* 170 (2014) 253-254 DOI:10.1016/j.ijcard.2013.11).

On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission. Any changes to the list of authors, including changes in order, additions or removals will require the submission of a new author agreement form approved and signed by all the original and added submitting authors.

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. If there are no conflicts of interest, the COI should read: "The authors report no relationships that could be construed as a conflict of interest".

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5 **Unobstructed Epicardial Coronary Arteries**
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108 **Grant support:** Bournemouth University PhD Scholarship, The Dorset Research Consortium and the Poole
109 Hospital Cardiology Research Fund

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111 **Conflicts of interest:** None to declare

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114 **Keywords:** Aortic valve calcification score, coronary microvascular dysfunction, calcific aortic valve disease.
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123 **Abstract:**
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125 **Background:** Although calcific aortic valve disease (CAVD) is associated with coronary atherosclerosis, it is not
126 known whether early CAVD is associated with coronary microcirculatory dysfunction (CMD). We sought to
127 investigate the relationship between myocardial blood flow reserve (MBFR) - a measure of CMD, and early
128 CAVD. We also determined whether this relationship was independent of coronary artery disease (CAD) and hs-
129 CRP, a marker of systemic inflammation.
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134 **Methods:** 183 patients with chest pain and unobstructed coronary arteries were studied. Aortic valve
135 calcification score (AVCS), coronary total plaque length (TPL), and coronary calcium score were quantified from
136 multislice CT. MBFR was assessed using vasodilator myocardial contrast echocardiography. Hs-CRP was
137 measured from venous blood using a particle-enhanced immunoassay.
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142 **Results:** Mean(\pm SD) participant age was 59.8(9.6) years. Mean AVCS was 68(258) AU, TPL was 15.6(22.2) mm,
143 and median coronary calcification score was 43.5AU. Mean MBFR was 2.20(0.52). Mean hs-CRP was 2.52(3.86)
144 mg/L. Multivariable linear regression modelling incorporating demographics, coronary plaque characteristics,
145 MBFR, and inflammatory markers, demonstrated that age ($\beta=0.05$, 95%CI:0.02,0.08, $P=0.007$), hs-CRP ($\beta=0.09$,
146 CI:0.02,0.16, $P=0.010$) and diabetes ($\beta=1.03$, CI:0.08,1.98, $P=0.033$), were positively associated with AVCS.
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181 **Conclusion:** Coronary microvascular function as determined by measurement of myocardial blood flow reserve
182 is an independent predictor of early CAVD. This effect is independent of the presence of coronary artery
183 disease and also systemic inflammation.
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183 **1. Introduction:**
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187 The development of calcific aortic valve disease (CAVD) has traditionally been attributed to a passive, age-
188 related degenerative phenomenon. However recent evidence suggests a more active mechanism. CT coronary
189 angiographic studies have found an association between aortic valve calcification and the presence of coronary
190 artery disease, which is an inflammatory process (1, 2). Epidemiologic studies have identified that risk factors
191 for atherosclerosis - older age, male sex, hypercholesterolemia, hypertension, metabolic syndrome, and
192 smoking, are also independently associated with the presence of CAVD (3). Histopathological studies have also
193 observed the accumulation of atherosclerotic end products such as LDL, inflammatory cell infiltrates and
194 microscopic calcification, within explanted or cadaveric CAVD specimens (4). In addition, more recent findings
195 have shown that markers of inflammation such as hs-CRP, are independently associated with aortic valve
196 calcification (5). In the light of these and other findings, several groups have suggested that CAVD and coronary
197 atherosclerosis share common active pathophysiological mechanisms (6, 7).
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209 The discovery of a link between both the early CAVD and coronary atherosclerosis has the potential to increase
210 understanding of the disease, improve risk stratification and provide therapeutic targets. Coronary
211 microvascular dysfunction (CMD) is a precursor to the development of coronary atherosclerosis (8). The
212 presence of CMD has been shown to predict the future development of coronary artery disease, and also
213 independently predict adverse cardiovascular and all-cause mortality. Therapies to improve CMD and outcome
214 have had some success (9-11). Whether or not CMD is independently associated with early CAVD is unknown.
215 Previous studies have attempted to examine whether there is a direct link between CMD and CAVD. However,
216 these have been limited to patients with established aortic stenosis which therefore represents late stage
217 CAVD, or assessed CAVD with echocardiography rather than CT (12, 13). Furthermore these studies either did
218 not exclude or quantify whether coronary artery disease was also present (14). This is important because even
219 the presence of mild non-obstructive coronary artery disease is known to be independently associated with
220 CMD and therefore a confounding factor (15)
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243 We sought to investigate the relationship between myocardial blood flow reserve (MBFR) - a measure of CMD,
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245 and early CAVD. We also determined whether this relationship was independent of coronary artery disease
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247 (CAD) and hs-CRP, a marker of systemic inflammation.
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252 **2. Methods:**

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256 **2.1. Study population:** This pre-determined study was part of another study investigating the relationship
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258 between chest pain typicality and its relationship to coronary microvascular function. This was a prospective,
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260 cross-sectional, observational study which recruited consecutive patients aged 30-80 years attending
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262 cardiology outpatient clinics (Jan 2011-March 2013) presenting with stable chest pain suggestive of myocardial
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264 ischaemia due to CAD and who were referred for diagnostic CT coronary angiography (CTA). Those with
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266 unobstructed coronary arteries underwent transthoracic echocardiography. Unobstructed CAD was defined as
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268 a quantitatively measured luminal diameter stenosis <50%. Patients were excluded if they had ≥50% luminal
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270 diameter narrowing, known ischemic heart disease, left ventricular hypertrophy, an ejection fraction <55%, or
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272 significant aortic valve disease. Specifically, those patients with a peak systolic transaortic valve velocity of
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274 >2m/s were excluded. Aortic valve calcification was quantified from the CTCA study. Participants then
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276 underwent vasodilator myocardial contrast echocardiography (MCE) to assess myocardial blood flow reserve
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278 (MBFR). Informed consent was obtained for each patient. The study complied with the Declaration of Helsinki
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280 and was approved by the local research ethics committee (H0102/78).
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283 **2.2. CTA study:** CTA imaging was performed using a 64-channel CT scanner (GE Lightspeed VCT, GE Medical
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285 Systems, USA). The mean heart rate during the scan was 64 beats/min. A low dose scout scan was performed
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287 to define anatomic landmarks for the contrast-enhanced study. Calcium scoring and helical scan data was
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289 performed on all patients using prospective ECG triggering at 75% of the R-R interval. Following this, a 20ml
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291 bolus of contrast (Niopram 370®) at 6mls/sec was injected and the timing of peak contrast enhancement in the
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293 aortic arch was used to determine the timing of scan acquisition. The contrast-enhanced scan used 80mls
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295 contrast injected at 6 ml/s, followed by a 50ml at 6mls/sec saline flush, during a single expiration breath hold.
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303 The CTA scan parameters were: collimator 20mm, slice thickness 0.625mm; gantry rotation 350ms; helical
304 acquisition using a pitch of 0.16; tube current 455-515 mA with ECG tube current modulation; tube voltage
305 range 100-140kV; rotation time, 350ms. The estimated radiation dose per patient was 3.3mSv. Reconstructed
306 CTA images were analysed on a dedicated 3-dimensional workstation (CardIQ Xpress, GE Medical Systems) with
307 curved multiplanar reformation and short-axis cross sectional viewing techniques. We measured the amount of
308 plaque present in the proximal, mid, and part of the distal sections, of the main vessel coronary artery tree.
309 This decision was made because these segments have greater image quality regarding contrast:noise ratio,
310 reduced observer variability, and contain the majority of clinically important plaque in the coronary tree (16,
311 17). This included the left main stem (segment 1), the first 80mm of the left anterior descending (divided
312 equally into segments 2 and 3), the first 30mm of the circumflex (segment 4) and the first 80mm of the right
313 coronary artery (segments 5 and 6).

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325 **2.3. Aortic Valve Calcification Score (AVCS):** Amount of aortic valve calcification is correlated with the degree
326 of aortic valve sclerosis applying multislice CT (18). For quantitative assessment of aortic valve calcification
327 using CT with a detection threshold of 130H, the aortic valve Agatston score was derived. Calcification was
328 attributed to the aortic valve if it was clearly part of the valve cusps. Supravalvular calcifications and
329 calcifications of the coronary arteries including the ostia were removed by manual segmentation. The Agatston
330 score was calculated by multiplying the lesion area by an attenuation factor derived from the maximal
331 Hounsfield units within the area, as previously described (19). Figure 1 illustrates this analysis.

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340 **2.4. Coronary artery plaque burden:** Total plaque length (TPL) was used as a surrogate measure of total
341 atherosclerotic burden as described by Naya (20). Plaque length was measured as the distance (mm) from the
342 proximal to the distal shoulder of each plaque. TPL was calculated for each patient by summing all the lengths
343 for each subject. For each plaque, the degree of epicardial luminal narrowing was also assessed by quantifying
344 the percentage diameter stenosis. This was calculated by dividing the minimal lumen diameter at each plaque
345 by the nearest proximal normal artery diameter. The sum of all stenoses present divided by the number of
346 stenosed plaques, determined the total mean stenosis per patient.

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363 **2.5. Coronary Calcium Score:** 2.5mm slice thickness, non-overlapping images were reconstructed using filtered
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365 back projection and a standard algorithm (GE). The total calcium burden in the coronary arteries was manually
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367 measured by planimetry according to the scoring algorithm of Agatston (19).
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372 **2.6. MCE study:** Patients underwent the MCE study having avoided all caffeine-containing products in the
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374 previous 24 hours. Patients withheld beta-blockers, nitrates and calcium antagonists the day before, and on
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376 the day of the test. MCE was performed using a commercial ultrasound machine iE33 (Philips Medical Systems)
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378 and SonoVue (Bracco Research SA) as the contrast agent given as a constant infusion. Real-time images were
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380 recorded within 3-4 minutes in the apical 4-, 2- and 3-chamber views with low-power settings at a mechanical
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382 index of 0.1. The focus was set at the mitral valve level. SonoVue was initially started at 60 mL/h through a
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384 peripheral vein cannula with the VueJect infusion syringe pump (Bracco Research, SA), which gently rotates
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386 and maintains the contrast agent in a suspension. Thereafter, the rate was set between 48 and 60 mL/h to
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388 maximize image quality with minimal attenuation. Once optimized, the machine settings were held constant
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390 throughout each participant study. Flash-impulse imaging at a high mechanical index (1.0) was performed to
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392 achieve complete myocardial bubble destruction, after which 10 end-systolic frames were recorded digitally in
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394 each apical view. After the resting images were acquired, dipyridamole was infused at 0.56 mg/kg over a 4-
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396 minute period. After an interval of 2 minutes, post-stress images were recorded within 3 to 4 minutes. This
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398 entire sequence took 14 minutes. Quantitative MCE analysis was performed offline using QLab V7.0 (Q-
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400 Laboratory, Philips Medical Systems) as previously described in detail (21). Briefly, quantitative assessment of
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402 myocardial perfusion was performed for 10 consecutive end-systolic frames after microbubble destruction. A
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404 region of interest was placed over the thickness of the myocardium. Plots of peak myocardial contrast intensity
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406 (representing myocardial blood volume A, dB) versus pulsing intervals (representing time) were automatically
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408 constructed to fit the monoexponential function conventional equation: $y=A(1 - e^{-\beta t})$. From these plots, the
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410 slope of the replenishment curve was determined (representing myocardial blood velocity β , dB/s). Figure 2
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412 illustrates this analysis technique. The product of A and β yielded baseline MBF (dB²/s) and post-dipyridamole
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414 MBF (stress MBF, dB²/s), respectively. We calculated MBFR by the ratio of stress MBF (MBFs) to baseline MBF
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416 (MBFb). MBFR was calculated by dividing the MBFs by MBFb of the same segment. Basal segments were not
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418 included in the analysis because of contrast attenuation. The remaining 10 mid- and apical cardiac segments
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423 were analyzed. A segment was not included in the analysis if there was artifact, inadequate microbubble
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425 destruction, attenuation, or a wide variation in contrast intensity to minimize errors.
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428 **2.7. Venous samples:** Peripheral venous samples for hs-CRP were taken at rest. Fasting glucose and lipid
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430 profiles were from within the previous 3 months. All assays were performed in duplicate by a single observer,
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432 blinded to the demographic data. Hs-CRP was determined with a particle-enhanced immunoassay, which has a
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434 detection limit of 0.1mg/L and an inter-assay CV <10% (Roche Diagnostics, UK).
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437 **2.8. Statistical Analysis:** Where appropriate, continuous variables were summarised using means, standard
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439 deviations and/or 95% confidence intervals. Ordinal and dichotomous variables were summarised using
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441 proportions or percentages. Indices of variance are bracketed after the respective value for central tendency.
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443 Normality was assessed using a Shapiro-Wilk test and if deemed necessary, heavily skewed data were
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445 transformed using a natural logarithmic transformation. General correlation was checked using a Pearson's
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447 correlation coefficient, and for categorical data, a Spearman's rank correlation (rho) test was employed.
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449 Statistical significance was tested using either a Student t-test for normally distributed continuous data or a
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451 Mann-Whitney U-test for non-normal continuous data. Ordinal and dichotomous data were tested using a
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453 Fischer exact test. Univariate regression was used initially to quantify the relationships between each of the
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455 explanatory variables and the main outcome variable MBFR against AVCS. Based on the results of the
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457 univariate regression, multivariable model building was performed using ordinary least-square regression and
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459 the resulting models were tested for coefficient (β) significance, model fit to data (adjusted R^2) and residual
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461 homoscedasticity and normality. If required, a leverage to squared residual plot was used to assess the effects
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463 of either high leverage or outlying values on the regression coefficients. A likelihood ratio (LR) test was
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465 employed to compare the fit of each successive iteration to the regression model. The level of significance was
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467 set at $P < 0.05$. For CTA studies, 10 patients' scans (60 segments) were re-analysed by KN, and then again by two
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469 additional separate observers who were level 2 accredited or above (KG, RB). All analyses were performed
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471 using STATA™ version 12.0.
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473 **3. Results:**

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483 Overall, our study included 183 participants whose baseline demographics are illustrated in Table 1. The mean
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485 age of participants was 59.8(\pm 9.6) years of whom 52.5% were male with a mean BMI of 27.2(\pm 3.8) kg/m². The
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487 mean hs-CRP was 2.52(\pm 3.86) mg/L, with 75 (41%) participants having elevated hs-CRP levels (defined as
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489 >2mg/L).

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493 **3.1. Aortic valve analysis:** In those with aortic valve calcification, the mean aortic valve calcification score
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495 (AVCS) was 68(\pm 258) AU. In our cohort, the maximum AVCS was 2874 AU, and 72 (39%) had an AVCS of zero.
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497 Due to the marked right skew present in AVCS, values were normalised using a natural logarithmic
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499 transformation.

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503 **3.2. Coronary artery plaque morphology:** From the 1096 segments available for analysis, 1016(92%) were
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505 interpretable. The total coronary tree length studied was 190mm plus the mean left main stem length (8mm+
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507 7mm). Plaque was present in 113(62%) of patients. There were 384 plaques in total and 53(29%) of patients
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509 had either one or two plaques present. The mean stenosis per patient was 3.1(0-22)% of whom 138(76%) had a
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511 mean stenosis of <5%. Values for total plaque length (TPL) were right skewed with a median (IQRs) of 19.3 (8.9,
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513 31.7) mm. The mean TPL was 15.6 mm, ranging from 0 to 132 mm. When present, the median coronary
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515 calcification score was 43.5(IQR 10.5-152) AU. Total coronary calcification score was also markedly right-
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517 skewed. Inter and intra-observer variability (kappa) for both aortic valve and coronary calcium scoring was 0.85
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519 and 1.0, respectively.

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523 **3.3. Myocardial blood flow:** The mean MBFR was 2.20(\pm 0.52), and 70 patients (38%) had an MBFR below 2.0.
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525 The intra- and inter-observer variability's for MBFR were 7.7% and 8.2%, respectively. The minimum number of
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527 analysable segments for baseline and stress was six for each, in keeping with previous published data (22).

528
529 Table 2 shows the results of univariate analysis performed on all demographic parameters in addition to total
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531 plaque length, coronary calcium score, hs-CRP and MBFR, in relation to aortic valve calcium score (AVCS). There
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533 were significant positive correlations between increasing age, total plaque length, and hs-CRP with AVCS. There
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535 was a significant negative correlation between MBFR, LDL and AVCS.

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545 Multivariate model analysis incorporated all univariate parameters with a P value <0.20, each as independent
546 explanatory variables, using stepwise deletion from a fully saturated model. Each iteration was checked using a
547 likelihood ratio test against the fully saturated null model. No significant interaction terms were identified. The
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549 final regression equation is demonstrated in figure 3.
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554 The tabulated values for regression coefficients (β), 95% confidence intervals and P-values for each β , are listed
555 in Table 3. Age, diabetes, BMI, MBFR, LDL and hs-CRP are all independent predictors of AVCS. Coronary calcium
556 score and TPL were included separately during the model evolution due to strong collinearity and neither were
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558 significant. As a result, the final model did not include either.
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564 Figure 3 shows the regression model used to predict values for aortic valve calcification score. In the model,
565 increasing age, presence of diabetes, and hs-CRP are independent positive predictors of $\ln(\text{AVCS})$, whereas an
566 increased MBFR, BMI, and LDL are negatively associated with $\ln(\text{AVCS})$ ($R^2=0.36$). From the model, an absolute
567 change in the MBFR value by -1.0 results in an increase in AVCS by a multiple of 2.39AU.
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572 573 574 575 **4. Discussion:** 576

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579 Coronary microvascular function as determined by measurement of myocardial blood flow reserve is an
580 independent predictor of early CAVD. This effect is independent of the presence of coronary artery disease and
581 also systemic inflammation. Importantly, although coronary artery disease is initially associated with CAVD,
582 when MBFR is included in the model, coronary artery disease is no longer predictive.
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588 **4.1. AVCS and microvascular function:** Previous studies have reported CMD in CAVD, however there are
589 several important differences with respect to our report. Banovic found that coronary flow reserve (CFR) using
590 Doppler echocardiography of the left anterior descending coronary artery, is reduced in asymptomatic but
591 haemodynamically significant moderate to severe AS with normal LV systolic function and unobstructed
592 epicardial coronary arteries (13). Importantly, they found that CFR was an independent predictor of mortality
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603 after multivariate analysis even after taking into account haemodynamic indices of AS. They proposed that
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605 lower CFR values in this context were caused by the upstream effects of haemodynamically significant AS, such
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607 as left ventricular hypertrophy and fibrosis, with consequent reduced capillary density. Similarly, Rajappan
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609 assessed CMD in patients with moderate to severe AS with unobstructed coronary arteries but used positron
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611 emission tomography to measure CMD (12). They found that parameters of AS severity such as aortic valve
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613 area and haemodynamic load were associated with CMD. Neither of these studies determined whether
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615 coronary artery disease was present even if mild. This is important because even the presence of mild early
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617 coronary artery disease is associated with CMD. For instance, Wang showed that increasing coronary calcium
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619 score in asymptomatic individuals is associated with reduced coronary perfusion reserve (15). In fact,
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621 endothelial dysfunction in the context of chest pain with unobstructed coronary arteries is a predictor of future
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623 coronary atherosclerosis (23).

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626 There is relatively limited data with regards to the relationship between early CAVD (without
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628 haemodynamically significant AS) and CMD. Bozbas assessed CFR in patients with aortic valve calcification
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630 without significant aortic stenosis. Aortic valve calcification was assessed using echocardiography (14). The
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632 authors found that mean CFR was 16% lower in the AVC group compared to control ($p < 0.001$), and concluded
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634 that CMD is present even during early CAVD. Multivariate analysis found that the presence of aortic valve
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636 calcification was an independent predictor of CMD. However, although their patient cohort was asymptomatic,
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638 they pointed out that their study had not excluded obstructive coronary artery disease.

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641 Our study provides novel data for the following reasons. Firstly, early CAVD was diagnosed using CT, which is
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643 more accurate than echocardiography in the assessment of aortic valve calcification (24). For example, one
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645 group reported that CT had a greater sensitivity and detected 32% more patients than echocardiography in
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647 their elderly screening cohort (24). The Agatston score for aortic valve calcification provides a much broader
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649 range for quantitative scoring than the three point system used in Bozbas study. Finally, obstructive coronary
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651 artery disease was excluded using CTCA whereas this was assumed from clinical history alone in previous
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653 studies.

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663 The role of microvascular dysfunction in relation to the development of CAVD is not yet clear. CMD has been
664 shown to correlate closely with endothelial dysfunction (25) and peripheral endothelial dysfunction assessed
665 using flow-mediated dilatation is also associated with aortic valve sclerosis. Therefore, when taken in
666 conjunction with our results, this suggests a systemic process (26). The recent discovery that valve endothelial
667 cells regulate the remodelling and integrity of the extracellular matrix within valve leaflets (27) may be
668 important. It has been proposed that endothelial dysfunction allows inflammatory cytokine entry into valve
669 leaflets which promotes mineralisation and ultimately leaflet calcification.
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678 **4.2. AVCS and inflammation:** We found that the marker of systemic inflammation hs-CRP is independently
679 associated with aortic valve calcification score and is consistent with other published data (28). Oxidative stress
680 forms the initiating event of an inflammatory cascade which ultimately results in valvular calcification. Hs-CRP
681 correlates strongly with oxidative stress and studies are underway regarding its use as a surveillance biomarker
682 in the detection of atherosclerosis (5, 29). Furthermore, histopathology studies of explanted calcified aortic
683 valves have found an abundance of leucocytes and macrophages (4). Our findings add to the literature in that
684 CMD has a positive association with AVCS which is independent of and additive to the presence of systemic
685 inflammation.
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695 **4.3. Other factors associated with early CAVD:** Our results indicated that Increasing age and presence of
696 diabetes were positively associated with AVCS. Neither of these findings are novel. The strong link between age
697 and valvular calcification is well established from epidemiology studies (3). Diabetes is a pro-inflammatory
698 condition which promotes macrophage deposition and consequent calcification (1).
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704 Unexpectedly, in our analysis, increasing LDL was negatively associated with AVCS and is contrary to findings
705 from previous studies (30, 31). Low-density lipoproteins have been implicated in the pathogenesis of CAVD.
706 Extracellular lipid accumulation has been identified in explanted CAVD leaflets within the subendothelial layer
707 with apolipoproteins, implying a plasma source (32). However, the role of LDL in the early stages of CAVD
708 development is unknown especially given the failure of statin trials to slow AS progression (33). Importantly
709 36% of this patient cohort were on statin therapy prior to recruitment, and therefore a proportion of the study
710 population may have a history of chronically elevated LDL. Furthermore, recent reports have suggested that
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723 lipid components other than LDL may be associated with AS progression and cardiovascular risk such as
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725 lipoprotein(a) (Lpa) and non-HDL, (34, 35).
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729 Increasing BMI was negatively associated with AVCS in our analysis. This was unexpected as a high BMI is
730 associated with both microvascular dysfunction and elevated systemic markers of inflammation, which
731 promote calcification (36, 37). However, observational data showing increased survival rates in higher BMI
732 patients presenting with acute coronary syndromes: the so-called obesity paradox, draws consideration of
733 whether higher BMI confers protection against certain disease processes (38).
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740 **4.4. Study Limitations:** The study was conducted at a single centre in the UK which means referral bias may
741 have affected our sample population. Furthermore our participants consisted of patients referred for the
742 investigation of chest pain, which is not representative of the general population. However, the recruitment of
743 this patient population enabled CT-based radiological investigation which otherwise would not have been
744 ethically possible, and is consistent with previous studies (2, 14).
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751 752 753 **5. Conclusion:** 754 755 756

757 Coronary microvascular function as determined by measurement of myocardial blood flow reserve is an
758 independent predictor of early CAVD. This effect is independent of the presence of coronary artery disease and
759 also systemic inflammation. Importantly, although coronary artery disease is initially associated with CAVD,
760 when MBFR is included in the model, coronary artery disease is no longer predictive.
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Table 1: Baseline Demographics

	All patients (n=183)
Age in years; mean (SD)	59.8 (9.6)
Male sex (%)	96 (52.4)
Diabetes (%)	18 (10.0)
BMI (kg/m²) (SD)	27.2 (3.8)
Smoking History (%)	
Non smoker	100 (55)
Ex-smoker	64 (35)
Current smoker	19 (10)
Hypertensive (%)	71 (38.8)
Family history (%)	91 (49.7)
Statin use (%)	66 (36.0)

BMI: Body mass index

Table 2: Univariate regression modelling of demographic variables, lipid profile and inflammation markers, coronary plaque parameters and microvascular function against aortic valve calcium score.

	β	95% CI	P-value
Age (yrs)	+0.07	+0.03, +0.10	0.01
Male sex (Y/N)	+0.05	-0.61, +0.71	0.08
Diabetes (Y/N)	+1.08	-0.11, +2.06	0.07
BMI (kg/m²)	-0.02	-0.12, +0.07	0.63
Smoking category (Y/N)	+0.31	-0.15, +0.77	0.19
Hypertension (Y/N)	+0.63	-0.02, +1.28	0.06
Family history (Y/N)	-0.36	-1.02, +0.30	0.29
Statin use (Y/N)	+0.63	-0.05, +1.30	0.07
LDL (mmol/l)	-0.45	-0.75, -0.15	0.003
Triglyceride (mmol/l)	+0.004	-0.33, +0.34	0.98
Total plaque length (mm)	+0.02	+0.01, +0.03	0.04
Coronary calcium score (AU)	+0.001	+0.001, +0.002	0.05
hs-CRP (mg/L)	+0.09	+0.01, +0.17	0.02
MBFR	-0.80	-1.41, -0.19	0.01

BMI: Body mass index, LDL: low-density lipoprotein, hs-CRP: high sensitivity C-reactive protein, MBFR:

myocardial blood flow reserve

Table 3: Multivariate regression modelling for predicting aortic valve calcification score using age, presence of diabetes, BMI, myocardial blood flow reserve, LDL, and hs-CRP

Variable	β	95% CI	P-value
Age (yrs)	+0.05	+0.02, +0.08	0.007
Diabetes (Y/N)	+1.03	+0.08, +1.98	0.033
BMI (kg/m ²)	-0.11	-0.21, -0.01	0.033
MBFR	-0.87	-1.44, -0.30	0.003
LDL (mmol/l)	-0.32	-0.61, -0.03	0.029
hs-CRP (mg/L)	+0.09	+0.02, +0.16	0.010

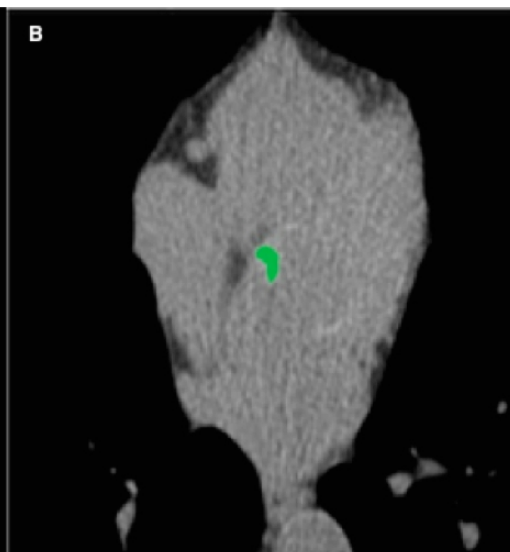
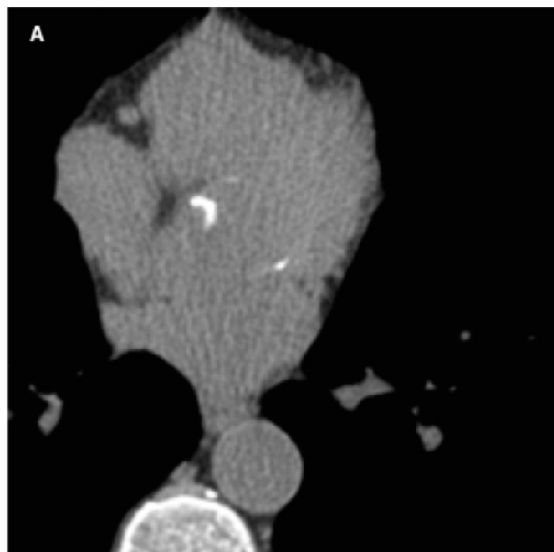
BMI: Body mass index, MBFR: Myocardial blood flow reserve, LDL: low-density lipoproteins, hs-CRP: high sensitivity C-reactive protein

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1087 **Figure 1.** Example of aortic valve calcium scoring using ECG-gated coronary CT images. Calcification of aortic
1088 valve cusps detected on axial image (A). Imaging software detects regions within the aortic cusps with a density
1089 threshold of greater than 130HU to derive calcium volume (B). Aortic valve calcium score is then calculated -
1090 denoted in this case as 'U1' (C)
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1096 **Figure 2.** Model used for quantitative analysis of myocardial segments. (A) Apical 4 chamber, (B) Apical 2
1097 chamber, (C) Apical 3 chamber.
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1102 **Figure 3.** Final model is described mathematically by $\ln(\text{AVCS}) = 5.83 + (0.05 \times \text{age}) + (1.03 \times \text{diabetes}) - (0.11 \times$
1103 $\text{BMI}) - (0.87 \times \text{MBFR}) - (0.32 \times \text{LDL}) + (0.09 \times \text{hs-CRP})$
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Artery	Lesions	Volume [mm ³]	Equiv. Mass [mg]	Score
LM	0	0.0	0.00	0.0
LAD	0	0.0	0.00	0.0
CX	0	0.0	0.00	0.0
RCA	0	0.0	0.00	0.0
TOTAL	0	0.0	0.00	0.0
U1	2	155.6	31.76	189.1
U2	0	0.0	0.00	0.0

Settings
Score Type: Agatston equivalent, Threshold: 130 HU (96.5 mg/cm² CaHA)
Mass calibration factor: 0.743

