Coronary artery calcification is inversely related to body morphology in patients with significant coronary artery disease: a three-dimensional intravascular ultrasound study

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Received 25 March 2013; accepted after revision 1 July 2013; online publish-ahead-of-print 31 July 2013

Aims
Emerging data have indicated unexpected complexity in the regulation of vascular and bone calcification. In particular, several recent studies have challenged the concept of a universally positive relationship between body morphology (weight, height, body mass index (BMI), body surface area (BSA)) and the extent of vascular calcification. We sought to clarify these discrepancies and investigated the relationship between index lesion coronary artery calcification (CAC) and body morphology in patients undergoing percutaneous coronary intervention (PCI) using three-dimensional intravascular ultrasound (IVUS).

Methods and results
We analysed CAC in patients who underwent PCI with pre-intervention IVUS imaging. The main outcome measure was the calcium index (CalcIndex); a three-dimensional IVUS-derived measure of total calcification per obstructive coronary lesion. A total of 346 patients (65.3 ± 10.6 years; 29.5% females) underwent PCI with IVUS-based CAC assessment. CalcIndex was categorized as zero–low (0–0.1399; n = 152) or intermediate–high (0.1400–1.2541; n = 194). All measures of body morphology were lower in patients with intermediate–high CalcIndex (height, P = 0.024; weight, P = 0.008; BMI, P = 0.064; BSA, P = 0.005). In adjusted multivariable models, weight and BSA were independent inverse predictors of intermediate–high CalcIndex (weight: odds ratio (OR) 0.986, P = 0.017; BSA: OR 0.323, P = 0.012) while CalcIndex also trended towards an inverse association with both height (P = 0.068) and BMI (P = 0.064). These independent inverse associations were consistent across multiple clinical subgroups, including stratification by age, race, gender, diabetes, and renal impairment.

Conclusion
Using three-dimensional IVUS to assess vascular calcification, these data confirm an independent, inverse relationship between body size and index lesion CAC in patients with obstructive coronary artery disease.

Keywords
Obesity • Vascular calcification • Body surface area • Weight

Introduction
Disturbances in mineral metabolism are common in older adults1 and are associated with adverse cardiovascular outcomes.2,3 As an example, low levels of serum 25-hydroxyvitamin D are associated with decreased bone mineral density4 while at the same time being associated with incident myocardial infarction and increased all-cause mortality.2,3 Of importance, low bone mineral density is an independent risk factor for cardiovascular events.4

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In older persons, it is known that an inverse relationship exists between bone mineral density and vascular calcification, such that lower bone mineral density is associated with increased vascular calcification. This recently described relationship has been dubbed the ‘vascular calcification paradox’. Furthermore, after middle age, a robust positive association exists between bone mineral density and various measures of body morphology such as body weight, body mass index (BMI), and body surface area (BSA). These relationships indicate profound complexity and interplay between the physiological pathways of vascular and skeletal ossification, and indirectly suggest that there may be an age-dependent component in their regulation. Furthermore, while numerous studies have suggested that a positive relationship exists between the extent of vascular calcification and body morphology, a number of very recent studies have suggested that this may be an overly simplistic outlook and that in certain populations this relationship may not hold true. In particular, isolated studies have now suggested that in older women or those with clinically significant coronary disease, there may be an inverse relationship between body size and vascular calcification.

Given these uncertainties, we sought to rigorously explore the relationship between index lesion coronary artery calcification (CAC) and body morphology in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI), using an independent data set and performing quantitative CAC assessment using three-dimensional intravascular ultrasound (IVUS) imaging.

Methods

We analysed 346 consecutive patients who underwent PCI with pre-intervention IVUS imaging. Detailed characteristics of these patients and the PCI procedure have been published previously. Only a single culprit target lesion and associated target vessel per patient were included in this study. IVUS of other vessels was not clinically indicated and was not performed. Key enrolment criteria were guideline-appropriate requirement for PCI, typically based on severe disease, positive stress test results, or presentation with unstable coronary syndromes; age 18 years; and signed informed consent. Exclusion criteria were presentation with ST-segment elevation myocardial infarction, syndromes; age 18 years; and signed informed consent. Exclusion criteria included positive stress test results, or presentation with unstable coronary artery disease. Exclusion criteria included positive stress test results, or presentation with unstable coronary artery disease, diabetes, and various measures of body morphology such as body weight, body mass index (BMI), and body surface area (BSA). These relationships indicate profound complexity and interplay between the physiological pathways of vascular and skeletal ossification, and indirectly suggest that there may be an age-dependent component in their regulation. Furthermore, while numerous studies have suggested that a positive relationship exists between the extent of vascular calcification and body morphology, a number of very recent studies have suggested that this may be an overly simplistic outlook and that in certain populations this relationship may not hold true. In particular, isolated studies have now suggested that in older women or those with clinically significant coronary disease, there may be an inverse relationship between body size and vascular calcification.

Intra ventricular ultrasound imaging

Target lesion IVUS imaging studies were performed after intracoronary administration of 200 μg nitroglycerine using a commercially available IVUS system (Atlantis SR Pro, 40 MHz catheter, Boston Scientific Corp., Natick, MA, USA; Eagle Eye, 20 MHz catheter or Revolution 45 MHz catheter, Volcano Corp., Rancho Cordova, CA, USA) and prior to PCI. The IVUS catheter was advanced distal to the stenosis, and imaging was performed with retrograde pull-back to the aorto-ostial junction of the coronary artery using an automatic pullback system at a speed of 0.5 mm/s. All analyses were performed offline without knowledge of patient body morphology using planimetry software (INDEC Systems Inc., Mountain View, CA, USA). The minimum lumen cross-sectional area (CSA) site was the image slice with the smallest lumen CSA. The reference sites were the most normal-appearing cross sections within 5 mm proximal and distal to the lesion but before any side branch and were used to calculate a mean reference. For each patient, the lesion with the smallest lumen CSA was chosen for analysis. The lesion itself was defined as the segment between the proximal and distal reference sites whose length (mm) was calculated using the pullback duration and pullback speed. Quantitative analysis included the measurement of the external elastic membrane (EEM) and lumen CSA every 1 mm within the length of the lesion. Plaque and media CSA were calculated as EEM – lumen CSA. Once a complete set of CSA measurements were obtained, EEM, plaque + media, and lumen volumes were calculated using Simpson’s rule. Plaque burden was calculated as plaque and media divided by EEM volume or CSA. A remodelling index was calculated as the lesion divided by the mean reference EEM CSA. Following two-dimensional analysis, high-resolution images of each IVUS pull-back were imported into dedicated software for three-dimensional reconstruction and analysis. Calcium was identified as an echo signal brighter than the adventitia with acoustic shadowing. The maximum arc of calcium (calcium length) within the lesion was measured with the electronic protractor centred on the lumen. Calcium length (mm) within the lesion was measured as the length of the lesion in which there was IVUS-detectable calcium. Calcium index (CalcIndex) was calculated as total calcium length/lesion length × maximum calcium arc/360° (Figure 1). CalcIndex represents the total amount of calcium per coronary lesion and was therefore selected a priori as the primary dependent outcome for this study. The use of three-dimensional IVUS to quantify arterial calcification has been validated by Virmani and co-workers and exhibits a high degree of correlation with ex vivo histopathological calcification assessment. The in vivo human application of this methodology has previously been reported by ourselves and others.

Statistical analyses

Continuous variables are expressed as mean and SD as indicated and compared using Student’s t-test or Wilcoxon rank-sum test if applicable. Discrete variables are presented as numbers and percentages and compared with the χ² test, unless the observation in any cell was <5, in which case Fisher’s exact test was used. We initially examined the distribution of CalcIndex and consistent with prior reports found it to be positively skewed, with 55/346 (15.9%) patients having a value of zero. This distribution pattern failed to fulfil the principal assumptions that underpin the classical linear regression model: (i) The relationship between dependent and independent variables was non-linear. (ii) The error distribution was not normal, and (iii) The
errors were heteroscedastic. For this reason and consistent also with prior studies examining associations of vascular calcification, CalcIndex was categorized as zero–low (0–0.1399; n = 152) or intermediate–high (0.1400–1.2541; n = 194). The independent associations between various parameters of body morphology (height, weight, BMI, and BSA) and CalcIndex were then assessed using binary logistic regression. Separate models were generated for each parameter of body morphology as the exposure of interest with intermediate–high CalcIndex as the dependent outcome. All fully adjusted models included the following candidate covariates selected using a stepwise algorithm with entry/exit criteria of 0.1/0.1: gender, age, race, current smoking, former smoking, hypertension, hyperlipidaemia, diabetes, CRI, and prior congestive heart failure. The associations between intermediate–high CalcIndex and both BSA and weight were also assessed separately in subgroups defined by: age, gender, race, diabetes, chronic renal impairment, smoking status, hyperlipidaemia, and hypertension. Current and former smokers were combined for this analysis as ‘smoking’. These models included stratification according to age, gender, renal impairment, and race/ethnicity. Interaction testing between each subgroup and BSA or weight on the outcome of intermediate–high CalcIndex was also performed. Statistical analyses were performed using the SAS software, version 9.2. (Cary, NC, USA).

Results

A total of 346 consecutive patients are included in this study who underwent index lesion PCI and pre-PCI three-dimensional IVUS assessment with offline computation of CalcIndex (Figure 1). The mean age was 65.3 ± 10.6 years (range 32.7–87.0 years), with 102 females (29.5%).

Patient demographics are presented in Table 1 and were stratified according to those with zero lesion calcification and tertiles of those with any calcification (low, intermediate, high). There was no significant trend for gender, race, or history of renal impairment among the groups of CalcIndex. Older patients tended to have greater CalcIndex (P = 0.08). Consistent with prior observations, a trend was noted for an association between a history of prior myocardial infarction and lower CalcIndex (P = 0.004). Lack of baseline aspirin therapy was associated with higher CalcIndex (P = 0.03), whereas the use of β-blockers was associated with increasing CalcIndex (P = 0.05).

With respect to body morphology, in these crude analyses presented in Table 1, an inverse association was observed between CalcIndex and patient height, weight, and BSA (P = 0.08, 0.07, 0.049, respectively). Consistent with prior reports of arterial calcification, we also identified that the distribution of CalcIndex was positively skewed, with 55 patients (15.9%) having no calcification detected by IVUS.

Owing to its known skewed distribution and consistent with prior studies, CalcIndex was classified as a binary variable (zero–low or intermediate–high) (see Section ‘Statistical analyses’). As shown in Figure 2, compared with patients classified as having zero–low CalcIndex, all measures of body morphology were lower in patients with intermediate–high CalcIndex in unadjusted comparisons (height, P = 0.024; weight, P = 0.008; BMI, P = 0.064; BSA, P = 0.005).
Lesion characteristics are presented in Table 2. Lesions located in the left anterior descending (LAD) coronary artery comprised 44% of all lesions. With the exception of a small number of lesions imaged in the diagonal branch of the LAD, there was no difference in the distribution of lesions with zero–low vs. intermediate–high CalcIndex according to anatomical location in the coronary tree (Table 2). IVUS imaging analyses revealed that reference vessel and three-dimensional vessel and lesion characteristics were concordant with CalcIndex, with greater CalcIndex being associated with various measures of increasing vessel and lesion size, including greater reference vessel EEM CSA, greater plaque burden and greater lesion length. There was no relationship between CalcIndex and cross-sectional lesion characteristics at the minimal lumen area site (Table 2).

Logistic regression was then performed to evaluate the relationships between body morphometric parameters (height, weight, BMI, BSA) and the presence of intermediate–high (vs. zero–low) CalcIndex (Table 3). In both unadjusted and adjusted multivariable regression models, all measures of body morphology displayed an inverse association with CalcIndex. In the adjusted multivariable models, both weight and BSA were significant inverse predictors of CalcIndex. We then assessed if the inverse association between BSA and CalcIndex was consistent across differing clinical subgroups. Across all examined subgroups, there were no significant differences identified, with the inverse association between BSA and CalcIndex persisting across groups differing according to age, gender, race, diabetes, renal impairment, smoking status, hyperlipidaemia, and hypertension.
Interaction 0.1 for all subgroups) (Figure 3A). Similarly, for the inverse relationship between weight and CalcIndex, there were no significant differences among all examined subgroups (Figure 3B).

Discussion

The complex biology of vascular calcification is only beginning to be understood. Important recent insights include the role of circulating calcifying cells, the possibility that osteoclast-like cells may increase vascular osseous tissue, and that a close association exists between bone metabolism and the vasculature. Of relevance, CAC is a positive predictor of future cardiovascular events and mortality.

In this study, we investigated the relationship between body morphology and CAC among patients undergoing PCI using three-dimensional IVUS. Although computed tomographic (CT) scanning is often used for this purpose, two-dimensional IVUS is known to offer superior sensitivity, while three-dimensional IVUS has been validated ex vivo and is highly accurate for the assessment and quantification of arterial calcification. The superior sensitivity of IVUS and CalcIndex for CAC detection is highlighted by the fact that in the CT-based MESA study, 40% of subjects had no detectable CAC, while only 15.9% (55/346) of our subjects had no index lesion calcification. Moreover, the current study represents one of the largest three-dimensional IVUS data sets ever analysed. The principal findings were (i) index lesion CalcIndex was inversely associated with body size, including weight, height, and BSA; (ii) the inverse relationship between CalcIndex and either weight or BSA persisted in multivariable regression models after adjustment for relevant clinical covariates; (iii) these relationships were consistent across multiple clinical subgroups.

To date, the overwhelming majority of studies that examined the relationship between CAC and body size was performed in homogeneous populations of middle aged Caucasians without known coronary artery disease. These studies, almost always performed using CT scanning, generally reported a positive association between CAC and body size. Because the current study used a more sensitive imaging modality in an older population of patients with significant coronary artery disease, our findings are not in conflict with these earlier reports. Rather, our data potentially indicate a more complex relationship between body morphology and CAC. Including the current study, a series of reports have suggested that a ‘U-shaped’ relationship exists between CAC and body size. That is, an initial positive association between body size and CAC may later become inverse due to older age or other factors. Interestingly, this hypothesis is consistent with the widely held belief that vascular calcification is more prevalent in ‘little old’ patients. Although our findings were similar between patients older vs. younger than 65 years of age (Figure 3), this may be due to the fact that there were few ‘young’ patients in this study, with only 59/346 (17.1%) being <55 years of age. By comparison, in many of the CT-based studies discussed above, the mean age was 55 years or less. Provocatively, in the CT-based Rotterdam study of older patients (mean age 72 years), obesity tended to be inversely related to the degree of arterial calcification in women.
There are multiple biological pathways that might account for our findings. We originally undertook these investigations because bone mineralization is inversely related to CAC,\(^5,6,8\) but positively associated with measures of body size including weight, BMI, and BSA.\(^9\) – 11 In addition, a reasonable temporal concordance exists between the approximate age of the onset of accelerated bone

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Table 2  Baseline lesion characteristics according to groups of none or low CalcIndex vs. intermediate or high CalcIndex

<table>
<thead>
<tr>
<th>Lesion location</th>
<th>Zero or low CalcIndex (0–0.1399), n = 152</th>
<th>Intermediate or high CalcIndex (0.1400–1.2541), n = 194</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left main</td>
<td>3.3% (5)</td>
<td>1.5% (3)</td>
<td>0.303</td>
</tr>
<tr>
<td>LAD</td>
<td>42.7% (65)</td>
<td>45.9% (89)</td>
<td>0.587</td>
</tr>
<tr>
<td>LAD branch (diagonal)</td>
<td>6.6% (10)</td>
<td>1.5% (3)</td>
<td>0.020</td>
</tr>
<tr>
<td>LCx</td>
<td>13.8% (21)</td>
<td>14.9% (29)</td>
<td>0.878</td>
</tr>
<tr>
<td>LCx branch (OM, LPL, ramus intermedius, LPDA)</td>
<td>7.9% (12)</td>
<td>7.2% (14)</td>
<td>0.839</td>
</tr>
<tr>
<td>RCA</td>
<td>22.4% (33)</td>
<td>26.8% (52)</td>
<td>0.315</td>
</tr>
<tr>
<td>RCA branch (RPL, RPDA, AV continuation)</td>
<td>4.0% (6)</td>
<td>2.1% (4)</td>
<td>0.345</td>
</tr>
</tbody>
</table>

Intravascular ultrasound

Reference site\(^a\)

- EEM CSA (mm\(^2\)) 11.5 ± 4.3 13.4 ± 4.9 0.0003
- Luminal CSA (mm\(^2\)) 6.6 ± 2.2 6.8 ± 2.3 0.3075
- Plaque burden 0.42 ± 0.10 0.48 ± 0.10 <0.0001

Minimum luminal area site

- EEM CSA (mm\(^2\)) 11.0 ± 4.2 11.7 ± 4.3 0.1403
- Luminal CSA (mm\(^2\)) 3.1 ± 1.2 3.2 ± 1.3 0.7081
- Plaque and media CSA (mm\(^2\)) 7.8 ± 3.7 8.5 ± 3.7 0.1137
- Plaque burden 0.70 ± 0.09 0.71 ± 0.09 0.1460

Three-dimensional IVUS data

- EEM volume (mm\(^3\)) 101.7 ± 73.5 148.3 ± 121.7 <0.0001
- Luminal volume (mm\(^3\)) 39.1 ± 25.8 51.7 ± 32.3 0.0001
- Plaque and media volume (mm\(^3\)) 62.6 ± 50.3 96.7 ± 91.7 <0.0001
- Plaque burden 0.59 ± 0.08 0.62 ± 0.08 0.0004
- Remodelling Index 0.96 ± 0.18 0.88 ± 0.17 0.0001
- Lesion length (mm)\(^b\) 8.9 ± 5.9 11.8 ± 9.2 0.0009
- Maximal calcium arc (°)\(^b\) 46.4 ± 46.7 199.6 ± 93.5 <0.0001
- Calcium length (mm)\(^b\) 2.3 ± 2.9 9.0 ± 6.4 <0.0001

Values are means ± SD or % (n).

\(^a\)Calculated as the average of the proximal and distal reference sites.

\(^b\)These variables are used to derive the CalcIndex (calcium length/lesion length × maximal calcium arc/360°).

Table 3  Unadjusted, partial, and adjusted multivariable regression models evaluating predictors of intermediate–high CalcIndex with measures of body morphology (height, weight, BMI, BSA) as independent covariates

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted Mutually adjusted for gender and age</th>
<th>Multivariable regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio  P-value</td>
<td>Odds ratio  P-value</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>0.985  0.025</td>
<td>0.977  0.051</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.985  0.009</td>
<td>0.986  0.022</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>0.964  0.066</td>
<td>0.967  0.093</td>
</tr>
<tr>
<td>BSA (m(^2))</td>
<td>0.299  0.005</td>
<td>0.330  0.014</td>
</tr>
</tbody>
</table>

Other independent covariates included in the adjusted multivariable models were gender, age, race, current smoking, former smoking, hypertension, hyperlipidaemia, diabetes, chronic renal impairment, and prior congestive heart failure.
Figure 3  Forest plots demonstrating associations between (A) BSA and CalcIndex, and (B) weight and CalcIndex, in clinically relevant subgroups. BSA and weight were treated as continuous variables. Current and former smokers were combined in this analysis as the ‘smoking’ category. Boxes represent age-, gender-, and race/ethnicity-adjusted ORs for CalcIndex; lines represent 95% confidence intervals. Abbreviations not previously defined: DM, diabetes mellitus.
loss\textsuperscript{37} and increasing vascular calcification.\textsuperscript{32} Therefore, a possible explanation for our findings may be that reduced body size with older age, in combination with other factors like menopause, leads to decreased bone mineral density which in turn leads to increased arterial calcification. In support of this, Shen et al.\textsuperscript{38} recently reported that a higher rate of bone loss is independently associated with an increased incidence of cardiovascular disease. Nevertheless, other explanations for our observations are also plausible, including that obese subjects with severe CAC do not survive to older age.

At the molecular level, numerous signalling pathways have been identified that regulate vascular calcification and bone mineralization. Notably, knockout of the klotho gene in mice leads to premature ageing, mediat vascular calcification, and reduced bone mineral density.\textsuperscript{39} In humans, a relatively common functional klotho variant is an independent risk factor for coronary artery disease.\textsuperscript{40} Similarly, genetic knockout of osteoprotegerin leads to mediat vascular calcification and decreased bone mineral density.\textsuperscript{41} Additional factors and signalling pathways that may be involved include fibroblast growth factor-23, fetuin-A,\textsuperscript{22,42} phosphate metabolism,\textsuperscript{43} and inflammation.\textsuperscript{26,27} Furthermore, circulating bone marrow-derived calcifying cells are also implicated in the bone-vascular axis.\textsuperscript{22} Future biomarker studies geared towards investigating these pathways will be critical for understanding the interactions between body size, bone mineralization, and vascular calcification.

Our results are in agreement with several other cardiovascular ‘obesity paradoxes’. These include (i) a survival advantage for obese patients following coronary revascularization\textsuperscript{14}; (ii) reduced B-type natriuretic peptide levels and mortality in obese patients with heart failure\textsuperscript{45,46}; (iii) reduced survival in lean patients undergoing valvular heart surgery\textsuperscript{47}; (iv) a higher prevalence of hypertension, left ventricular hypertrophy, and increased mortality in lean haemodialysis patients\textsuperscript{48}; and (v) improved survival and a lower risk of major vascular events after ischaemic stroke in overweight and obese patients.\textsuperscript{49,50} An important next step to delineate these ‘paradoxical’ relationships, including the current findings, is to define the relative importance of the morphological components that contribute to obesity, including lean mass vs. fat mass, and visceral vs. subcutaneous adipose tissue. Additional study is also required to determine whether vascular calcification plays a mechanistic role in some of these ‘obesity paradoxes’, like the survival advantage seen in obese patients after coronary revascularization. In other words, our findings provide support to the hypothesis that among an older population of patients with clinically significant coronary artery disease, one of the reasons why lean patients with a low body weight and/or BMI may ‘paradoxically’ suffer from more cardiovascular events than obese patients may be due their increased burden of calcific vascular disease.

### Study limitations

We did not measure total CAC in the entire coronary tree, or other measures of body size or adiposity such as the waist/hip ratio. Body habitus at the time of PCI was unlikely to reflect lifetime BMI, BSA or weight. Grey scale IVUS is limited when compared with virtual histology (VH) IVUS to assess other plaque components such as a necrotic core, and it would be of relevance to compare VH-IVUS plaque components with body morphology parameters. Although this data set represents one of the largest three-dimensional IVUS data sets ever compiled, it remains relatively underpowered to examine complex biological associations.

### Conclusions

Converging lines of evidence indicate a complex, age-dependent interplay between CAC and body morphology. In this large three-dimensional IVUS data set, we identified an independent, inverse relationship between body size and index lesion CAC in patients with significant coronary artery disease. These findings alter our framework for understanding vascular calcification and open the door to further studies investigating the interactions between body morphology, bone, and vascular disease. Moreover, our data indicate that reduced body weight or lower BSA are independent clinical risk factors for advanced calcific coronary artery disease.

### Acknowledgement

We thank Qi Zheng for her assistance with data preparation and formatting.

### Funding

No specific funding was used to perform this study.

### Conflict of interest:

The following authors have no conflicts of interest to declare: S.M.E., J.R.L., A.P.C., A.N.-K., N.G., A.H., U.B., S.S., M.F., and V.F. J.K. is supported by National Institutes of Health Grant K08HL111330 and has received research support from AstraZeneca. A.M. has received a research grant and acted as consultant for Boston Scientific. G.S.M. is a consultant and has received grant support from Boston Scientific and Volcano. G.D.’s spouse has received consultant honoraria from Boston Scientific.

### References

CAC and body morphology


