Long-term prognosis and outcome in patients with a chest pain syndrome and myocardial bridging: a 64-slice coronary computed tomography angiography study

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Background
Small case series have associated coronary myocardial bridging (MB) with adverse cardiac events. However, the clinical significance of MB in unselected patients with chest pain remains unclear. The purpose of this study was to explore the relation between the presence of isolated MB and subsequent adverse cardiac events in symptomatic patients referred for coronary computed tomography angiography (CCTA).

Methods and results
Three hundred and thirty-four consecutive patients (age 57 ± 13 years, 43% female) with chest pain and no prior history of coronary artery disease (CAD) who underwent 64-slice CCTA and had no obstructive CAD (≥50% coronary luminal obstruction) were included. Patients were followed for cardiac events [cardiovascular (CV) death or non-fatal myocardial infarction (MI)] over 6.1 ± 1 years. Outcomes were compared between patients with MB vs. those without MB using the Cox models. MB was present in 117 out of 334 (35%) patients on CCTA and 80% of MB involved the mid-distal left anterior descending coronary artery. During a mean follow-up duration of 6.1 ± 1 years, cardiac events occurred in 6 out of 117 (5.1%) patients with, and 7 out of 217 (3.2%) patients without MB (P = 0.40). Univariate predictors of cardiac events were hypertension [hazards ratio (HR) = 10.6, P = 0.002], diabetes mellitus (HR = 4.8, P = 0.01), and older age (HR = 1.1, P = 0.0004). The association of hypertension and age with adverse cardiac events remained statistically significant after adjusting for other variables. Neither the presence nor the extent of MB was associated with an increased risk of cardiac events.

Conclusion
MB is a common finding on CCTA among patients presenting with chest pain but no obstructive CAD. No association was evident between MB and the risk of CV death or MI.

Keywords
Coronary computed tomography angiography • Prognosis • Myocardial bridging • Coronary artery disease

Introduction
Myocardial bridging (MB) occurs when a segment of an epicardial coronary artery takes an intramyocardial course, causing it to be covered by a bridge of myocardium,1 thereby leading to systolic compression of the tunnelled segment. However, there is variability in the severity of MB and compression. The artery may lie in a muscular gorge with a very thin overlying muscle segment when systolic compression may occur by a twisting action of deep muscle fibres rather than by the overlying bridge.2 MB was first reported at autopsy in the year 17372 and angiographically in 1960.3 MB is usually confined to the mid to distal portion of the left anterior descending coronary artery (LAD), and its reported prevalence has varied substantially depending on

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the imaging modality and methods employed. While prevalence using invasive angiography was reported to range from 0.15 to 16%, a prevalence of ~40% was reported following treatment with nitroglycerine. A recent study using intravascular ultrasound of the LAD reported a prevalence of 23% in patients with advanced symptomatic coronary artery disease (CAD), and autopsy reports (considered the gold standard) have shown a variable prevalence ranging from 15 to 80%. Coronary computed tomography angiography (CCTA) using contemporary multi-slice scanners may be a useful non-invasive method to demonstrate MB, and initial reports have shown a prevalence of 18–58%.

The presence of MB has been associated with a variety of adverse cardiac events such as acute coronary syndromes, coronary spasm, and even sudden death, but the data are derived from small series of selected patients. Thus, the precise clinical significance and therapeutic implications of MB remains unknown. The availability of 64-slice CCTA has made it possible to non-invasively detect MB. Hence, the aim of the present study was to describe the prevalence and anatomic characteristics of MB in relation to patient outcomes, among a cohort of consecutive symptomatic patients without obstructive atherosclerotic CAD undergoing CCTA.

Methods

This was a prospectively planned study with prospective collection of clinical data. Written informed consent for long-term follow-up was obtained prospectively in accordance with Institutional Review Board requirements. Outcome data were collected retrospectively from computerized records at the end of the study period.

Patients

During a 12-month period (January–December 2005), 648 patients with chest pain syndromes were referred for 64-slice CCTA. Of these, 314 had prior history of obstructive CAD or coronary revascularization, or had obstructive CAD (>50% coronary luminal obstruction) on CCTA and were excluded from further analysis to avoid CAD-related events. The study population therefore consisted of 334 consecutive symptomatic patients with diagnostic quality CTA scans without known obstructive CAD and no obstructive disease on current CCTA. We did not exclude symptomatic patients with compromised left ventricular function or valvular heart disease who were referred for CCTA to rule out obstructive CAD.

A routine structured interview on the day of CCTA provided information regarding baseline data and risk factors: (i) diabetes mellitus (patient history and/or treatment with insulin or oral hypoglycaemic agents); (ii) hypercholesterolaemia (total serum cholesterol level ≥5 mmol/L or treatment with lipid-lowering drugs); (iii) systemic hypertension (blood pressure >140/90 mmHg or treatment with anti-hypertensive medication); (iv) family history of CAD (CAD in first-degree relatives <55 (male) or <65 (female) years of age); and (v) smoking history (previous or current cigarette smoking).

Imaging protocol

CCTA was performed using a 64-channel scanner (Brilliance 64, Philips Healthcare, Cleveland, OH, USA), with retrospective electrocardiographic (ECG) gating. Oral and/or intravenous β-blockers (verapamil in asthmatic patients) were used to lower heart rate when >70 bpm. Sublingual nitroglycerine (0.4 mg) was given prior to CCTA, provided that systolic blood pressure was ≥110 mmHg. The coronary artery calcium (CAC) score (Agatston units) was measured on a non-enhanced scan (3 mm slice thickness reconstruction) and a contrast-enhanced scan was then performed using a bolus of contrast medium (Ultravist 370 mg I/mL, Schering AG, Berlin, Germany) injected into an antecubital vein at a flow rate of 5–6 mL/s, followed by a 50 mL saline chaser bolus. Scanning was performed at 120 kV, effective tube current 600–1000 mAs, detector collimation 64 × 0.625 mm, 0.42 s gantry rotation time, and pitch 0.2 as a standard. ECG-based tube current modulation was used to decrease radiation when possible. We used multi-cycle scan image reconstruction with CC filter (Philips) and slice thickness reconstruction of 0.67 mm with 50% overlap and a spatial resolution cut-off of ~10 lp/cm. Reconstruction was performed using a window centred at 75% of the R–R interval as default (to coincide with ventricular diastasis). For heart rates above 70 bpm, an earlier reconstruction phase (usually 50% or less) was frequently used (coinciding with isovolumic relaxation). If motion artefacts were apparent, additional reconstruction windows were analysed.

CCTA analysis

CCTA were analysed using a number of available methods, including axial views, cross-sectional imaging (‘double oblique’), and multi-planar reformation (MPR). MB was diagnosed when a segment of an epicardial coronary artery took an intramyocardial course causing it to be covered by a bridge of myocardium. We included, as have others, arterial segments present in a myocardial gorge such that they might be compressed by surrounding muscle fibres even if not fully encased by visible bridging fibres. MB (intramyocardial) segments were identified prospectively at the time of primary CCTA analysis and then the identified segments were further analysed retrospectively to define further MB details. Reconstructed MPR images were analysed for the presence of coronary atherosclerosis and the presence of MB. MB segments were categorized as complete encasement with myocardium or partial encasement with myocardium. Partial encasement by CCTA referred to arterial segments located in a deep gorge surrounded by myocardium but not covered completely (360°), where a small portion of their diameter (in an axial view) may only be covered by a thin layer of muscle or fibrous-fatty tissue. Those partially encased variants (figure 1) were included (as in previous reports) because it was reported that they also may be compressed during systole by the surrounding muscle.

MB segments were also measured for length and depth (maximal distance from the epicardial surface) using measurements tools available on the workstation such as cross-sectional (‘double oblique’) orientation for measurement of the vessel deepest location of MB and curved and straight multi-planar reformation for evaluation of MB length (figure 2). The MB muscle index was also calculated by multiplying MB length and maximal thickness (depth).

Assessment of clinical outcome events

Patients were followed for a mean duration of 6.1 ± 1 years. Retrospective analysis of electronic records of hospitalizations and mortality was undertaken at the end of the study period. The HMO record system allowed us to track all hospitalizations (nationwide) and death certificates (from the national registry of the Ministry of the Interior) in a single computerized medical record.

The composite clinical endpoint in this study (adverse cardiac event) was defined as cardiovascular (CV) death or non-fatal myocardial infarction (MI). CV death was defined as any death with no clear
non-cardiac cause. MI was diagnosed according to standard definition (serum cardiac biomarker elevation with symptoms of ischaemia and/or ECG changes indicative of new ischaemia/infarction). Since patients were referred to CCTA for evaluation of symptoms, all CCTA findings were made known to patients and referring physicians.

**Figure 1** Axial (A, see arrows) and curved multiplanar reformation (B) of normal LAD with full epicardial course, partial encasement MB, and MB with full encasement.

**Figure 2** CT workstation analysis methodology for measurement of MB length and maximal depth: curved multiplanar reformation used to identify MB and location of maximal depth (A), cross-sectional imaging to measure maximal depth (B) and (straight) multiplanar reformation to evaluate MB length (C).

**Statistical analysis**

Statistical analysis was performed using SPSS (V.18, PASW Statistics, Chicago, IL, USA). Differences in baseline characteristics across the two study groups (with and without MB) were compared using analysis of variance or Student’s t-test for continuous variables and \( \chi^2 \) for
categorical variables. Extent of CAC in study groups was examined with a non-parametric test (Mann–Whitney U-test) and CAC scores were normalized by logarithmic conversion of CAC score + 1 prior to regression analysis. Association between MB, CAD risk factors, and non-obstructive CAD on CCTA was examined using logistic regression. The Cox time-based regression analysis was performed to examine predictive values for adverse cardiac events. In an attempt to avoid ‘over fitting’ a multi-variate model due to the limited number of outcome events, serial bivariate analysis was performed to assess the predictive value of variables while controlling for other variables serially. Hazard ratios (HRs) were then calculated [including 95% confidence intervals (CI)]. Event-free survival curves were constructed using the Kaplan–Meier method and differences between the groups examined using the log-rank test. A P-value of <0.05 was considered significant.

**Results**

**Patients**

Three hundred and thirty-four patients with chest pain but without obstructive CAD were included in the study. Of the 334 patients, 64 (19%) had typical angina, 263 had atypical angina or non-anginal chest pain (79%), and 8 patients (2%) had angina equivalent symptoms (dyspnoea) as their chief complaint. Twelve patients had a history of cardiomyopathy or significant valvular disease (two had both cardiomyopathy and valvular disease). Baseline patient characteristics are presented in Table 1.

**CCTA data**

All 334 CCTA studies were of diagnostic quality and all available segments were analysed. All patients were in sinus rhythm and the mean heart rate during CCTA was 64 ± 9 (range 42–87) bpm. The mean contrast dose was 79 ± 15 (range 40–120) mL. The mean estimated effective radiation dose (dose length product x 0.014) for CT (including both the non-contrast and contrast-enhanced scans) was calculated to be 11.1 ± 1.9 (range 7.1–16.2) mSv varying primarily in relation to patient weight, scan length, and whether ECG-based tube current modulation was used.

**Table 1** Baseline characteristics of 334 symptomatic patients undergoing 64-slice CCTA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients</th>
<th>Patients without MB</th>
<th>Patient with MB</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>334</td>
<td>217</td>
<td>117</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>57 ± 13</td>
<td>57 ± 12</td>
<td>57 ± 13</td>
<td>0.3</td>
</tr>
<tr>
<td>Female</td>
<td>145 (43%)</td>
<td>105 (48%)</td>
<td>40 (34%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td>121 (36%)</td>
<td>84 (39%)</td>
<td>37 (31%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>42 (12%)</td>
<td>25 (11%)</td>
<td>17 (14%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>127 (38%)</td>
<td>78 (36%)</td>
<td>49 (42%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Smoking history</td>
<td>68 (20%)</td>
<td>42 (19%)</td>
<td>26 (22%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>45 (13%)</td>
<td>24 (11%)</td>
<td>21 (18%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>6 (2%)</td>
<td>5 (2%)</td>
<td>1 (0.8%)</td>
<td>0.34</td>
</tr>
<tr>
<td>History of significant valvular disease</td>
<td>7 (2%)</td>
<td>4 (1.8%)</td>
<td>3 (2.5%)</td>
<td>0.7</td>
</tr>
<tr>
<td>History of left ventricular dysfunction</td>
<td>7 (2%)</td>
<td>4 (1.8%)</td>
<td>3 (2.5%)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**Table 2** Coronary arterial distribution of MB among 117 patients with MB [n (%) of patients with MB]

<table>
<thead>
<tr>
<th>Location</th>
<th>n (%) of patients with MB</th>
</tr>
</thead>
<tbody>
<tr>
<td>All LAD</td>
<td>94 (80)</td>
</tr>
<tr>
<td>Mid or distal LAD</td>
<td>84 (71)</td>
</tr>
<tr>
<td>Diagonal branch</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Marginal branch</td>
<td>15 (13)</td>
</tr>
<tr>
<td>Ramus intermedium branch</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

**Prevalence and characteristics of MB**

One hundred and seventeen patients (35%) had MB on CCTA (Figure 1). As previously suggested, MB tended to be more prevalent among patients with left coronary dominance (20/43, 47%) than in those with right dominance (94/280, 34%) or balanced circulation (3/11, 27%) (P = 0.09).

In the majority (84, 71%) of patients with MB, MB segments involved the LAD (mid or distal of main vessel); in 33 (29%), MB was confined to other segments of the coronary vasculature, mostly to a diagonal or a marginal branch. Seventy-three per cent of MB demonstrated complete myocardial encasement. Exact vessel distribution and anatomic description of MB segments by CCTA are given in Tables 2 and 3.

**Prevalence of non-obstructive coronary atherosclerosis**

One hundred and seventy-three patients (52%) had (non-obstructive) coronary atherosclerosis per CCTA. The prevalence of non-obstructive CAD was higher among patients with MB (74/117, 63%) than in those without MB (99/217, 45%) (P = 0.0002). The greater prevalence of CAD among patients with MB remained significant following correction for CAD risk factors (age, gender, hypertension, diabetes, hyperlipidaemia, family history, and smoking history). Consistent with the latter, CAC score was also higher in patients with MB; CAC score >0
was found in 66 (56.4%) patients with MB vs. 55 patients (25.3%) in patients without MB ($P < 0.001$) [median 3 (inter-quartile range 0, 97) vs. 0 (0, 1) respectively, $P < 0.001$]. In 59 out of 74 (80%) patients with MB and CAD (non-obstructive), CAD was detected proximal to the MB segment.

**Patient outcome**

The mean follow-up was 6.1 ± 1 (range 0.2–6.9) years and was similar for both study groups (Table 4).

During the follow-up, there were 13 patients who suffered an outcome event: CV death in 10 patients (including two fatal MI) and non-fatal MI in 3 patients (event rate 0.6%/year). CV death or MI occurred in 6 out of 117 (5.1%) patients with MB (incidence 0.8%/year), and in 7 out of 217 (3.2%) patients without MB (incidence 0.5%/year) ($P = 0.40$) (Table 4).

Of the 10 CV deaths, 6 (3 in each group) were heart failure-related events among the 12 patients with non-ischaemic cardiomyopathy (idiopathic dilated cardiomyopathy or the result of longstanding valvular disease). Another nine patients died of non-cardiac causes (Table 4).

Of note, during the follow-up period, none of the patients with MB underwent coronary revascularization (stent or surgery) for the purpose of treating MB.

Analysis of the MI episodes in the two patients with MB who suffered MI during follow-up (and underwent invasive angiography) showed that the culprit lesion was proximal to the MB segment in both. In one patient with anterior MI, the culprit was the proximal LAD just proximal to mid-LAD MB, and in the other patient, the culprit lesion was in the first marginal branch proximal to a bridged segment.

**Predictors of outcome events**

Univariate variables associated with CV death or MI were hypertension, diabetes mellitus, and increasing age (Table 5). The presence of non-obstructive coronary atheroma on CCTA was not associated with a statistically significant increased risk of outcome events and in keeping with this, neither the normalized (log) CAC score nor CAC score were significant predictors of CV death or MI: [log (CAC + 1)] 1.16, 95% CI 0.94–1.4 per unit log CAC + 1, $P = 0.16$; CAC > 0, HR 1.09, 95% CI 0.36–3.35, $P = 0.87$).

Most importantly, MB was not associated with increased risk of adverse outcomes ($P = 0.40$). Increased depth and length of the MB segments, or their product (‘MB muscle index’) were also not predictors of events. The Kaplan–Meier curves in relation to the presence or absence of MB are shown in Figure 3.

Multi-variable analysis (serial bivariate) showed that the association of hypertension and age with adverse cardiac events remained statistically significant after adjusting for other variables such as other coronary risk factors, presence of CAD by CCTA, or presence of MB.

**Discussion**

The major finding from this study is that among a cohort of symptomatic patients referred for CCTA and who had no obstructive CAD, we observed a relatively high 35% prevalence of MB. In this cohort: (i) a very low rate of cardiac outcome events was found over a follow-up period of more than 6 years, and (ii) adverse CV outcome events were no more frequent than in patients without MB. This was so despite a higher CAC score and greater prevalence of non-obstructive atherosclerotic disease in the MB cohort probably related to a greater proportion of men with MB.
The findings have important clinical implications as the contribution of MB to the clinical symptoms of patients with chest pain is difficult to determine in daily practice and its management in symptomatic patients without obstructive CAD poses a common dilemma.

MB segments are usually narrower than proximal segments and occasionally also narrower than distal segments. While the narrowing is greater during systole, it may still be apparent in diastole. Better appreciation of the physiological significance of MB in symptomatic patients can be achieved using invasive haemodynamic assessment. This may be achieved by estimation of the coronary flow reserve (CFR), where early diastolic ‘fingertip phenomenon’ may be seen in the CFR tracing representing a sudden reduction in myocardial tension and resistance at the level of the microcirculation or by estimation of the fractional flow reserve (FFR) (especially the diastolic FFR) during stimulation of heart rate and contractility with dobutamine stress.

Despite appreciation of the haemodynamic significance (usually with invasive methods) of MB, the contribution of MB segments to the clinical scenario and to cardiac events is difficult to estimate. MB segments were reported to be relatively ‘immune’ to the atherosclerotic process, even when other segments of the coronary arteries were involved. MB segments may be protected from erosclerotic process, even when other segments of the coronary arteries were reported to be relatively ‘immune’ to the atherosclerotic process. The findings have important clinical implications as the contribution of MB to the clinical symptoms of patients with chest pain is difficult to determine in daily practice and its management in symptomatic patients without obstructive CAD poses a common dilemma.

In an attempt to address clinical needs in patients with MB, various therapeutic options have been suggested to treat symptomatic patients, including medical treatment (especially β-adrenergic blocker and non-dihydropyridine calcium antagonists), coronary stenting (considered controversial), and surgery (myotomy). Our findings suggest that MB (per CCTA) has a benign prognosis in the large majority of patients, and it is therefore unlikely that coronary intervention would reduce this further.

**Limitations**

This study may have selection bias and perhaps higher prevalence of MB than in the general population, as patients with more symptoms (or inconclusive stress test results) were more likely to be referred for CCTA and the prevalence of MB may vary significantly with patient selection. However, our aim was to compare the rate of ‘hard’ outcome events in relation to the finding of MB in this very group of patients with chest pain but no obstructive CAD referred for CCTA. Owing to selection of patients without obstructive coronary disease, overall event rates were low, limiting the positive predictive value of the study. In patients with both MB and obstructive CAD, the changes in flow dynamics might conceivably lead to an interaction between the MB and the obstruction, leading to a higher rate of events than in patients with CAD alone. The data in the current study relate only to individuals without obstructive CAD.

In addition, the lack of association between non-obstructive CAD (and CAC score) and outcome events may be related to the low power for this in our study and the low event rate overall as the association between non-obstructive CAD per CCTA and outcome events had been demonstrated.
A further limitation of our study is the lack of information on long-term pharmacotherapy. Inequality in preventive therapy for non-obstructive atherosclerotic coronary disease could lead to (or hide) a differing rate of outcomes in the MB and non-MB cohorts, although we have no reason to suspect a systematic difference in this regard. A systematic bias in pharmacotherapy directed at symptoms related to the myocardial bridge may have been present, but the effectiveness of such treatment in the prevention of hard outcome events is doubtful.

Since this was a retrospective outcome analysis, no prior assessment of required study size was performed. Post-factum, we calculated that given the observed event rate in the non-MB group of 3.2%, the study had 80% power to detect a 12% event rate in the MB group with an $\alpha$ of 0.05 over the 6 years of follow-up. Thus, an annual event rate of up to 2% in the MB cohort might have been missed. On the other hand, a 6-year follow-up is relatively limiting and even in this relatively large clinical cohort of MB patients can clearly not address the issue of lifetime risk of events.

Conclusions

MB is a relatively common finding on CCTA among patients presenting with chest pain but no obstructive CAD and is not always confined to the LAD. No association was evident between MB on CCTA and increased risk for CV death or MI during 6 years of follow-up.

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References