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Authors: Jaskanwal DS Sara, MBChB; Michel T. Corban, M.D; Megha Prasad, M.D; Abhiram Prasad, M.D; Rajiv Gulati, M.D, PhD; Lilach O Lerman, M.D, PhD; Amir Lerman, M.D

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The Prevalence of Myocardial Bridging Associated with Coronary Endothelial Dysfunction in Patients with Chest Pain and Non-Obstructive Coronary Artery Disease

Jaskanwal DS Sara, MBChB¹, Michel T. Corban¹, Megha Prasad, MD¹, Abhiram Prasad, MD¹, Rajiv Gulati, MD, PhD¹, Lilach O Lerman, MD, PhD², Amir Lerman, MD¹

¹Division of Cardiovascular Diseases, Mayo College of Medicine, Rochester, MN, USA
²Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

Short Title: Myocardial Bridging and Endothelial Dysfunction
Introduction

Myocardial bridging (MB), characterized by the epicardial coronary vessel diving into the myocardium, is present in up to 1/3rd of adults and is associated with angina and acute coronary syndromes. MB is accompanied by altered blood flow mechanics, regional changes in wall shear stress and accelerated atherosclerosis potentially through its effects on endothelial function. However, the association between MB and endothelial dysfunction remains incompletely understood. The purpose of this study was to determine the association between myocardial bridging and coronary endothelial dysfunction.

Methods and Results

Patients presenting with chest pain and found to have nonobstructive CAD (stenosis < 40%) at angiography underwent an invasive assessment of epicardial and microvascular endothelial function. Epicardial endothelial function was assessed by measuring the percent change in coronary artery diameter in response to intracoronary infusions of acetylcholine (%ΔCADACH). Epicardial endothelial dysfunction was defined as a %ΔCADACH of < -20%. Microvascular endothelial function was assessed by the percent change in coronary blood flow in response to intracoronary infusions of acetylcholine (%ΔCBFACH), and microvascular endothelial dysfunction was defined as a %ΔCBFACH of < 50%. MB was diagnosed angiographically by identifying the characteristic reduction in minimal luminal diameter during systole. Patients were divided into those with and without MB, and the frequency of epicardial endothelial dysfunction and microvascular endothelial dysfunction was compared between patients with versus those without MB. Between 1993 and 2012, 1,469 patients (mean age 50.4 years, 35% male) underwent coronary angiography and invasive testing of endothelial function. Three hundred eighty eight (26.4%) had epicardial endothelial dysfunction in at least one segment of the LAD and 763 (51.9%) had microvascular endothelial dysfunction. Two hundred eight (14.2%) patients were found to have MB in the LAD, of which 110 (52.9%) had MB in the mid segment only, 52 (25%) had MB in the mid segment only, 52 (25%) had MB in the
distal segment only and 46 (22.1%) had bridging in both the mid and distal segments. Patients with any MB had a significantly higher frequency of endothelial dysfunction within the mid and/or distal vessel segment compared to patients without MB (60.1% vs. 50.4%, p=0.012). Patients with any MB had a tendency towards a higher frequency of microvascular endothelial dysfunction compared to those without MB (57.7% vs. 51.0%, p=0.075). In multivariate analyses, mid and/or distal vessel MB was a significant predictor of mid and/or distal vessel epicardial endothelial dysfunction (OR, 95% CI, 1.44, 1.04 – 2.00, p=0.029) and of microvascular endothelial dysfunction (OR, 95% CI, 1.34, 1.00 – 1.82, p=0.050).

Conclusion

MB co-localizes with epicardial endothelial dysfunction and is significantly associated with microvascular endothelial dysfunction in symptomatic patients with nonobstructive CAD supporting its potential role as a mechanism for angina in symptomatic patients with MB. Patients with MB may therefore benefit from current treatment programs implemented in patients with endothelial dysfunction.

Classifications

Stable Angina

Single Vessel Disease

Miscellaneous

Other Technique
Condensed Abstract

The association between myocardial bridging (MB) and endothelial dysfunction remains incompletely understood. In the current study, we evaluated the relationship between invasively measured epicardial and microvascular coronary endothelial dysfunction and MB in patients with chest pain and nonobstructive coronary disease. Amongst 1,469 patients who underwent coronary angiography and invasive testing of endothelial function, 208 (14.2%) had MB. Patients with MB had a higher frequency of epicardial endothelial dysfunction within the same vessel segment compared to patients without MB. In multivariate analyses, MB was a significant predictor of co-localized epicardial endothelial dysfunction and microvascular endothelial dysfunction separately. These findings support the potential role of endothelial dysfunction as a mechanism for angina in symptomatic patients with MB.

Abbreviations

BMI: Body Mass Index

CAD: Coronary Artery Disease

CBF: Coronary Blood Flow

HDL: High Density Lipoprotein

LDL: Low Density Lipoprotein

MI: Myocardial Infarction

MB: Myocardial bridging


Introduction

Myocardial bridging (MB), characterized by an epicardial coronary artery ‘diving’ into the myocardium and systolic compression of the tunneled segment, is present on average in one third of adults. However, this number may underestimate the true prevalence due to under diagnosis (1, 2).

Concurrent pharmacologic provocation testing may help to uncover MB in up to 40% of individuals by enhancing systolic myocardial compression (3). MB is generally considered to be a benign condition, however its presence has been linked to angina, acute coronary syndromes (4, 5), and left ventricular dysfunction (6). Although ischemia related to MB is thought to explain these clinical manifestations (7), systolic compression of the tunneled segment alone is unlikely to be sufficient to account for severe ischemia and associated symptoms (2, 8). We have previously shown that MB is associated with impaired endothelial-dependent epicardial vasorelaxation (9), which may exacerbate the myocardial ischemia beyond structural compression alone, and may play a key role in further understanding the pathophysiology of MB.

Endothelial dysfunction represents one of the earliest stages of atherosclerosis, and is associated with plaque progression and a several fold increased risk of ischemic cardiac events (10, 11). In clinical practice it is most often recognized by an abnormal response to endothelial-dependent vasodilating agents such as acetylcholine (12). In the coronary vasculature, an attenuated increase or decrease in coronary blood flow (CBF) (13, 14) in response to acetylcholine marks the presence of microvascular endothelial dysfunction, whereas epicardial vasoconstriction indicates epicardial endothelial dysfunction (12).
MB has been shown to lead to regional alterations in concentrations of vasoactive agents such as nitric oxide synthase and endothelin-1 (15) as well as local variations in shear stress and endothelial cell morphology (2, 15). Endothelial dysfunction is characterized by decreased bioavailability of nitric oxide (16), and is also influenced by flow related shear stress (17). However the link between MB and endothelial dysfunction is incompletely understood. We aimed to evaluate the association of MB and invasively determined epicardial and microvascular coronary endothelial dysfunction in a large cohort of patients presenting with chest pain in the absence of obstructive CAD on angiography.

**Methods**

**Study Protocol**

The following protocol was approved by the Mayo Clinic Institutional Review Board. Patients were referred by their physician for assessment of chest pain. Consecutive patients presented to the cardiac catheterization laboratory in the fasting state and vasoactive cardiovascular medications such as nitrates and calcium channel blockers, were discontinued for at least 48 hours prior to catheterization. Routine clinically indicated diagnostic coronary angiography was performed on all patients using standard clinical protocols. Angiograms were reviewed prior to the infusion of any pharmacological agents. Patients with greater than 40% diameter stenosis of any coronary artery were excluded (14, 18), and the remaining patients underwent an invasive assessment of coronary endothelial function.
After intravenous administration of 5,000 - 7,000U of heparin, a Doppler guidewire (Flowire, Volcano) 0.014 inches in diameter within a 3-F. Slip-Cath Infusion Catheter (Cook Medical) was positioned into the left anterior descending coronary artery, 2-3mm distal to the tip of the infusion catheter. When measuring changes in coronary blood flow to assess microvascular endothelial function, the infusion catheter was always placed in the mid-portion of the LAD. Epicardial endothelial function was evaluated by measuring changes in coronary artery diameter separately in each of the proximal, mid, and distal vessel segments. In each case the infusion catheter with the Doppler guidewire 2-3 mm distal to the tip of the infusion catheter was placed in segment that was being interrogated, such that the tip of the Doppler guidewire sat approximately in the middle of each respective segment. Coronary artery diameter was measured in the middle of each vessel segment, at the location of the tip of the Doppler guidewire. Additional methodology related to the invasive assessment of coronary endothelial function has been described elsewhere (14, 18).

We retrospectively reviewed the coronary angiogram reports that were documented at the time of each coronary angiogram for all patients who underwent an invasive assessment of coronary endothelial function. The presence of MB was determined visually at coronary angiography by identifying segments of the coronary artery that underwent the characteristic “milking effect” between systole and diastole (8). Bridging was also characterized depending on the segment of the coronary artery in which it was identified (Figure 1).

**Baseline Characteristics**

Data was collected on conventional cardiovascular risk factors including hypertension, diabetes mellitus, hyperlipidemia, smoking status, body mass index (BMI), and biochemical parameters including serum
total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides and creatinine. Smoking was categorized as a history of current smoking, former smoking or never smoking. Hypertension was defined as a history of hypertension treated with anti-hypertensives; diabetes was defined as a history of diabetes treated with oral medication or insulin, and hyperlipidemia was defined as a history of total cholesterol levels of >240mg/dL or treatment with lipid-lowering therapy. All blood levels documented had been drawn within six weeks of the index procedure. Information was also collected on past medical history including a history of MI, and other vascular diseases (defined as a documented history of peripheral vascular disease, stroke or transient ischemic attack).

**Statistical Analysis**

Patients were stratified by presence or absence of MB. Continuous variables are presented as a mean (standard deviation) where data is approximately normally distributed and as a median (Quartile 1, Quartile 3) for skewed data. Categorical variables are presented as frequencies and percentages. Differences between the groups were tested using Student’s t-test and Wilcoxon rank-sum test for continuous variables and Pearson’s chi-squared test for proportions. Univariate and multivariate logistic regression models were fitted to assess the association between a MB and epicardial endothelial dysfunction and microvascular endothelial dysfunction. All patients with MB had mid and/or distal vessel segment bridging and thus when assessing the relationship between bridging and epicardial endothelial dysfunction, we identified the percentage of patients with mid and/or distal segment epicardial endothelial dysfunction only, and excluded the frequency of endothelial dysfunction in the proximal vessel segment. A p-value less than 0.05 was considered significant and all statistical analyses were performed using JMP 9 software (SAS Institute, Inc., Cary, NC, USA).
Results

Sample Overview

Between 1993 and 2012, 1,469 patients (mean age 50.4 years, 35% male) underwent coronary angiography and invasive testing of endothelial function. Two hundred and eight patients were found to have MB (14.2%) on coronary angiogram, all of which were within the left anterior descending coronary artery. Of these patients, 110 (52.9%) had MB in only the mid segment of the vessel, 52 (25.0%) had MB in only the distal and 46 (22.1%) had bridging in both the mid and distal segment of the vessel. No patient had bridging in the proximal segment of the vessel.

Amongst all patients, 151 (10.3%) did not undergo an assessment of epicardial endothelial dysfunction and 1 patient (0.1%) did not undergo an assessment of microvascular endothelial dysfunction. Six hundred sixty two patients (50.2%) had epicardial endothelial dysfunction in at least one segment of their epicardial artery defined as an abnormal %ΔCADAch (constriction of vessel diameter of 20% or more in response to intracoronary infusion of acetylcholine) and 763 (51.9%) had microvascular endothelial dysfunction defined as an abnormal %ΔCBFΔach (an increase of coronary blood flow of less than 50% after intracoronary infusion of acetylcholine compared to baseline). Of the 662 patients with epicardial endothelial dysfunction, 208 (31.4%) had concomitant microvascular endothelial dysfunction, and 180 patients (27.2%) had isolated epicardial endothelial dysfunction in the absence of microvascular endothelial dysfunction. Overall, 943 patients (64.2%) of all patients had evidence of epicardial and/or microvascular endothelial dysfunction. Amongst those with epicardial endothelial dysfunction, 18 patients (4.6%) had isolated proximal vessel endothelial dysfunction; 134 patients (34.5%) had isolated mid vessel endothelial dysfunction; 236 patients (60.8%) had isolated distal vessel endothelial dysfunction;
dysfunction; 14 (3.6%) had proximal and mid vessel endothelial dysfunction; 221 (57.0%) had mid and distal vessel endothelial dysfunction; and 39 patients (10.1%) had proximal, mid and distal vessel endothelial dysfunction. Amongst patients with epicardial endothelial dysfunction, 591 patients (89.3%) had mid and/or distal vessel endothelial dysfunction, and no proximal endothelial dysfunction. This group included all patients with mid and distal vessel endothelial dysfunction, isolated mid vessel endothelial dysfunction and isolated distal vessel endothelial dysfunction (Figure 2). There were no procedure related complications such as coronary dissection, myocardial infarction, stroke, life-threatening arrhythmia, major bleeding or death.

**Patient Characteristics**

Table 1 outlines differences in clinical profile between patients with versus those without MB. Overall, patients with MB were younger, and had a higher proportion of males compared to patients without MB. In addition, patients with MB had a lower frequency of hypertension, hyperlipidemia, and history of vascular disease compared to patients without MB, and also had a significantly lower total cholesterol, and glucose. All other clinical and biochemical parameters were not significantly different between groups.

**Frequency of Endothelial Dysfunction in Patients with Myocardial Bridging**

When assessing the prevalence of epicardial endothelial dysfunction amongst patients with versus those without MB, 1,318 patients underwent an invasive assessment of epicardial endothelial function. Patients who did not undergo a concurrent invasive assessment of epicardial endothelial dysfunction

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were not significantly different compared to those that did undergo an assessment for endothelial dysfunction with regards to demographic and clinical variables.

Patients with any MB, localized to the mid and/or distal vessel segment, had a significantly higher frequency of mid and/or distal endothelial dysfunction (60.1% vs. 50.4%, p=0.012) compared to patients without any MB (Figure 3). The frequency of proximal vessel endothelial dysfunction did not differ significantly between patients with versus those without any MB (8.2% vs. 6.8%, p=0.488). Patients with any MB had a tendency towards a higher frequency of microvascular endothelial dysfunction compared to patients without any MB but this did not reach statistical significance (57.7% vs. 51.0%, p=0.075) (Figure 3). When stratifying all patients by age, patients aged ≤ 50 years with any MB had a significantly higher frequency of microvascular endothelial dysfunction compared to patients without any MB (57.3% vs. 44.2%, p=0.010), suggesting that age may modify the effect of MB on the frequency of microvascular endothelial dysfunction. Amongst patients aged > 50 years the frequency of microvascular endothelial dysfunction did not vary significantly between patients with versus those without MB.

**Univariate and Multivariate Association**

In a univariate analysis, MB in the mid and/or distal segment was significantly associated with mid and/or distal vessel epicardial endothelial dysfunction, odds ratio (95% CI) 1.50 (1.09 – 2.06), p=0.012. This association remained significant after adjusting for age, sex, smoking status, hypertension, hyperlipidemia, diabetes mellitus, and vascular disease (Supplement, Table 1). MB in the mid and/or distal segment was not significantly associated with proximal vessel endothelial dysfunction in a univariate or multivariate analysis.

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After stratifying by age, there was a significant association between mid and/or distal MB and microvascular endothelial dysfunction amongst patients aged ≤ 50 years, odds ratio (95% CI): 1.69 (1.13 – 2.52), p=0.010 but not amongst patients aged > 50 years. In a multivariate analysis MB was associated with borderline significance with microvascular endothelial dysfunction (Supplement, Table 2).

Discussion

The current study has four main findings. First, MB is angiographically present in 14.2% of patients presenting with chest pain and non-obstructive CAD. Second, patients with MB are younger, more likely to be male, and have fewer traditional cardiovascular risk factors compared to those without MB. Third, in patients with MB epicardial endothelial dysfunction often co-localizes with the same segment of the vessel, suggesting an underlying association between the two pathophysiologic processes. Fourth, MB was significantly associated with microvascular endothelial dysfunction. Thus, the current study supports a potential role for MB as a mechanism of endothelial dysfunction in patients with chest pain and non-obstructive CAD.

The current study demonstrated that MB is prevalent in patients presenting with chest pain and non-obstructive CAD at angiography and that the majority of bridging occurred in the mid-segment of the vessel. Our findings are in keeping with the results of other studies which have shown a prevalence of MB ranging from 0.5% to 29.5% (19-22). Importantly, the current study evaluated 1,469 patients,
making it, to our knowledge, the largest study to investigate the prevalence of MB in patients with angina and non-obstructive CAD. The current study also extends the findings of these previous studies by evaluating the clinical profile of patients with MB. We showed that patients with MB were on average younger and more likely to be male than patients without MB. Patients with MB also had a lower prevalence of hypertension, hyperlipidemia and a history of vascular disease as well as statistically significant, though modestly lower levels of total cholesterol and glucose suggesting that conventional cardiovascular risk factors are less likely to contribute to endothelial dysfunction in patients with MB.

We previously showed that MB is associated with impaired endothelial-dependent epicardial vasorelaxation in a smaller cohort (9), suggesting that epicardial endothelial dysfunction may contribute to lumen obstruction. The current study extends these findings by evaluating a large unselected population of patients with chest pain who underwent routine coronary angiography, including evaluation of MB, as well as invasive assessment of coronary endothelial dysfunction. We found that MB had a higher frequency of epicardial endothelial dysfunction within the same segment of the vessel that was affected by the bridge compared to patients without MB. MB was a significant predictor of epicardial endothelial dysfunction in the same bridged segment both in a univariate analysis as well as after adjusting for conventional cardiovascular risk factors. Other studies have also linked MB and endothelial dysfunction within the bridged segment (9, 23). We further extend the findings of these previous studies by the spatial selectivity of this link, because we found no difference in the frequency of epicardial endothelial dysfunction proximal to the segment with bridging between patients with versus those without MB. Furthermore, a novel aspect of the current study is the relationship with the coronary microcirculation. We found that MB is a significant predictor of microvascular endothelial dysfunction after adjusting for conventional cardiovascular risk factors, further supporting the role of...
endothelial dysfunction as the potential mechanism of myocardial ischemia in symptomatic patients with MB. These findings may also have implications on therapy in patients with MB.

Despite being viewed as a benign condition, MB has been linked to angina and acute coronary syndromes (4, 5). MB related ischemia is thought to underpin the symptoms and cardiovascular events experienced by these patients, and indeed studies have shown reversible perfusion abnormalities during stress myocardial single photon emission computed tomography in patients with MB (24). However, the degree of phasic vessel compression is unlikely to account for severe ischemia and the associated clinical manifestations in patients with MB (8). Thus other contributing factors may play a role. Alterations in blood flow hemodynamics within the MB segment are consistent with a high pressure and high shear stress chamber (25). High intravascular pressure has been shown to be associated with impaired endothelial mediated relaxation in animal models (26). We recently showed that flow related shear stress is an important factor for endothelial dysfunction in patients with early stages of coronary atherosclerosis (27) as extremes in shear stress toward either end of the spectrum can be harmful to the health and function of the endothelium (17, 28). The results of the current study demonstrate that epicardial endothelial dysfunction is significantly associated with MB and co-localizes with the bridged segment of the involved vessel. Endothelial dysfunction represents the first stage of atherosclerosis, and may lead to ischemia as well as an increased risk of cardiovascular events (10, 11) and thus could play a role in explaining the syndrome of chest pain and adverse cardiac events experienced by patients with MB.
Previous studies have suggested that the segment immediately proximal to the bridge in patients with MB is most prone to atherosclerosis development (29). This is thought to be related to relatively lower flow rates at the entrance of the bridge with concomitant low and oscillatory shear stress (2), increased vascular cell adhesion molecule-1 expression (30) and a pro-atherogenic endothelial cell phenotype (31).

However, in the current study we did not find a significantly higher frequency of endothelial dysfunction in the segment proximal to the bridge in patients with MB as compared to those without MB. The precise relationship between MB, regional flow hemodynamics, shear stress and endothelial dysfunction remains poorly understood and is evidently complex and multi-faceted. For example, levels of nitric oxide and endothelin-1 have been shown to be lower in bridged segments compared to segments proximal and distal to the bridge (15). Discordant variations in either chemical could shift the balance to pathologic vasoconstriction and differences in regional endothelial function depending on the location of the bridge. Indeed, while some reports have shown that bridged segments are typically spared from atherosclerosis in (32), other reports have shown atherosclerotic disease in bridged segments (33).

Further work is required to better delineate the precise relationship between MB, its resultant changes in hemodynamic flow and atherogenesis.

The current study also shows that MB was significantly associated with microvascular endothelial dysfunction measured as an abnormal coronary blood flow response to acetylcholine. It may be that a variety of vasoactive chemicals such as nitric oxide synthase, and endothelin-1 whose concentrations become altered in patients with MB (15) influence microvascular function remotely, particularly as endothelial dysfunction is itself characterized by altered bioavailability of vasoactive chemicals (16). Interestingly, age appeared to modify the effect of MB on microvascular endothelial dysfunction. The bioavailability of different vasoactive substances is known to vary with age (34) and thus there may be
interdependence between bridging and patient age which in turn leads to variations in vasoactive substance bioavailability and subsequent endothelial dysfunction. This relationship requires further study.

Limitations

This study has a number of limitations. First, this study evaluated patients referred to a tertiary referral center for coronary angiography and so represents a select population. Second, we did not follow patients prospectively for cardiovascular events nor was the direct relationship between MB, endothelial dysfunction and ischemia demonstrated. Third, our analyses did not factor in the length or depth of each bridged segment which may play a role in whether patients have endothelial dysfunction and to what degree.

Conclusion

MB co-localizes with epicardial endothelial dysfunction and is significantly associated with both epicardial and microvascular endothelial dysfunction in patients presenting with chest pain and non-obstructive CAD supporting its potential role as a mechanism for angina in symptomatic patients with MB. These findings also shed new light on the potential pathophysiological basis for the link between MB and cardiovascular events which may be mediated through endothelial dysfunction.
Impact on Daily Practice

The current study shows that myocardial bridging is angiographically present in 14.2% of patients presenting with chest pain and non-obstructive coronary disease. These patients are younger, more likely to be male, and have fewer traditional cardiovascular risk factors compared to patients without bridging. In patients with myocardial bridging, epicardial endothelial dysfunction often co-localizes within the same segment of the vessel, and is independently associated with both epicardial and microvascular endothelial dysfunction. These findings suggest an underlying association between the two pathophysiologic processes; supports the potential role of endothelial dysfunction as a mechanism for angina in symptomatic patients with myocardial bridging; and could shed new light on the potential pathophysiological basis for the link between myocardial bridging and cardiovascular events which may be mediated through endothelial dysfunction.

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Conflicts of Interest: None declared
References


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Figure Legends

Figure 1
Coronary Angiogram Images Demonstrating Mid and Distal Myocardial Bridging in the Left Anterior Descending Coronary Artery

A – Baseline; B – Bridging in the mid and distal vessel evident with systolic phasic compression; C – After intracoronary infusion of acetylcholine exacerbating vasoconstriction; D – After intracoronary infusion of nitroglycerin resulting in generalized vasodilation helping to uncover mid-distal bridging

Figure 2
Flow Chart Outlining the Number of Patients who underwent an Invasive Assessment of Coronary Endothelial Function and the Proportions of Patients with Epicardial and Microvascular Endothelial Dysfunction and Myocardial Bridging

Figure 3
Bar Chart Comparing Differences in Percentage of Patients with Mid and/or Distal Vessel Epicardial Endothelial Dysfunction and Microvascular Endothelial Dysfunction Between Patients With and Without Mid and/or Distal Vessel Myocardial Bridging

Amongst 1,469 patients in the cohort, 151 (10.3%) did not undergo an assessment of epicardial endothelial dysfunction and 1 patient (0.1%) did not undergo an assessment of microvascular endothelial dysfunction. For the frequency of myocardial bridging versus no myocardial bridging in patients with epicardial endothelial dysfunction, n=1,318, and for those with microvascular endothelial dysfunction, n=1,468
Table 1 - Summary of Clinical Characteristics Between Patients with and without Myocardial Bridging

<table>
<thead>
<tr>
<th></th>
<th>Patients with Myocardial Bridging</th>
<th>Patients without Myocardial Bridging</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>48.3 (13.5)</td>
<td>50.7 (12.1)</td>
<td>0.018*</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>100 (48.1%)</td>
<td>413 (32.8%)</td>
<td>&lt;0.001*</td>
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<tr>
<td>BMI, kg/m² (SD)</td>
<td>28.3 (5.4)</td>
<td>28.9 (6.2)</td>
<td>0.111</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>74 (35.8%)</td>
<td>554 (44.0%)</td>
<td>0.049*</td>
</tr>
<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>11 (5.3%)</td>
<td>118 (9.4%)</td>
<td>0.121</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>100 (48.1%)</td>
<td>693 (55.0%)</td>
<td>0.038*</td>
</tr>
<tr>
<td>History of MI, n (%)</td>
<td>36 (17.4%)</td>
<td>183 (14.5%)</td>
<td>0.059</td>
</tr>
<tr>
<td>History of Vascular Disease, n (%)</td>
<td>12 (5.8%)</td>
<td>100 (7.9%)</td>
<td>0.003*</td>
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<tr>
<td>Smoking Status, n (%)</td>
<td></td>
<td></td>
<td>0.988</td>
</tr>
<tr>
<td>• Never Smoked</td>
<td>107 (51.4%)</td>
<td>652 (51.7%)</td>
<td></td>
</tr>
<tr>
<td>• Former Smoker</td>
<td>75 (36.1%)</td>
<td>459 (36.4%)</td>
<td></td>
</tr>
<tr>
<td>• Current Smoker</td>
<td>26 (12.5%)</td>
<td>150 (11.9%)</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol, mg/dL (SD)</td>
<td>181.9 (42.5)</td>
<td>188.8 (44.2)</td>
<td>0.036*</td>
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<tr>
<td>HDL-C, mg/dL (SD)</td>
<td>52.2 (16.9)</td>
<td>53.8 (17.4)</td>
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<td>LDL-C, mg/dL (SD)</td>
<td>104.0 (35.7)</td>
<td>107.5 (37.6)</td>
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<tr>
<td>Triglycerides, mg/dL (SD)</td>
<td>126.2 (71.0)</td>
<td>136.6 (95.2)</td>
<td>0.071</td>
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<td>Creatinine, mg/dL (SD)</td>
<td>1.0 (0.4)</td>
<td>1.0 (0.7)</td>
<td>0.778</td>
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<td>Glucose, mg/dL (SD)</td>
<td>96.4 (14.2)</td>
<td>100.3 (26.1)</td>
<td>0.002*</td>
</tr>
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</table>

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Abbreviations - BMI: Body Mass Index; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; MI: Myocardial Infarction
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## Supplementary Table 1 Univariate and Multivariate Analysis of Association Between Myocardial Bridging and Epicardial Endothelial Dysfunction

<table>
<thead>
<tr>
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<th>Odds Ratio for Mid and/or Distal Epicardial Endothelial Dysfunction</th>
<th>Confidence Interval</th>
<th>P value</th>
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<tr>
<td><strong>Univariate Analysis</strong></td>
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<tr>
<td>Mid and/or Distal Vessel</td>
<td>1.50</td>
<td>1.09 – 2.06</td>
<td>0.012*</td>
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<td>Myocardial Bridging</td>
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<tr>
<td><strong>Multivariate Analysis</strong>*</td>
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<td>Mid and/or Distal Vessel</td>
<td>1.44</td>
<td>1.04 – 2.00</td>
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<td>1.64</td>
<td>1.30 – 2.09</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Current Smoker</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>(vs. never smoker)</td>
<td>1.24</td>
<td>0.85 – 1.81</td>
<td>0.261</td>
</tr>
<tr>
<td>(vs. former smoker)</td>
<td>1.37</td>
<td>0.93 – 2.03</td>
<td>0.112</td>
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<tr>
<td>Hypertension</td>
<td>0.90</td>
<td>0.71 – 1.15</td>
<td>0.417</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>0.89</td>
<td>0.59 – 1.32</td>
<td>0.550</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.26</td>
<td>1.00 – 1.60</td>
<td>0.054</td>
</tr>
<tr>
<td>History of Vascular Disease</td>
<td>1.13</td>
<td>0.74 – 1.72</td>
<td>0.574</td>
</tr>
</tbody>
</table>

*multivariate analysis adjusted for age, sex, smoking status, hypertension, diabetes mellitus, hyperlipidemia, and vascular disease

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**Supplementary Table 2** Univariate and Multivariate Analysis of Association Between Myocardial Bridging and Microvascular Endothelial Dysfunction

<table>
<thead>
<tr>
<th>N=763</th>
<th>Odds Ratio for Microvascular Endothelial Dysfunction</th>
<th>Confidence Interval</th>
<th>P value</th>
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<td>0.97 – 1.76</td>
<td>0.075</td>
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<td><strong>Multivariate Analysis</strong>*</td>
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<td></td>
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<td>Myocardial Bridging</td>
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<td>1.00 – 1.82</td>
<td>0.050*</td>
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<td>(vs. former smoker)</td>
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<td>Hyperlipidemia</td>
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<td>0.972</td>
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</tbody>
</table>

*multivariate analysis adjusted for age, sex, smoking status, hypertension, diabetes mellitus, hyperlipidemia, and vascular disease