Anatomic Properties of Myocardial Bridge Predisposing to Myocardial Infarction

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Background—A myocardial bridge (MB) that partially covers the course of the left anterior descending coronary artery (LAD) sometimes causes myocardial ischemia, primarily because of hemodynamic deterioration, but without atherosclerosis. However, the mechanism of occurrence of myocardial infarction (MI) as a result of an MB in patients with spontaneously developing atherosclerosis is unclear.

Methods and Results—One hundred consecutive autopsied MI hearts either with MBs [MI(+)MB(+) group; n=46] or without MBs (n=54) were obtained, as were 200 normal hearts, 100 with MBs [MI(−)MB(+) group] and 100 without MBs. By microscopy on LADs that were consecutively cross-sectioned at 5-mm intervals, the extent and distribution of LAD atherosclerosis were investigated histomorphometrically in conjunction with the anatomic properties of the MB, such as its thickness, length, and location and the MB muscle index (MB thickness multiplied by MB length), according to MI and MB status. In the MI(+)MB(+) group, the MB showed a significantly greater thickness and greater MB muscle index (P<0.05) than in the MI(−)MB(+) group. The intima-media ratio (intimal area/medial area) within 1.0 cm of the left coronary ostium was also greater (P<0.05) in the MI(+)MB(+) group than in the other groups. In addition, in the MI(+)MB(+) group, the location of the segment that exhibited the greatest intima-media ratio in the LAD proximal to the MB correlated significantly (P<0.001) with the location of the MB entrance, and furthermore, atherosclerosis progression in the LAD proximal to the MB was largest at 2.0 cm from the MB entrance.

Conclusions—In the proximal LAD with an MB, MB muscle index is associated with a shift of coronary disease more proximally, an effect that may increase the risk of MI. (Circulation. 2009;120:376-383.)

Key Words: myocardium myocardial infarction anatomy atherosclerosis

The coronary artery that runs through epicardial adipose tissue is often covered in part with myocardial tissue. This structure is known as a myocardial bridge (MB); it exists almost exclusively in the left anterior descending coronary artery (LAD), and it is regarded as a common anatomic variant rather than a congenital anomaly. The frequency of an MB in the LAD is high, sometimes >50% by autopsy, but it is <5% by angiography. Because MBs have been identified angiographically indirectly through a “milking effect” phenomenon induced by systolic compression of the MB, a thin or short MB is often missed. The use of other invasive imaging, such as intracoronary ultrasound and Doppler, has improved MB detection. More recently, multidetector computed tomography (CT) has been used non-invasively to detect the MB itself directly, and surprisingly, the use of multidetector CT for myocardial ischemia increases...
the detection rate for MBs >1 mm in thickness to a rate almost equal to that of autopsy.

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The clinical outcome of patients with MBs has been considered benign; however, the significance of an MB to myocardial infarction (MI) without coronary atherosclerosis, have been reported. In most of these cases, the bridged LAD showed no fixed intimal lesion but demonstrated vigorous compression by MB contraction during systole. Such symptomatic MBs are located more proximally in the LAD and tend to be longer and/or thicker. In normal hearts, the anatomic properties of an MB, such as its location, length, and thickness, modulate atherosclerosis in the LAD. Furthermore, the LAD segment proximal to the MB usually exhibits eccentric and severe atherosclerotic lesions. By intracoronary ultrasound imaging, these relationships between the presence of an MB and the characteristics of atherosclerotic evolution in the LAD segment proximal to the MB may signify the occurrence of MI. However, it is still not clear how the anatomic properties of the MB relate to the occurrence of MI with spontaneous atherosclerosis progression in the LAD. In the present study, we attempted to explore the effect of an MB on MI occurrence from the viewpoint of anatomic properties of the MB in the LAD by comprehensive histomorphometry of 100 consecutive autopsied MI hearts and 200 normal control hearts with or without MB.

Methods

Materials

A total of 100 hearts with MI were obtained from consecutive autopsies at each institute participating in the Tokyo Study Group on Myocardial Bridge from 2003 to 2007. We retrospectively collected MI hearts in which acute or old infarct >1 cm in diameter was recognized at the area supplied by the LAD. Full-length LADs were removed from the left coronary ostium to the cardiac apex together with the surrounding adipose and myocardial tissues. These were defined as the MI(+) group. All LADs were fixed with 10% formaldehyde and consecutively sectioned at 5-mm intervals, followed by paraffin embedding. All thin sections were treated with hematoxylin-eosin and elastic van Gieson stains. By microscopy, the MI(+) group was subdivided into 2 groups: The MI(+)MB(+) group, which had an MB anywhere in the LAD (Figure 1), and the MI(+)MB(−) group, which had no MB in the LAD. The MI(+) group included 22 cases with stenting in the LAD (Table 1). The stents were situated at segments proximal to the MB in all 9 cases in the MI(+)MB(+) group. The stent was removed from the cross-sectioned LAD before paraffin embedding. The 6 cases with aorta-LAD bypass were found in the MI(+) group, but the MI(+)MB(+) group had only 1 such case (Table 1) in which a bypass vessel was anastomosed to the segment distal to the MB. For LAD with an aorta-LAD bypass, the bypass was removed from the LAD before it was cross-sectioned at 5-mm intervals.

As an age- and sex-matched control group that corresponded to each of the 100 MI hearts, 100 hearts that showed no MI and no MB in the LAD [the MI(−)MB(−) group] and 100 hearts that showed no MI with an MB in the LAD [the MI(−)MB(+) group] were extracted from autopsies at the same institutes. Causes of death of these control cases were varied, such as cancers, pneumonia, renal failure, or liver failure, without cardiac lesions. Full-length LADs were removed and treated by the same methods as in the MI(+) group.

The history of risk factors for MI, such as hypertension and hypercholesterolemia, was compared among the groups. The presence of hypertension and hypercholesterolemia was evaluated by the presence of a history of antihypertensive therapy or cholesterol-lowering therapy.

Written informed consent for use of the autopsied specimens in the present study was given by relatives of the patients in all cases. The present study was approved by the Ethics Committee of Toho University School of Medicine.

Anatomic Properties of MB

In hearts with an MB, the distance from the left coronary ostium to the first MB segment was defined by 5-mm intervals as the MB location. The number of consecutive sections that included the MB multiplied by 5 mm was defined as the MB length. Thickness of the myocardium covering the LAD was measured microscopically for the entire length of the MB, and the highest value was defined as the MB thickness. Because both the length and thickness of the MB are closely related to atherosclerosis development in the LAD segment proximal to the MB, their synergy may generate contractile force exerted by the MB. In the present study, to assess the mass volume of the MB in each case, the value of MB thickness (in micrometers) multiplied by MB length (in centimeters) was defined as the MB muscle index (MMI). In the MI(−)MB(+) group, 21 cases had multiple MBs in the LAD, as did 8 cases in the MI(+)MB(+) group, and for such cases, only the anatomic properties of the MB in the most proximal portion of the LAD were considered.

Intima-Media Ratio and Atherosclerotic Lesion

The area of the intima and media in all LAD sections was measured with a Visual 32 image-analysis system (Rise System, Sendai, Japan) to assess the extent of atherosclerosis. The area ratio of the intima to the media was defined as the intima-media ratio. The area ratio of the intima to the media was defined as the intima-media ratio. By this method, the intima-media ratio was usually 0.2 to 0.8 in almost-normal LADs and <1.5 in LAD segments that had diffuse intimal thickening or mild eccentric raised lesions; however, it increased with progression.
Statistical Analysis

Mean age and mean heart weight at autopsy were compared among the 4 groups [MI(−)MB(−), MI(−)MB(+), MI(+1)MB(−), and MI(+1)MB(+)] by 1-way ANOVA with Scheffé F test for multiple comparisons. Statistical comparisons of sex ratio and risk factors among the 4 groups were analyzed by χ² test, and then multiple comparison was performed with Bonferroni correction. Frequency of acute/old infarction and cause of death were compared between the 2 MI groups; however, MB length, MB thickness, and MB location were considered for the following analyses.

Intimal lesions of each LAD section were evaluated according to the American Heart Association classification system. In MB(+) cases, the ratio of sections with fibroatheroma or lesions more severe than fibroatheroma in the LAD segments proximal to the MB was measured, and for MB(−) groups, the ratio of sections with fibroatheroma or lesions worse than fibroatheroma in the proximal LAD segments from the left coronary ostium to 4.5 cm (10 sections) was measured.

Results

Background of Patients

Mean age and sex ratio were not different among the 4 groups (Table 1). In the 2 MI(+) groups, MI appeared to occur at a younger age in patients with an MB, but there was no statistical difference in mean age between the MB(−) and MB(+) groups. Hypertension and hypercholesterolemia were more frequent in the MI(+) groups than in the MI(−) groups; however, the difference in frequency of these conditions between the MI(+)MB(−) and MI(+)MB(+) groups was not recognized.

The ratio of acute MI to old MI cases and cause of death showed no significant difference between the 2 MI groups (Table 2). Therefore, we combined both the acute and old MI cases as an MI(+) group in the present study. The MI(+)MB(−) group included 18 cases with stenting or aorta-LAD bypass operation, and the MI(+)MB(+) group included 10 such cases.
Intima-Media Ratio at 5-mm Intervals for a Distance of 10 cm

Intima-Media Ratio in Non-MI Cases by MB Status

In the MI(−)MB(−) group, the intima-media ratio from the left coronary ostium up to 1.0 cm was modest, increased from 1.5 to 3.5 cm from the ostium, and displayed a subsequent decrease to 10.0 cm from the ostium.

Conversely, the intima-media ratio from the left coronary ostium to 1.0 cm in the MI(+)MB(+) group was greater than that at the corresponding site in the MI(+)MB(−) group. The intima-media ratio from 1.0 to 3.5 cm remained high, subsequently decreased up to 5.5 cm, and showed a gradual decrease up to 10.0 cm from the ostium.

In the MI(+)MB(−) group, fibroatheroma and more severe lesions were found in 224 (62.2%) of 360 sections in proximal LAD segments from the ostium up to 4.5 cm. In the MI(−)MB(+) group, these intimal lesions were recognized in 224 (67.3%) of 333 sections in LAD segments proximal to the MB. The ratio of severe intimal lesions in proximal LAD segments was higher in the MI(+) groups than in the MI(−) groups. In the MI(+)MB(+) group, the intima-media ratio beneath the MB (Figure 2D) was significantly lower than that proximal to the MB, and the ratio distal to the MB was also lower than that proximal to the MB.

Intima-Media Ratio by MI Status

Variations in the intima-media ratio in the 4 groups are indicated in Figure 3. In the non-MB groups, there was no significant difference in intima-media ratio from the left coronary ostium up to 1.0 cm between the MI(−)MB(−) and MI(−)MB(+) groups, and the intima-media ratio from 1.5 cm up to 6.0 cm was greater in the MI(+)MB(−) group than in the MI(−)MB(−) group. Conversely, the intima-media ratio in the MI(+)MB(+) group was consistently greater than in the MI(+)MB(+) group from the left coronary ostium up to 7.5 cm.

Atherosclerosis Distribution Within the LAD by Location of MB Entrance

For the 2 MB(+) groups, the relationship between the location of the MB entrance and the location of the segment that exhibited the greatest intima-media ratio is shown in Figure 4A and 4B. Pearson correlation coefficient method

Anatomic Properties of MB

All anatomic properties of MB are indicated in Table 3. MB location in the MI(−)MB(+) group was not different from that in the MI(+)MB(+) group. MB length tended to be longer in the MI(+)MB(+) group than in the MI(−)MB(+) group, but there was no statistical difference between the 2 groups. MB thickness in the MI(+)MB(+) group was significantly (P=0.0481) greater than in the MI(−)MB(+) group. MMI was significantly (P=0.0390) greater in the MI(+)MB(+) group than in the MI(−)MB(+) group.

Intima-Media Ratio in Non-MI Cases by MB Status

Intima-media ratio at 5-mm intervals for a distance of 10 cm from the left coronary ostium in MI(−) cases is shown in Figure 2A. In the MI(−)MB(−) group, the intima-media ratio increased up to 2 cm from the left coronary ostium and subsequently decreased. The intima-media ratio in the MI(−)MB(+) group increased up to 1 cm from the left coronary ostium, remained at a high level up to 3 cm from the ostium, and subsequently decreased, but intima-media ratios from 3.5 to 7.5 cm were significantly lower than in the MI(−)MB(+) group.

In the MI(−)MB(−) group, fibroatheroma and more severe lesions were found in 418 (41.8%) of 1000 sections in the proximal LAD from the ostium to 4.5 cm. In the MI(−)MB(+) group, these types of intimal lesions were recognized in 394 (43.1%) of 914 sections in LAD segments proximal to the MB. The ratio of severe intimal lesions in proximal LAD segments was higher in the MI(+) groups than in the MI(−) groups. In the MI(+)MB(+) group, the intima-media ratio beneath the MB (Figure 2D) was significantly lower than that proximal to the MB, and the ratio distal to the MB was also lower than that proximal to the MB.

Intima-Media Ratio in MI Cases by MB Status

The cases that had a stent or an aortocoronary bypass in the LAD were excluded from the MI(+) group. Intima-media ratios at 5-mm intervals for a distance of 10 cm from the left coronary ostium in MI(+) cases are shown in Figure 2C. In the MI(+)MB(−) group, the intima-media ratio from the left coronary ostium up to 1.0 cm was modest, increased from 1.5 to 3.5 cm from the ostium, and displayed a subsequent decrease to 10.0 cm from the ostium.

Anatomic Properties of MB

All anatomic properties of MB are indicated in Table 3. MB location in the MI(−)MB(+) group was not different from that in the MI(+)MB(+) group. MB length tended to be longer in the MI(+)MB(+) group than in the MI(−)MB(+) group, but there was no statistical difference between the 2 groups. MB thickness in the MI(+)MB(+) group was significantly (P=0.0481) greater than in the MI(−)MB(+) group. MMI was significantly (P=0.0390) greater in the MI(+)MB(+) group than in the MI(−)MB(+) group.

Table 2. Background in MI Cases With MB

<table>
<thead>
<tr>
<th>Background in MI Cases</th>
<th>MI and MB Status</th>
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<tr>
<td></td>
<td>MI(+)/MB(−) (n=54)</td>
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<tr>
<td>Acute MI/chronic MI</td>
<td>26/28</td>
</tr>
<tr>
<td>Cause of death: acute/chronic heart failure</td>
<td>31/23</td>
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<tr>
<td>No. of cases with stenting/bypass operation</td>
<td>13/5</td>
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Table 3. Anatomic Properties in Cases With MB

<table>
<thead>
<tr>
<th>Anatomic Properties in MB Cases</th>
<th>MI(−)/MB(+) (n=100)</th>
<th>MI(+)MB(−) (n=46)</th>
<th>P</th>
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<tr>
<td>MB location, cm</td>
<td>4.57±1.25</td>
<td>4.80±1.17</td>
<td>0.29</td>
</tr>
<tr>
<td>MB length, cm</td>
<td>1.39±0.83</td>
<td>1.70±1.15</td>
<td>0.07</td>
</tr>
<tr>
<td>MB thickness, μm</td>
<td>797±526</td>
<td>1005±703</td>
<td>0.0481</td>
</tr>
<tr>
<td>MMI</td>
<td>0.0390</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1294.3</td>
<td>1997.6</td>
<td></td>
</tr>
<tr>
<td>Median (minimum–maximum)</td>
<td>834.5 (99–6888)</td>
<td>1197.5 (80–11 830)</td>
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</tbody>
</table>
demonstrated a positive correlation in both groups. The coefficient was greater in the MI(−)MB(−) group than in the MI(−)MB(+) group, and thus, the correlation between the 2 factors was stronger in the MI(−)MB(+) group than in the MI(−)MB(−) group.

The intima-media ratio at 5-mm intervals from the MB entrance (0 cm) upward to the left coronary ostium is shown in Figure 4C. In the MI(−)MB(+) group, intima-media ratios from 1.0 cm up to 5.0 cm from the MB entrance showed no significant fluctuation. On the other hand, in the MI(+)MB(+) group, the intima-media ratio showed a peak in the proximal segment 2.0 cm from the MB entrance, which indicated an aggregation of the severe stenotic lesion in the proximal site at 2.0 cm from the MB entrance.

**Discussion**

The present study demonstrates that the anatomic properties of an MB (its thickness, length, and location) predispose to MI occurrence through augmentation of the natural history of atherosclerosis and the convergence of increased atherosclerosis at the prescribed site of the LAD segment proximal to the MB. To date, symptomatic MB cases have been seen in conjunction with conditions of physiological deterioration, such as coronary stenosis by MB contraction, coronary spasm under the MB, and tachycardia during strenuous conditions. However, the present study clearly demonstrates that MBs with a large MMI predispose a person to MI occurrence through modulation of spontaneously developing atherosclerosis.
but an MB often induces the myocardial ischemic conditions
intima-media ratio at intervals of 5 mm is the same as for Figure
of the LADs in the 4 groups are indicated. Each value of the
/H11001) groups. Variations in the intima-media ratios
Figure 3.
son between the MI(MB) group and the MI(H11001)MB(H11002) group, whereas in the MI(H11001)MB(H11002) group, the location of the MB entrance correlated weakly with the location of the segment that exhibited the greatest intima-media ratio, this tendency was strongly correlated in the MI(+)+MB(+) group. This difference between the MI(+)+MB(+) and MI(−)-MB(+) groups is caused by the difference in the MMI between them, which corroborates the role of the MMI as a decisive factor in localization of the most preferential site for atherosclerosis in the LAD segment proximal to the MB. It has been recognized generally that the most stenotic LAD lesion for anterior wall MI appears within 2 to 3 cm of the origin of the LAD28 or at a site 3 to 4 cm away from the left coronary ostium. In the present study, in the MI(+)+MB(−) group, the greatest intima-media ratio was observed 3.5 cm away from the left coronary ostium, which is consistent with the report of a previous study.28 However, in the MI(+)+MB(+) group, the most stenotic lesion was observed 2.0 cm away from the left coronary ostium, being more proximally situated than in the MI(+)+MB(−) group. This difference in the preferential site for atherosclerosis within the entire LAD course between the 2 MI(+) groups was not found in the 2 control MI(−) groups. The presence of an MB with a greater MMI thus contributes to a shift of the severe intimal lesion upward to the left coronary ostium. In addition, the site of the greatest intima-media ratio in LAD segments proximal to the MB was situated 2.0 cm away from the MB in the MI(+)+MB(+) group, whereas the MI(−)-MB(+) group showed no significant peak of the intima-media ratio in LAD segments proximal to the MB. These findings indicate that the increase in MMI plays a role in the aggregation of the atherosclerosis progression at the prescribed site such as the proximal segment at 2.0 cm from the MB entrance.

In conclusion, in addition to the suppressive effect on atherosclerosis development in LAD segments beneath the MB in previous studies4,11,29 and the present study, which results from an alteration of the hemodynamic force of blood flow toward high shear stress beneath the MB,30,31 it is evident for the first time from the present study that certain anatomic

In general, the majority of MBs are benign clinically, but an MB often induces the myocardial ischemic conditions of acute MI,15,21 ventricular fibrillation,14 cardiac sudden death,23 and atrioventricular block.21 However, the majority of such patients exhibit no considerable atherosclerosis in the LAD; their symptoms are caused by the hemodynamic alterations brought about by MB contraction. In fact, a decrease or loss of coronary compression by the MB at systole through administration of a β-blocker or surgical myotomy of MB relieves ischemic symptoms.24,25 Conversely, patients in the MI(+)MB(+) group in the present study exhibited atherosclerosis development in the LAD at a similar extent to that of the MI(+)MB(−) group, although a thicker MB and greater MMI were observed in the MI(+)MB(+) group than in the MI(−)-MB(+) group. In MI hearts, it is thought that anatomic properties of the MB, such as its thickness and length, may exacerbate the preexisting coronary atherosclerosis.

In the present study, the pivotal roles of thickness and length of the MB on MI occurrence were evident. The intima-media ratio in LAD segments from the left coronary ostium up to 7.5 cm away in the MI(+)MB(+) group was greater than in the MI(−)-MB(+) group. This does not suggest that the natural history of atherosclerosis in the former group may not be exacerbated by other risk factors, such as hypercholesterolemia or hypertension.26 In the present study, the intima-media ratio in the proximal short segments from the left coronary ostium up to 1.0 cm away in the MI(+)MB(+) group was greater than in the MI(+)MB(−) group, whereas in the MI(+)MB(−) group, it was not different from that in the MI(−)-MB(−) group. This characteristic pattern of the intima-media ratio in such short

LAD segments in the MI(+)MB(+) group is caused primarily by an increase of MMI. In our previous study using normal hearts, the difference in the intima-media ratio between segments proximal to the MB and segments beneath the MB was regulated by both the thickness and length of the MB.11 In addition, the atherosclerosis process in LAD segments proximal to the MB is subject to the complex hemodynamics caused by retrograde blood flow from the MB squeezing at systole.5,22 It is thus plausible that an increase of the MMI underlies an increase of contractile force by MB contraction, resulting in an increase of retrograde blood flow toward LAD segments proximal to the MB, which ultimately enhances the progression of atherosclerosis in the proximal LAD. The severity of atherosclerosis progression in proximal segments in the MI(+)+MB(+) group may originate independently from the large value of the MMI.
properties of the MB enhance the development of atherosclerosis in the LAD proximal to the MB, resulting in MI. The present study thus reveals that the MB plays the role of a "double-edged sword" in the development of coronary atherosclerosis in the LAD.

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Disclosures
None.

References
CLINICAL PERSPECTIVE

A myocardial bridge (MB) that partially covers the course of the left anterior descending coronary artery may cause myocardial ischemia. In patients with myocardial infarction and an MB, the thickness of the MB and the MB muscle index (MB thickness times MB length) were significantly greater than in patients without myocardial infarction. Morphometric analyses of the left anterior descending coronary artery in MB patients with myocardial infarction demonstrated that the location of severe atherosclerotic disease in the left anterior descending coronary artery proximal to the MB correlated with the location of the MB entrance, and atherosclerosis progression in the LAD proximal to the MB was largest at 2.0 cm from the MB entrance. Thus, a greater MB muscle index was associated with a shift in severe left anterior descending coronary artery disease more proximally toward the coronary ostium. Clinicians should be aware of these associations when managing patients with an MB.
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