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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Myocardial Bridging: Diagnosis, Functional Assessment, and Management

JACC State-of-the-Art Review

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ABSTRACT

Myocardial bridging (MB) is a congenital coronary anomaly in which a segment of the epicardial coronary artery traverses through the myocardium for a portion of its length. The muscle overlying the artery is termed a myocardial bridge, and the intramyocardial segment is referred to as a tunneled artery. MB can occur in any coronary artery, although is most commonly seen in the left anterior descending artery. Although traditionally considered benign in nature, increasing attention is being given to specific subsets of MB associated with ischemic symptomatology. The advent of contemporary functional and anatomic imaging modalities, both invasive and noninvasive, have dramatically improved our understanding of dynamic pathophysiology associated with MBs. This review provides a contemporary overview of epidemiology, pathobiology, diagnosis, functional assessment, and management of MBs. (J Am Coll Cardiol 2021;78:2196–2212)

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The coronary arteries typically course between the peri- and epicardium. A partial or total encasement of the coronary arteries by myocardial fibers is termed myocardial bridging (MB). The muscle overlying the artery is termed a "myocardial bridge," and the intramyocardial segment of the artery is referred to as a "tunneled artery." The first autopsy description of MB dates to physician Henric Reyman (1) in 1732, during which time it was thought to be a benign cardiovascular anomaly. MB may occur in any epicardial coronary artery but most often arises in the left anterior descending artery (LAD). Although MB is benign in most cases, it represents a diagnostic and therapeutic challenge in a subset of symptomatic patients.

EPIDEMIOLOGY

The true prevalence of MB is not accurately known; however, MB is likely present to some degree in approximately 1 in 3 adults (2). Rates of MB detection vary significantly according to the imaging modality used to identify these coronary variants. The most commonly studied methods to determine prevalence in the general population include coronary angiography (CA), coronary computed tomography angiography (CCTA), and autopsy studies. The reported prevalence of MB is between 2% and 6% for CA and 19% and 22% for CCTA (2,3). The variation in prevalence among imaging modalities across individual studies depends largely on heterogeneous target populations,

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HIGHLIGHTS

- Myocardial bridging is a common coronary anomaly in which a coronary artery segment traverses through the myocardium, but functional imaging and hemodynamic characterization in symptomatic patients are necessary to identify those who benefit from treatment.
- Medical management with beta-blockers and calcium-channel blockers are first-line therapeutic strategies, reserving revascularization for those who do not respond sufficiently to medication therapy.
- Percutaneous coronary intervention and surgical myotomy are the revascularization strategies of choice, depending on lesion length, depth, concomitant atherosclerosis, operator expertise, and patient preference.

type of imaging device used, and the inclusion versus exclusion of "superficial" MB (4-6). Autopsy studies are considered the gold standard in identification of MB, with a prevalence approaching 33%-42% (2,7,8). In terms of anatomical location, 67%-98% of MBs are located in the LAD, most commonly in the proximal- and mid-LAD segments. The left circumflex and right coronary artery are less commonly affected (9).

Considering the high rate of MB detected at autopsy, CCTA is considered the more sensitive modality, compared with CA and intravascular imaging, for general diagnostic purposes. Several factors have been identified to account for the significant discordance in prevalence of MB across imaging modalities; these include the highly variable length and depth of myocardial mass overlying the tunneled artery, the axial orientation of the coronary artery alongside myocardial fibers, the presence of a fixed stenosis proximal to the MB, the existence of connective or adipose tissue opposing the tunneled segment, a concomitant aortic outflow obstruction, intrinsic tone of the coronary artery wall, significant hypotension, vasopressor use at the time of imaging, and intraobserver variability (10). Nitroglycerin also notably augments the degree of systolic compression during angiography, potentially influencing the detection and perceived severity of MB (11). Alternatively, the use of intravascular ultrasound (IVUS) may increase the detected prevalence of MB during CA up to 23% in some dedicated studies (3,12).

PATHOPHYSIOLOGY

For many years, MB was considered an entirely benign phenomenon. This was chiefly based on the observation that almost all (~85%) coronary blood flow occurs during diastole, while MB is characterized by systolic arterial compression. Therefore, only approximately 15% of coronary blood flow is at risk of being compromised by significant MB, a seemingly clinically irrelevant fraction. The reality, however, is more complex and is characterized by the interplay between anatomic and physiologic factors that influence each other dynamically, not only throughout the cardiac cycle, but also during the life of the patient.

MB is a congenital anatomic anomaly characterized by a length of tunneled artery beneath a section of myocardium. The depth of the tunneled segment and the length of the segment play an integral role in providing the substrate that eventually leads to ischemic symptoms in some cases. The depth of the tunneled artery (1-2 mm superficial, >2 mm deep) (13) is related to (but not the sole determinant of) the degree of systolic compression and course of the artery. The depth of the MB also has implications for treatment, especially when considering surgical intervention. The length of the tunneled segment is important not only as it relates to the amount of the affected artery, but also to the number of branches affected by the MB. This is especially clinically relevant when considering LAD MBs that affect diagonal or septal branches.

Unlike classic atherosclerotic plaque that produces a fixed stenosis, MB produces a dynamic effect that varies with cardiac cycle, heart rate, and sympathetic tone. Despite being considered a chiefly systolic phenomenon, angiographic ultrasound and IVUS studies have shown vessel compression in systole is followed by a delay in the increase in luminal diameter during diastole (14,15). This may be due to localized phasic artery spasm caused by myocardial bridge contraction. This delay impedes rapid early-diastolic hyperemia most significantly in the subendocardium (16) that is more subject to ischemia. The phenomenon is drastically exaggerated in the presence of high sympathetic tone (as seen with exercise or dobutamine infusion) for a few reasons. Increased sympathetic tone increases heart rate and thereby decreases diastolic perfusion time. In addition, increased strength of contraction across the MB delays relaxation beyond systole into the early-

ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stents
CA = coronary angiography
CAD = coronary artery disease
CCTA = coronary computed tomography angiography
FFR = fractional flow reserve
iFR = instantaneous wave-free ratio
ISR = in-stent restenosis
IVUS = intravascular ultrasound
LAD = left anterior descending artery
MB = myocardial bridging
OCT = optical coherence tomography
PCI = percutaneous coronary intervention
TLR = target lesion revascularization

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diastolic phase, further impairing flow. Finally, high sympathetic tone also increases coronary vasoconstriction. In the setting of high sympathetic tone, the MB-induced delay in rapid early-diastolic coronary flow serves to severely attenuate the natural stress hyperemia response, thereby exacerbating supply-demand mismatch (17). For these reasons, it is imperative that accurate clinical assessment of MB uses a modality that incorporates the milieu of high sympathetic tone.

Another important pathophysiological consequence of MB is that of "branch steal," which is most apparent in the case of septal perforator arteries. As blood flows through the tunneled artery in end systole/early diastole, it passes through a constricted segment that serves to increase fluid velocity, thereby decreasing perfusion pressure at the ostium of the septal branch due to the Venturi effect. Others, however, point out that the relatively modest increases in velocity seen in vivo in Doppler flow velocity measurements are unlikely to result in large enough pressure gradients across side-branch arteries to account for the observed effect. Instead, they argue that the phenomenon follows chiefly from classic fluid dynamic entrance and viscous pressure loss in the narrowed segment (17). In either case, the presence of "branch steal" in MB is supported by studies that show lower diastolic pressures in the intrabridge segment than in the distal artery (14), as well as the observation that mild-moderate MBs more often result in local/septal ischemia as compared with ischemia in the distal myocardium. This observation is further supported by the distinctive abnormality of focal septal buckling with apical sparing seen in patients with MB during exercise echocardiography (18).

CORONARY ATHEROSCLEROSIS AND MB. The development of atherosclerotic coronary disease has been associated with MB. Recent studies have elucidated how biomechanical forces from MB affect the coronary artery over time and may help to explain both the characteristic pattern of atherosclerosis progression associated with MB and several of the clinical presentations. Under normal conditions, coronary arteries are subject to multiple mechanical forces, including compressive stress, tensile stress, and shear stress (19). Shear stress or wall shear stress (WSS) is the frictional force that acts tangentially to flow and has been shown to play a role in the development of endothelial dysfunction and atherosclerosis (20,21), possibly by inducing alterations in several inflammatory pathways. Doppler studies of MBs show that systolic compression of the tunneled artery produce retrograde flow proximal to the MB (22). This results in abrupt breakage of the propagating antegrade systolic wave and creates an area of low WSS that has been posited to explain the development of atherosclerotic plaque immediately proximal to the MB (23,24). However, these altered biomechanical forces are also potentially responsible for some nonatherosclerotic complications associated with MB. It is likely that high compressive stress exerted by the MB on the tunneled artery could cause intimal injury that could propagate to dissection (25).

Another frequently seen characteristic of MB is the relative freedom from plaque within the tunneled segment of the artery. This can be explained by a few observations. First, MB results in separation of the bridged segment from perivascular adipose tissue in the epicardium that is associated with proinflammatory signaling pathways (26). Furthermore, optical coherence tomography (OCT) imaging has identified a lack of adventitial vaso vasorum, which normally act as a conduit for diffusing inflammatory cells and cytokines from the perivascular adipose tissue, at MB (27). Second, compression of the tunneled artery may improve lymphatic drainage (28), and finally, the tunneled segment is exposed to high or physiologic WSS as a result of elevated velocities that have been associated with atheroprotective pathways in vitro (29). As a counterpoint to the development of CAD, some authors have proposed that MB may instead act as a potentially protective element against severe obstructive CAD elsewhere in the coronary system; however, mechanisms and robust data are as of yet lacking (30).

These many pathophysiological factors interact together with clinical variables such as advancing age and comorbid conditions resulting in new symptoms of ischemia in previously asymptomatic patients. Atherosclerotic plaque occurring proximal to the MB results in decreased pressure downstream that exacerbates ischemia caused by the MB. Second, left ventricular diastolic dysfunction and left ventricular hypertrophy worsen supply-demand mismatch, as well as reduce microvascular reserve via compression of the microvasculature. Third, coronary vasospasm and endothelial dysfunction associated with the MB can cause myocardial ischemia (31).

Overall, it is the rare patient with the right combination of physiologic, rather than anatomic, changes related to MB who develops symptomatic disease. The process that underlies this develops over the course of years in a complex interplay related to MB length/depth, fluid dynamics and their long-term biologic effects, CAD, and left ventricular changes.

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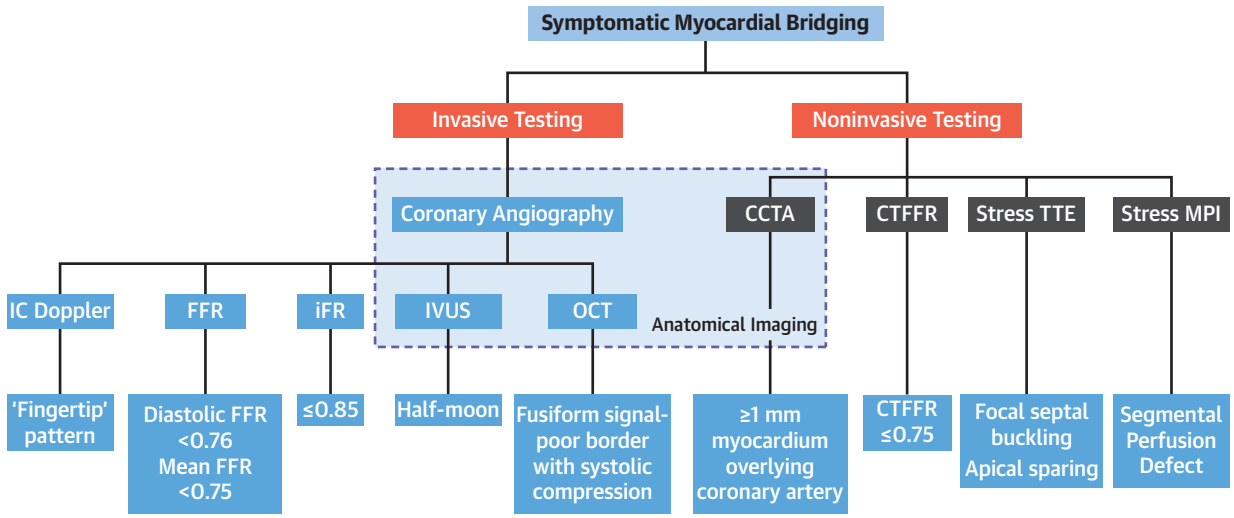
FIGURE 1 **Invasive and Noninvasive Imaging Modalities of MB**



Select invasive and noninvasive imaging modalities for the anatomic and functional characterization of MB. The classic finding of MB during invasive coronary angiography is systolic compression of the tunneled arterial segment with a "step-down" or "step-up" demarcating the affected area followed by decompression in diastole that may be complete or partial. Positive findings for each respective imaging modality are detailed with descriptions of classic and/or pathognomonic findings. CCTA = coronary computed tomographic angiography; CTFFR = computed tomography fractional flow reserve; FFR = fractional flow reserve; IC = intracoronary; iFR = intracoronary wave-free ratio; IVUS = intravascular ultrasound; MB = myocardial bridging; MPI = myocardial perfusion imaging; OCT = optical coherence tomography; TTE = transthoracic echocardiography.

CLASSIFICATION. The Schwarz classification (2009) has been proposed as a guide for directing therapy for MB. In their retrospective study of 157 patients with MB at 5-year follow-up, patients with type A MB, defined as those with clinical symptoms but no objective signs of ischemia (incidental finding on angiography), did well with reassurance alone (80% reported improved symptoms). Type B patients with objective signs of ischemia by noninvasive testing and type C patients with altered intracoronary hemodynamics (quantitative CA/coronary flow reserve/intracoronary Doppler) were treated with beta-blockers or calcium-channel blockers. Of those with type C lesions (n = 37), 24 patients (65%) required stenting with bare-metal stents (BMS) due to lack of improvement with medical therapy. Four cases of in-stent restenosis (ISR) were identified at the prescribed 7-week angiographic follow-up requiring target lesion revascularization (TLR), but all were symptom- and event-free at 2- and 5-year follow-up. Based on this, the authors propose that patients with type A MB receive reassurance or medical therapy for persistent symptoms; patients with type B receive medical therapy followed by invasive hemodynamic assessment and possible stenting for refractory symptoms; and patients with type C receive medical therapy (even in the absence of ischemia on noninvasive test) followed by stenting for refractory symptoms (32). This simple treatment schema has recently been brought into question with iterative advancements in the pathobiology of MB.

CLINICAL PRESENTATION

MB is typically an asymptomatic, benign finding discovered during CA. Although the vast majority of MBs are "normal variants," numerous case reports and series have documented the association between MB and angina or angina-equivalent syndromes. Patients with MB may present with stable or unstable angina, vasospastic angina, or acute coronary syndrome (ACS) related to MB complications (33,34). ACS presentations in MB are thought to be the result of coronary spasm, thrombosis, coronary dissection, or the development of focal atherosclerosis immediately proximal to the MB (35). A study of 298,558 patients undergoing CA revealed that patients with MB were younger, had higher rates of smoking, and lower rates of cardiovascular risk factors such as diabetes, chronic kidney disease, prior myocardial infarction, and prior percutaneous coronary intervention (PCI). In a subset of patients presenting with ACS, patients with MB were more likely to present with unstable

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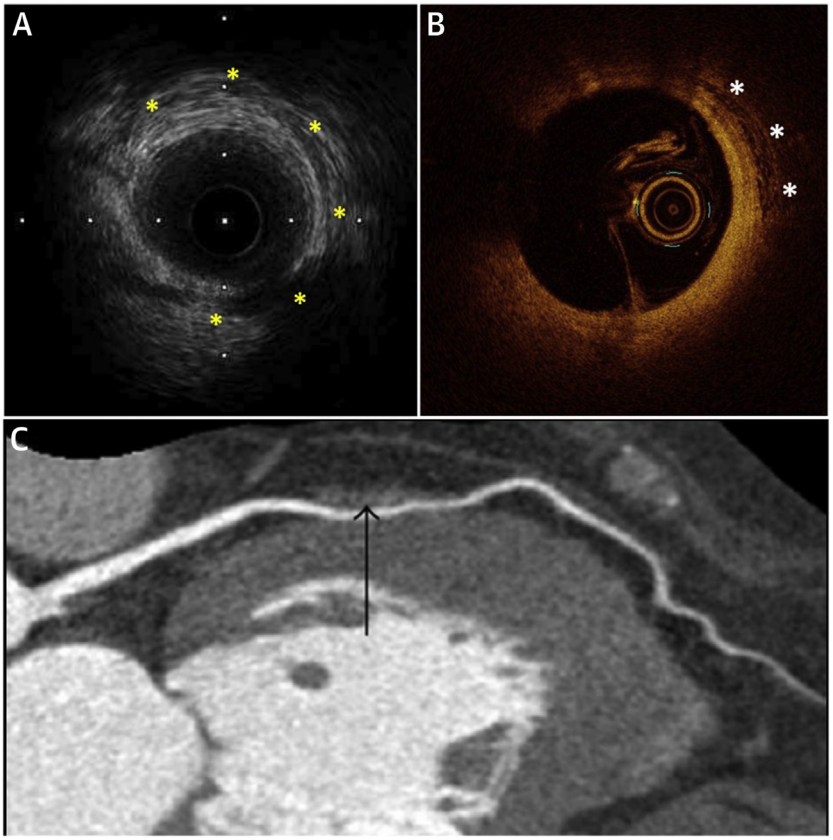
FIGURE 2 IVUS and OCT of LAD Myocardial Bridge



(A) IVUS image of LAD myocardial bridging (MB) demonstrating the characteristic "half-moon" phenomenon **(yellow asterisk)**. **(B)** OCT demonstrating a mid-LAD MB heterogeneous signal-poor fusiform area with well-delineated borders **(white asterisk)**. **(C)** Coronary computed tomography imaging of a mid-LAD MB **(arrow)** overlying a tunneled arterial segment. IVUS = intravascular ultrasound; LAD = left anterior descending; OCT = optical coherence tomography.

angina rather than troponin-positive myocardial infarction such as ST-segment elevation or non-ST-segment elevation myocardial infarction. The higher incidence of MB among smokers may be associated with increased tendency toward coronary artery spasm with cigarette smoking (36). Less common syndromes that have been associated with MB include exercise-induced ventricular dysrhythmias, ventricular rupture, angina with normal coronary arteries, sudden cardiac death, Takotsubo cardiomyopathy, left ventricular dysfunction, and Wellens syndrome (37-41). Clinically, the surface electrocardiogram rarely shows abnormalities in asymptomatic, resting patients, although repolarization abnormalities may infrequently be seen during exercise stress testing (42). Practically, there is a significant diagnostic challenge in attributing whether symptoms in a patient with MB are: 1) directly related to the MB; 2) indirectly related to coronary vasospasm; 3) related to atherosclerotic coronary disease; or 4) clinically unrelated to the MB (10,23).

ANGIOGRAPHIC AND FUNCTIONAL ASSESSMENT

Numerous invasive techniques can be used in the catheterization laboratory for detailed assessment of MB, including angiography, IVUS, OCT, Doppler flow wire (DFW), and pressure wire methods (**Figure 1**) (43). The classic angiographic finding of MB is the systolic narrowing or "milking" of the vessel. This is associated with a "step-down" and "step-up" demarcating the affected coronary segment with either complete or partial decompression in diastole. A significant "milking effect" is present when there is a visual ≥70% reduction in the minimal luminal diameter during systole and persistent ≥35%

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reduction in minimal luminal diameter during mid- to late-diastole. Importantly, routine CA is an insensitive imaging modality for the detection of MB, with most bridges not visible on angiography and only 5% demonstrating the classic milking effect. The use of intracoronary vasodilators, such as nitroglycerin, can increase angiographic sensitivity significantly by augmenting the severity of the compression related to MB; therefore, nitroglycerin should be administered immediately before CA for the purposes of detailed MB assessment if hemodynamics allow (44). Furthermore, important consideration should be paid to optimal angiographic views. CA is hampered by the presence of complex hemodynamics at the MB site, cyclical changes in lumen dimensions, and noncircular lumen morphology poorly delineated on 2-dimensional angiography.

IVUS has been used throughout a multitude of studies in the angiographic assessment of MB. Three-dimensional visualization of the anatomy at the site of MB allows for accurate measurements of the lumen diameter and vessel wall morphology. The characteristic finding is a "half-moon" sign, representing an echolucent area present immediately adjacent to the vessel lumen that persists throughout the cardiac cycle. Although there has been debate as to the nature of the "half-moon" echolucency, Yamada et al (45) demonstrated in a cadaveric study using IVUS and histo-pathological assessment that the echolucency identified by IVUS did indeed represent a muscle band overlying the tunneled arterial segment. IVUS allows for objective measurement and quantification of the phasic compression of the tunneled arterial segment (45). Nonetheless, the key limitation of IVUS in the assessment of MB revolves around a lack of functional information relating to coronary arterial flow (Video 1).

Compared with CA, OCT can provide more information about MBs, specifically, enabling the examination of vulnerable plaque and more detailed observation of the morphology of the coronary arteries. The resolution of OCT is approximately 10 μm, approximately 10 times greater than that achieved with standard IVUS systems (46). Use of OCT may therefore be associated with improved detection and anatomic characterization of atherosclerotic lesions compared with IVUS. In one series examining the safety and feasibility of OCT for the detection of MB, varying degrees of fibrous intimal hyperplasia were seen in the vascular segments immediately proximal to the MB, but not in the middle and distal arterial segments. Given the focality and phasic systolic compression of MB, close attention must be paid to ensure that the proximal and distal portions of the bridge are not missed. Pullback protocols using both IVUS and OCT risk underestimating the length of MB, particularly if rapid pullback is performed. This effect may be even more pronounced in bradycardic patients. Despite its higher resolution, OCT may not be the optimal imaging modality to detect MB, mainly because of its limited penetration and rapid OCT fiber pullback and image acquisition (20 mm/s vs 0.5 mm/s in IVUS). OCT can be performed manually with the fiberoptic lens left stationary in the MB; however, this is not routinely performed. IVUS is therefore preferred over OCT for the intracoronary assessment of MB, and should be ideally performed using a slow pullback with manual technique (**Figure 2**).

In contrast to CA, IVUS, and OCT, DFW, and pressure wire techniques can be used to assess MB both functionally and physiologically. MBs are dynamic stenoses, dependent on the degree of extravascular compression, and it is generally posited that their assessment should not be limited to anatomic or morphologic characteristics alone. The introduction of chronotropic or inotropic stressors (whether pharmacologic or exercise related) into the comprehensive assessment of MBs are of crucial importance.

An intracoronary DFW involves selective catheterization of the suspected MB segment with passage of the wire distal to the lesion segment. The characteristic velocity pattern, termed the "fingertip phenomenon" is observed at the MB segment, representing 3 distinct phases: 1) rapid early-diastolic flow acceleration; 2) rapid mid-diastolic deceleration; and 3) a mid-to-late diastolic plateau phase. An additional flow pattern, consisting of retrograde systolic arterial flow immediately proximal to the bridged segment, also may be seen. Multiple pharmacologic agents can be used alongside DFW to simulate the effect of coronary vasospasm or vigorous systolic myocardial obstruction, including dobutamine, adenosine, or acetylcholine (47).

Fractional flow reserve (FFR) has been widely used for the assessment of MB using a pressure wire and infusion of adenosine. Although FFR is generally accepted as the gold standard for the functional assessment of obstructive atherosclerotic plaque, its use in dynamic MBs is unfortunately inadequate. In fixed stenotic lesions, the difference between mean and diastolic FFR (dFFR) values has been demonstrated to be nonsignificant. However, for dynamic obstruction related to MB, the properties of dFFR present certain theoretical advantages over conventional "mean pressure" FFR (48). First, the restriction of measurements to diastole avoids the influence of negative intracoronary gradients on overall pressure measurements, and second, it allows identification

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TABLE 1 Diagnostic Imaging Modalities for Myocardial Bridging

Imaging Modality	Description	Diagnostic Criteria	Advantages	Disadvantages	Functional Information
Invasive techniques					
Coronary angiography	Selective catheterization of coronary arteries with contrast injection; can be used with nitroglycerin	Milking effect	• Frequently used • Anatomic assessment • Quantification of systolic compression	• Invasive • No physiological value	No
Intravascular ultrasound	Selective catheterization of coronary arteries with insertion of a probe across the lesion of interest; allows for 3D arterial visualization	Half-moon sign	• Identifies proximal plaque • Quantification of arterial compression and MLA • Identifies negative arterial remodeling	• No physiological value • May underestimate the length of a bridge if rapid pullback	No
Optical coherence tomography	Selective catheterization of coronary arteries and insertion of a fiberoptic probe across the lesion	Fusiform, signal poor border with systolic compression	• Identifies proximal plaque • Identifies neoatherosclerosis • Quantification of MB arc thickness	• High pullback velocity and pullback protocols risk misidentifying proximal and distal MB edges • Stationary OCT assessment is not widely used	No
Intracoronary Doppler wire	Selective catheterization of coronary arteries and insertion of a pressure wire across the lesion of interest	Fingertip sign	• Functional evaluation of coronary lesions • Assessment of microvascular disease • Can simulate dynamic systolic obstruction • Endothelial function testing	• Pharmacotherapies required • Longer procedural time • Pharmacotherapy side effects • No standardized cutoffs for dobutamine/adenosine	Yes
Fractional flow reserve	Selective catheterization of coronary arteries and insertion of a pressure wire across the lesion of interest	FFR ≤0.75	• Functional evaluation of: i) Fixed lesions ii) Dynamic lesions • Widely available	• Longer procedural time • Pharmacotherapies required (adenosine) • Pharmacotherapy side effects • Diastolic FFR not commonly accessible (Pd/Pa may underestimate severity)	Yes
Instantaneous free wave ratio	Selective catheterization of coronary arteries and insertion of a wire across the lesion of interest	iFR ≤0.85	• Diastolic-specific index • Functional evaluation of both fixed and dynamic lesions • Adenosine not mandatory	• Longer procedural time	Yes

Continued on the next page

and quantification of the MB on diastolic coronary blood flow. Prior data from Tarantini et al (49) demonstrated that following dobutamine infusion, when coronary compression was maximal and patients developed symptoms/ischemic changes, median FFR did not significantly change. This finding potentially relates to the artificial reduction in systolic pressure gradients due to distal pressure overshooting. With this in mind, dFFR has proven to be an overall more sensitive modality for functional assessment of MB than conventional FFR. An FFR of ≤0.75 has previously been identified as a cutoff in predicting those likely to have MB-related ischemia, with similar cutoffs proposed for dFFR (≤0.76). The use of intravenous dobutamine also has been investigated as a pharmacological adjunct for use during FFR to increase the strength of myocardial contraction. Prior studies have demonstrated that the combination of intravenous dobutamine with intracoronary adenosine can increase the likelihood of unmasking larger diastolic pressure gradients in MB (45,50). Unfortunately, although conventional FFR has become a ubiquitous assessment tool across contemporary catheterization labs for the evaluation of fixed stenoses, the use of dFFR remains cumbersome and time-consuming, and is not routinely performed in most laboratories.

Instantaneous wave-free ratio (iFR) has been increasingly used in the functional assessment of MB over the past 5 years. The iFR has numerous benefits that may be particularly advantageous in the assessment of MB. Namely, it is a diastolic-specific flow index and it allows for anatomic mapping via coregistration software (iFR scout; Philips). In a physiological study comparing FFR and iFR for the evaluation of MB, use of iFR was associated with a significantly higher proportion of positive obstructive bridges. Under nonhyperemic conditions, the iFR wire is advanced past the MB and measurement of the diastolic wave-free period is possible, a period in

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TABLE 1 Continued

Imaging Modality	Description	Diagnostic Criteria	Advantages	Disadvantages	Functional Information
Noninvasive techniques					
Cardiac computed tomographic angiography	Contrast-enhanced CT allowing for 3D reconstruction and visualization of the coronary arteries	≥1 mm of myocardium overlying the coronary artery defines "any MB" ≥2 mm defines "deep MB" ≥5 mm defines "very deep MB"	• More accurate anatomic assessment compared with CAG • Well validated • Shows concomitant atherosclerosis • Highly sensitive	• Overdetection of minor MB may lead to unnecessary downstream testing • Relation of symptom severity to depth of MB unclear	No
Computed tomographic fraction flow reserve	Contrast-enhanced CT with computational fluid dynamics to estimate myocardial stenosis	FFR ≤0.75 (Gray Zone 0.75-0.80)	• Functional assessment of ischemia at rest	• Tested only in patients with proximal MB stenosis • Requires contrast injection	Yes (Experimental)
Single-photon emission computed tomography	Nuclear imaging test that allows for functional myocardial perfusion imaging	Reversible or segmental perfusion defects during stress	• Physiological assessment of functional effect of MB • Readily available	• No anatomic value • Low spatial resolution for subendocardial defects • Requires radioactive tracer injection	Yes
Positron emission tomography	Nuclear imaging test that allows for functional and quantitative myocardial perfusion imaging	Reversible or segmental perfusion defects during stress	• Physiological assessment of functional effect of MB • Readily available	• No anatomic value • Low spatial resolution for subendocardial defects • Requires radioactive tracer injection	Yes
Stress transthoracic echocardiography	Echocardiography stress imaging using ultrasound enhancing agents to assess for myocardial hypokinesis	Segmental hypokinesis during stress	• Physiological assessment of functional effect of MB • Readily available	• No anatomic value • Requires ultrasound enhancing agent	Yes
Cardiac magnetic resonance imaging	MRI imaging to assess for segmental myocardial perfusion defects	Segmental subendocardial perfusion defects during stress	• Physiological assessment of functional effect of MB	• No anatomic value • Contrast exposure	Yes

CAG = coronary angiography; CT = computed tomography; FFR = fractional flow reserve; iFR = instantaneous free wave ratio; MB = myocardial bridging; MLA = minimal luminal area; MRI = magnetic resonance imaging; OCT = optical coherence tomography; Pd/Pa = Distal coronary pressure/Proximal coronary pressure; 3D = 3-dimensional.

which the intrabeat microvascular resistance is constant and coronary flow is at its peak. Of note, iFR has only been formally validated in resting conditions with a cutoff value considered ≤0.89. The use of a inotropic infusion with iFR to measure MB hemodynamics in both rest and stress states remains experimental (47). Some centers have also reported using iFR both pre- and postintervention to demonstrate normalization of the MB segment after revascularization, although evidence is lacking to support this approach.

NONINVASIVE ASSESSMENT

Although there is no gold standard for diagnosing MB in vivo, the original definition and classification was developed using CA. Since then, other modalities have been used to assess the clinical and anatomic significance of MB. The use of CCTA to investigate chest pain syndromes has been increasing rapidly. The advantage of CCTA advantage lies in its high spatial resolution and the ability to easily visualize not only the coronary artery lumen, but also all surrounding structures in 3 dimensions (51). This allows accurate assessment of the vessel wall and the surrounding myocardium as well as the lumen. Using CCTA, the rate of detection of MB has been reported to be up to 58% (5,52). CCTA is useful for classifying the course of the artery as normal (within the epicardial fat), superficial intramyocardial, or deep intramyocardial, which may have ramifications for treatment (4). Superficial and shorter-length MBs are likely more amenable to PCI. On the other hand, very deep (≥5 mm) or long (≥25 mm) MBs are presumably better treated with a surgical approach, although data are lacking.

Technical limitations, including reduced temporal resolution, restrict the use of CCTA in assessing physiological significance of an MB. Typically, a patient undergoing CCTA receives some combination of beta-blockers, calcium-channel blockers, and/or ivabradine as well as nitroglycerin (usually sublingual) before scanning. This serves to improve the quality of the film by prolonging diastasis and inducing vasodilation of the coronaries. The use of dobutamine and/or exercise to induce the physiologic

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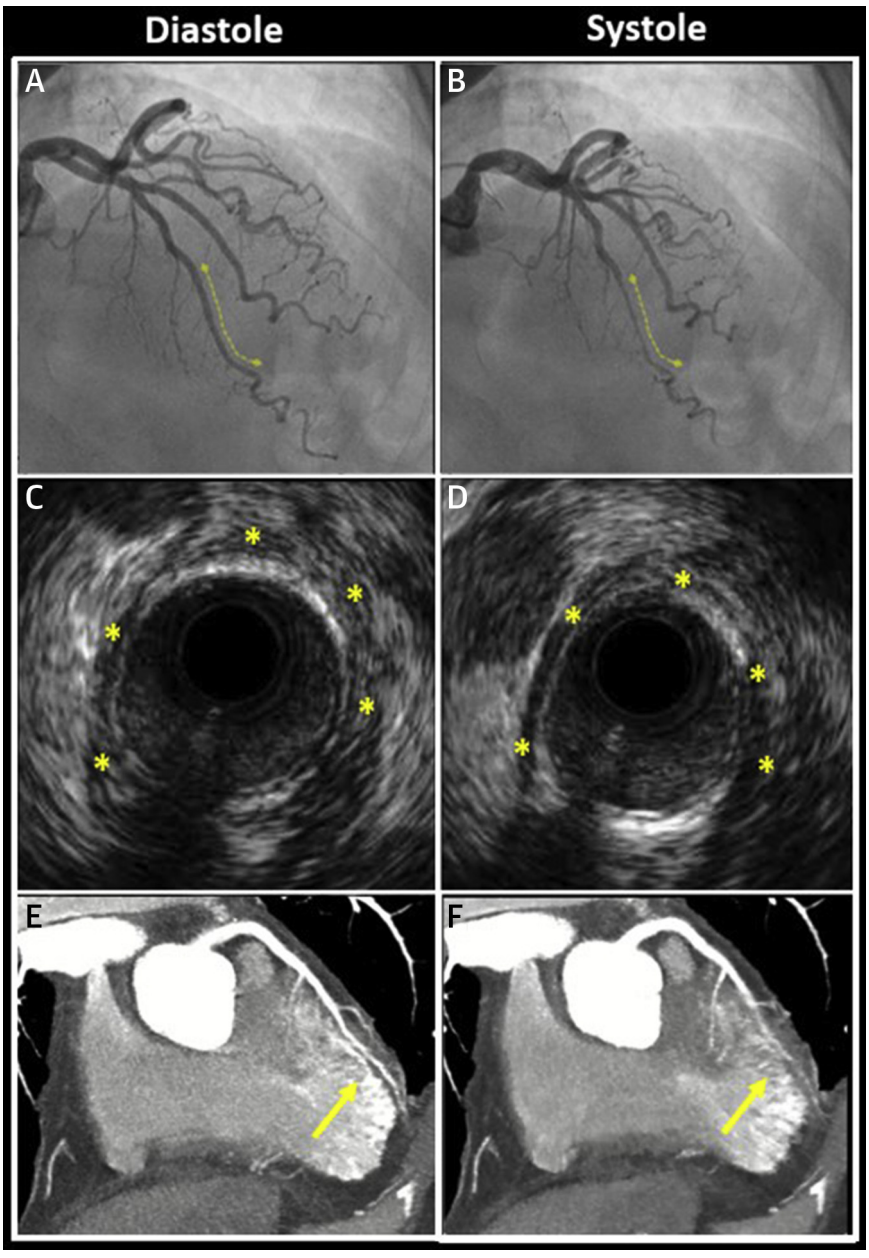
FIGURE 3 Angiography, IVUS, and CCTA of a Diffuse Mid-LAD Myocardial Bridge



(A and B) Coronary angiography demonstrating a classic "milking effect" of the LAD coronary artery. Extrinsic myocardial compression occurs during systole, leading to luminal narrowing of the tunneled vascular segment **(yellow lines)**. **(C and D)** IVUS images of MB **(yellow asterisks)** corresponding to diastole **(C)** and systole **(D)**. **(E and F)** Coronary computed tomography images of LAD myocardial bridge in diastole **(E)** and systole **(F)** demonstrating systolic compression of the tunneled artery **(arrows)**. MLA = minimal lumen area; other abbreviations as in Figures 1 and 2.

milieu in which MBs are most likely to produce symptoms therefore presents a significant technical challenge. Indeed, some studies exploring the clinical relevance of MB assessed by CCTA have concluded that MBs cause little to no impairment in coronary blood flow (13). However, these limitations, as well as patient selection, may have influenced study results (53). Finally, the use of CCTA is limited by radiation and contrast exposure. New advances in computational fluid dynamics have increased with use of

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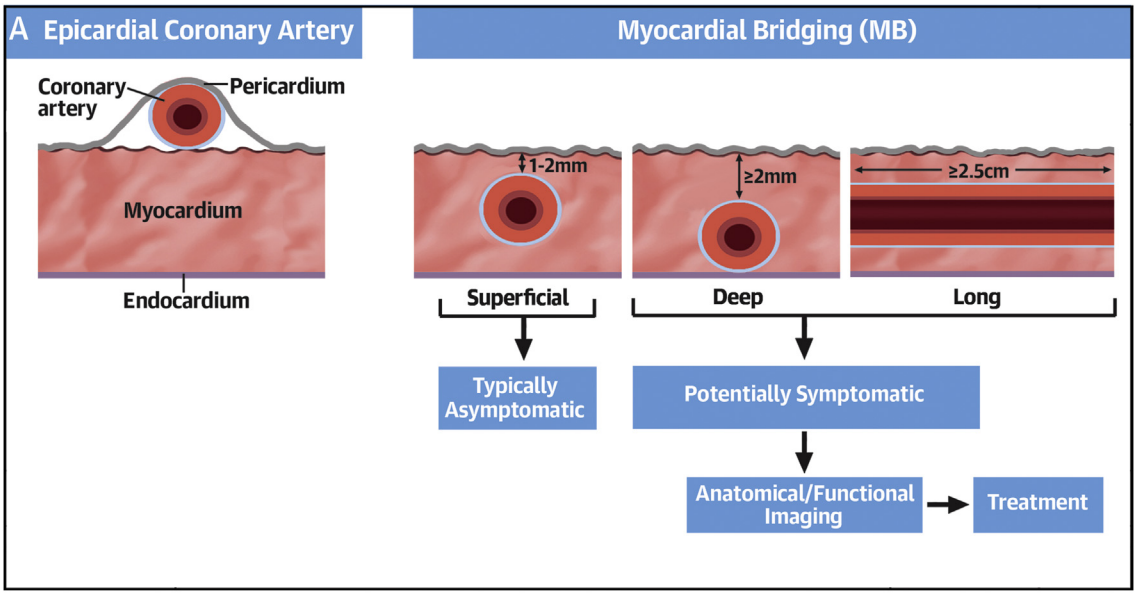
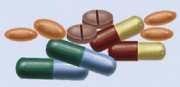
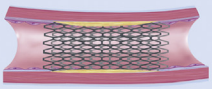
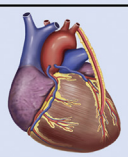
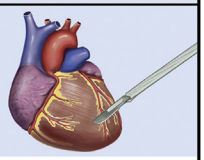
CENTRAL ILLUSTRATION **Anatomic Properties of Myocardial Bridging and Overview of Treatment Modalities**



B **Treatment Modalities**

	Medical Therapy	Percutaneous Coronary Intervention	Coronary Artery Bypass Surgery	Surgical Myotomy
				
Treatment Goal	• Decrease HR • RF modification	• Reinforce the intramural coronary artery	• Bypass the compressed arterial segment	• Remove the overlying MB
Clinical Issues	• First line treatment • Trial nitrate cessation • Avoid pure vasodilators	• High radial strength, second generation DES recommended • Intravascular imaging critical to avoid over or under expansion • Avoid bioresorbable stents	• Suitable for long or very deep MB • Saphenous grafts may be preferred to arterial grafts due to potentially lower rates of graft failure	• Consider as first line surgical treatment at experienced myotomy centers • Technically challenging

Sternheim, D. et al. J Am Coll Cardiol. 2021;78(22):2196–2212.

(A) An MB is present when at least 1 mm of myocardium overlies the tunneled arterial segment. A superficial MB is defined as 1- to 2-mm depth of overlying myocardium. A deep MB is defined as ≥2 mm of overlying myocardium. A very deep MB is defined as ≥5 mm of overlying myocardium. A long MB is defined as ≥25 mm of overlying myocardium. Anatomic and functional imaging are important in defining the bridge severity and hemodynamic effect if symptoms are present and/or treatment is being considered. **(B)** Treatment modalities for symptomatic MB are briefly summarized. Medical therapy is first line for those requiring treatment. If no improvement in symptoms despite maximally titrated medical therapy, PCI, CABG, or surgical myotomy can be considered depending on lesion anatomy, local expertise, and patient preference. CABG = coronary artery bypass grafting; DES = drug-eluting stent; MB = myocardial bridging; PCI = percutaneous coronary intervention.

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CT-derived FFR. Although this has been applied to studying MB, more research is needed to validate this approach, which may be curbed by some of the same limitations that apply to both CCTA and classic invasive FFR (54) (**Table 1**).

Cardiac magnetic resonance imaging (MRI) can also provide anatomic information and has been used to interrogate MB in the setting of hypertrophic cardiomyopathy (55); however, its routine use is limited by technical challenges and lack of spatial resolution (56).

Myocardial perfusion imaging (MPI) is frequently performed to interrogate chest pain syndromes as well as to assess for ischemia related to MBs. MPI can be performed using various imaging techniques (single-photon emission computed tomography [SPECT], positron emission tomography, MRI), as well as various stress protocols (eg, exercise, dobutamine, adenosine, regadenoson, dipyridamole). In a study of SPECT in MB, Gawor et al (56) related the amount of ischemia detected to the degree of systolic luminal narrowing on CA; however, the routine use of MPI has been limited by the heterogeneity of approaches as well as lower spatial resolution for subendocardial defects (57).

Stress echocardiography can be helpful in assessing MB. In addition to identifying reversible stress-induced myocardial hypokinesis in the distribution of the affected coronary artery, a unique pattern of septal buckling with apical sparing has been described that is associated with LAD MB (19). This represents a promising noninvasive avenue for assessing hemodynamic relevance of MB (58). In addition, studies using echocardiographic strain imaging (speckle tracking) have shown that hemodynamically significant LAD MB as determined by invasive dFFR have lower septal longitudinal strain with exercise when compared with matched controls (35) (**Figure 3**).

MANAGEMENT

The treatment of symptomatic MB remains a clinical challenge. Consideration of the individual patient's symptoms, coronary and cardiac anatomy, degree of ischemia, and comorbid conditions (in particular, the presence of CAD, hypertrophic cardiomyopathy, valvular heart disease, and other cardiomyopathies) is critical, as these factors may play a large role in the outcomes of patients with MB. There are no major cardiovascular society guideline recommendations for the diagnosis or management of MB. Medical management should be considered the initial therapeutic strategy in the treatment of MB. Close clinical follow-up and risk factor modification should be emphasized. If symptoms are recalcitrant to maximal medical therapy, revascularization should be considered with either PCI or surgery, including coronary artery bypass grafting (CABG) or myotomy. Preprocedural anatomic planning with CCTA is critical to guide the revascularization strategy (**Central Illustration**).

PHARMACOLOGIC THERAPY. For most patients with symptomatic MB, pharmacologic therapy remains the mainstay of treatment. Although no randomized clinical trial data exist, beta-blockers are generally considered first-line pharmacologic therapy because of their negative chronotropic and inotropic effects. Beta-blockers decrease heart rate and thereby increase diastolic filling time, allowing for decompression of the tunneled segment; this is in addition to the advantageous reduction in overall sympathetic drive (10,32,35). Data for this come from pioneering work by Schwarz et al (15), who revealed that administration of esmolol during atrial pacing reversed a patient's symptoms and signs of ischemia during invasive hemodynamic assessment of patients with symptomatic MB. Some studies have suggested the preferential use of nebivolol due to its highly B1 selective nature and possible beneficial effects on endothelial dysfunction (35).

Calcium-channel blockers are also frequently used in the treatment of symptomatic MB and are preferred in patients with contraindications to beta-blockers such as bronchospasm. In addition, calcium-channel blockers may have vasodilatory effects that might be beneficial in patients with concomitant vasospasm (23).

Ivabradine, a specific inhibitor of hyperpolarization-activated cyclic nucleotide gated channels (f-channels) in the sinoatrial node, may play a role as a second-line agent due to its ability to lower heart rate. Ivabradine can be considered for patients unable to tolerate beta-blockers/calcium-channel blockers or those who do not achieve an adequately controlled heart rate despite maximally tolerated treatment with beta-blockers/calcium-channel blockers. It is important to note that the use of ivabradine in MB is off-label and generally should be reserved for those patients with MB also meeting criteria according to reduced ejection fraction and advanced New York Heart Association symptoms (59).

Vasodilating agents such as nitroglycerin should be used with extreme caution in patients with MB. Nitrates have been shown to worsen systolic narrowing on angiography as well as worsen clinical symptoms (60). This is likely due to intensifying systolic

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compression of the tunneled artery and vasodilating coronary segments adjacent to the bridge, thereby exacerbating retrograde flow (44). Nitrates also can precipitate reflex tachycardia. However, nitrates have antispasmodic properties and can decrease preload, which may be useful in the presence of concomitant coronary vasospasm, if suspected (23).

Finally, MB has been associated with an increased risk of atherosclerosis, especially proximal to the MB, as discussed (45). Therefore, aggressive cardiovascular risk factor modification is recommended, and antiplatelet therapy should be considered once atherosclerosis is detected (10,49).

PERCUTANEOUS INTERVENTION. The biopathological rationale for the use of PCI in MB is predicated on protecting the stented arterial segment from systolic compression during exercise and physiological stress. Randomized data are lacking for the use of PCI in the treatment of MB, and treatment has been historically reserved for patients who have refractory anginal symptoms despite optimal anti-anginal therapy (61). Despite this, the use of PCI for MB is growing in the United States. Although retrospective data have demonstrated PCI to be hemodynamically effective in MB (15,62), the availability and ease of PCI probably constitute the key factors for its growing use in MB, rather than robust clinical evidence (63). PCI has previously been associated with both hemodynamic and symptom improvements in MB; however, no studies have demonstrated complete normalization of perfusion defects following stent implantation. In addition, concerns have previously been raised about the long-term efficacy of PCI strategies for MB. Registry data examining PCI in MB have previously demonstrated high rates of ISR at 1 year, with rates of ISR of up to 75% for BMS and 25% for drug-eluting stents (DES) (64). In addition, limited case series have described stent perforation rates of up to 6% in addition to rare cases of stent fracture and stent thrombosis following PCI for MB lesions (65-67). It should be recognized that rates of ISR described in prior studies may be limited by the preponderance of BMS, first-generation DES, and lack of intravascular imaging. Although data are needed, the use of high radial strength second-generation DES combined with accurate stent sizing using intravascular imaging may potentially improve medium- to long-term outcomes in PCI for MB.

From examining the available retrospective evidence comparing BMS with DES for the treatment of MB, there are 2 key conclusions. First, BMS have significantly higher rates of target vessel revascularization compared with first-generation DES, and second, stent implantation in patients with symptomatic MB risks high rates of early ISR potentially related to bridge-associated luminal narrowing. The ideal stent for PCI in MB is a high radial strength drug-eluting platform. An everolimus-eluting platinum chromium second-generation DES has recently been developed demonstrating exceptional radial strength compared with cobalt alloy and stainless-steel platforms (68,69). Future-generation stents may potentially achieve even greater safety profiles related to their ability to better tolerate radial stress forces from cyclical systolic compression. Protection of the stented vascular segment during endothelialization may theoretically result in greater luminal gain, therefore potentially providing more durable long-term results.

Bioresorbable stent platforms should generally be avoided given their lack of radial strength. A “temporary” bioresorbable vascular scaffold that disappears over time was initially considered an attractive therapeutic target given the ability to assess for symptom improvement without committing a patient to the risks of mechanical failure and ISR associated with metallic stent scaffolds. It was subsequently observed that compression from the bridge appears to crush the scaffold as it loses integrity during the process of resorption. Future bioresorbable scaffolds may be designed with enough upfront radial strength to achieve greater luminal gain and allow for formation of a thin fibrous endoluminal layer that withstands systolic compression during the resorption phase. Whether scaffolds with these biomechanical properties can be developed and withstand the scrutiny of angiographic and outcome studies remains to be seen (70).

Taken together, there are currently no randomized data to guide the use of PCI versus medical management in patients with symptomatic MB. Most reported complications associated with PCI in MB have involved bare-metal or first-generation drug-eluting scaffolds, thus significantly limiting the contemporary interpretation of these results in the era of second-generation DES. Importantly, if treatment with coronary stenting is planned, dobutamine challenge may be beneficial in the accurate sizing of stent length so as to avoid incomplete coverage of the MB, which can be hazardous (63). A second-generation DES with high radial strength should be used to maximize resistance from cyclical systolic compression.

Given the primary concerns of ISR and stent fracture, we support the usage of these second-generation platforms to further mitigate risk. To ensure optimal deployment within the tunneled segment, stent inflation should be performed toward the recommended pressure limit (10,24). Oversizing

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of the stent should similarly be avoided to prevent severe complications, such as coronary perforation. There exist no data regarding the optimal choice of dual antiplatelet therapy following PCI for MB. Therefore, the choice of $P2Y_{12}$ inhibitor is operator dependent, typically reflecting dual antiplatelet therapy guidelines for the presenting syndrome (stable angina vs ACS).

SURGICAL TREATMENT. Surgery is an effective, although invasive, treatment for symptomatic MB refractory to maximally tolerated medical therapy. Surgical options for MB include CABG or supraarterial myotomy, also known as "unroofing." CABG can be completed on or off cardiopulmonary bypass using either arterial or saphenous vein grafts. Most commonly, LAD MBs are bypassed using the left internal mammary artery (LIMA), although there is some evidence to suggest that a saphenous vein graft may be preferable in some cases (71). Complications of CABG have been well described, but in the case of MB, the chief concern is graft failure, likely due to competitive flow (72,73). To date, the largest retrospective study examining bypass grafting with LIMA to LAD for MB demonstrated very high rates of arterial graft failure. Overall, only 10% of arterial grafts were patent with competitive flow at 18 months, with 60% of grafts demonstrating complete occlusion. Saphenous vein grafts, on the other hand, demonstrated patency rates of almost 80%. A novel technique, "myocardial bridge bypass grafting," in which a free LIMA is anastomosed to the LAD proximal and distal to the MB, has been recently described but requires further study (74).

In a myotomy, the surgeon carefully dissects the artery from the overlying myocardium. This can be performed on or off pump, and recently has been successful in selected cases via mini thoracotomy foregoing traditional sternotomy (75). Potential complications include ventricular wall perforation (usually of the right ventricle with an LAD MB and deep endomyocardial course), artery perforation, ventricular aneurysm formation, incomplete unroofing, and postoperative bleeding.

Recently, there has been increased interest in myotomy, in both pediatric and adult patients (75-78). Myotomy has the advantage of relieving the upstream pathophysiologic abnormality and therefore is an attractive treatment option. However, as Hemmati et al (76,77) point out, there is a high incidence of late recurrent chest pain after successful myotomy in adult patients, up to 60% at 3-year follow-up. This is perhaps related to endothelial dysfunction attributable to the MB that persists even after relief of MB compression (76,77). Therefore, myotomy may be best suited for a pediatric population that has had less time to develop sequelae of MB. Interestingly, IVUS examination of pediatric patients undergoing myotomy for refractory symptomatic MB showed atherosclerotic plaque proximal to the tunneled segment, even though the average patient age was only 15.6 years (28,78). Overall, myotomy has been shown to be a safe and effective treatment for symptomatic MB, especially with favorable anatomy (nontortuous artery, shorter and more superficial intramyocardial course), thorough preoperative planning, and when performed at an experienced center.

There is limited evidence comparing CABG to myotomy for the treatment of symptomatic MBs. CABG has previously been favored over myotomy in cases of extensive (>25 mm) or deep (>5 mm) myocardial bridges, or when the coronary segment fails to decompress completely in diastole; however, there are few data to guide this recommendation. In a recent observational study of CABG vs myotomy, Ji et al (79) describe 54 patients who underwent surgery for symptomatic MB (31 myotomy, 23 CABG); 41% of the patients with CABG met criteria for a major adverse cardiovascular event vs 7% in the myotomy group. On follow-up CCTA, 9 of the 23 patients who underwent LIMA to LAD grafting experienced graft failure. Notably, all 10 patients who were found to have >50% proximal stenosis on preoperative angiography and subsequently underwent CABG were found to have patent grafts on follow-up (79). This further supports competitive flow as a major factor contributing to bypass graft patency in MB. The choice of surgical treatment should use an individualized approach that considers the patient's anatomy, clinical characteristics, and available surgical expertise. In cases in which CABG is planned for the upfront treatment of MB, saphenous venous grafting should be considered (80).

THERAPEUTIC STRATEGY

Based on the available evidence and expert experience, we propose the following management strategy for symptomatic MB. For patients without clinical symptoms, therapeutic focus should be on risk factor modification, including appropriate treatment of concomitant CAD, and relief of potential triggers. For patients with clinical symptoms, objective signs of ischemia, and/or abnormal intracoronary hemodynamics (iFR or dFFR with dobutamine challenge as the preferred modalities), pharmacologic treatment should be initiated beginning with beta-blockers and/or calcium-channel blockers. Vasodilators, such

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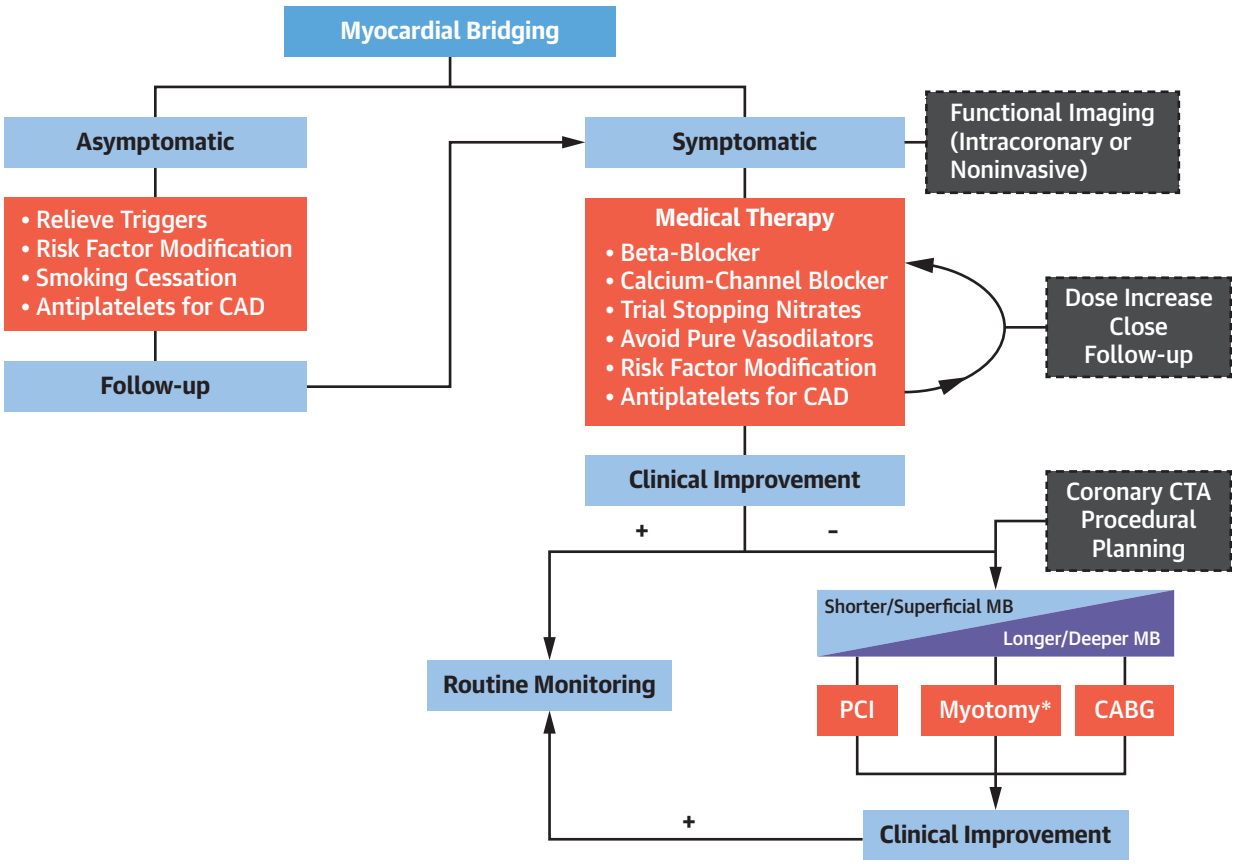
FIGURE 4 Management Algorithm for Asymptomatic and Symptomatic MB



Flow diagram with proposed strategy for the management of asymptomatic and symptomatic MB. Triggers include coronary vasospasm, smoking and stimulants (cocaine), physiological stress, poor functional exercise reserve. *Surgical myotomy should be considered as a first-line therapy if performed at an experienced myotomy center *and* if favorable anatomy is present. CABG = coronary artery bypass grafting, CAD = coronary artery disease; CTA = computed tomography angiography; MB = myocardial bridging; PCI = percutaneous coronary intervention.

as nitrates, should generally be avoided in all but very rare cases associated with significant vasospasm. Frequent outpatient monitoring for clinical improvement and up-titration of oral medical therapies are key. Similarly, consideration of other causes of angina with normal coronary arteries, such as microvascular dysfunction, are important to rule out.

If symptoms persist despite maximally tolerated medical therapy, an interventional option should be considered. For most patients, we suggest PCI as the upfront interventional strategy. Noninvasive imaging with CCTA should be considered before revascularization to assess the length, depth, and anatomic characteristics of the MB. PCI offers a less invasive, effective option for relief of symptoms and improvement in intracoronary hemodynamics (14). Specific factors favoring the use of PCI in MB include shorter lesion length and more superficial depth (<2 mm) of the tunneled segment. Deep or long MB, particularly those that cannot be addressed with a single stent, should prompt an assessment for surgical revascularization. Although PCI of MB has been associated with reports of stent fracture, stent thrombosis, and perforation during stent deployment, we believe that these concerns can be reliably mitigated using second-generation DES, accurate stent sizing aided by detailed intravascular imaging, and preferential use of high radial strength platforms (65-67). PCI of MB also has been associated with increased risk of ISR (64). Although the use of DES decreases rates of TLR compared with BMS, restenosis still likely occurs more frequently with PCI for MB than for atherosclerotic lesions. In the event of ISR requiring TLR due to persistent symptoms refractory to medical management, we suggest pursuing CABG. This strategy has several advantages. First, the bypass graft is

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likely to be successful and durable given the lack of competitive flow from the proximal ISR. Second, it uses widespread expertise and experience in PCI and CABG and is therefore more accessible. Third, initial PCI can serve as a "trial" to see if improvement in intracoronary hemodynamics leads to symptomatic relief. It is clinically challenging to pinpoint the etiology of a patient's symptoms in many cases, even with evidence of ischemia on noninvasive testing or abnormal intracoronary hemodynamics. This sequence of treatments increases the likelihood that any surgical intervention will definitively address the patient's symptoms (**Figure 4**).

Alternatively, myotomy can be considered as the first-line interventional strategy in selected cases. Patient selection should focus on favorable anatomy, including a nontortuous affected artery with a superficial and shorter intramyocardial course, and younger patient age, including pediatric patients. Myotomy is best performed at a center with high-volume experience to avoid complications related to challenging anatomy (ie, dense adhesions from prior sternotomy, right ventricle overlying the LAD, MB abutting the right ventricular outflow tract) (75). Thorough preoperative assessment with IVUS and CCTA may be helpful in avoiding complications during myotomy (81).

CONCLUSIONS

MB is a common congenital anomaly encountered frequently in clinical practice. Although generally benign, consideration should be given to identifying and treating the subset of patients with symptomatic disease. Noninvasive imaging techniques such as CCTA have greatly improved the anatomic characterization of MB, and intracoronary hemodynamics (iFR, dFFR) have improved our ability to characterize symptoms producing MB. In symptomatic patients, medical therapy is usually an effective option. For those failing medical therapies, multimodality anatomic and hemodynamic characterization may aid in guiding safer revascularization. PCI as the favored revascularization technique allows for confirmation of the MB as the symptom-producing lesion, in addition to advantageous hemodynamics for CABG in the event of stent-related complications. Myotomy should be considered in patients with favorable intramyocardial anatomy at experienced, high-volume MB centers. Additional research is needed to better identify patients in whom MB is pathologic. Randomized trials and long-term registry data are required to define the natural history, patient selection, and optimal treatment strategies for MB.

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KEY WORDS myocardial bridge, myocardial bridging, state-of-the-art review

APPENDIX For a supplemental video, please see the online version of this paper.

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