Importance of Diastolic Fractional Flow Reserve and Dobutamine Challenge in Physiologic Assessment of Myocardial Bridging

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OBJECTIVES
This study reports a comparative assessment of the hemodynamic relevance of myocardial bridges (MB) using two modalities of fractional flow reserve (FFR), with and without concomitant inotropic challenge.

BACKGROUND
Extravascular coronary compression by means of MB is modulated by myocardial inotropism and causes intracoronary systolic pressure overshooting and negative systolic gradients across the MB. The former characteristic suggests that adequate hemodynamic assessment of MB should include inotropic stimulation. The latter characteristic might interfere with FFR by decreasing the mean pressure gradient.

METHODS
We compared the hemodynamic relevance of 12 lone MB in symptomatic patients using conventional (mean) and diastolic FFR. Diastolic FFR was obtained from post-processed, digitally acquired electrocardiogram and pressure signals. Previously validated cut off values of 0.75 (mean FFR) and 0.76 (diastolic FFR) for hemodynamic relevance were used. Measurements were performed at baseline and after incremental intravenous dobutamine doses.

RESULTS
Fractional flow reserve decreased during dobutamine challenge: mean FFR was 0.90 ± 0.04 at baseline and 0.84 ± 0.06 after dobutamine (p = 0.008); similarly, diastolic FFR was 0.88 ± 0.05 and 0.77 ± 0.10 before and after dobutamine, respectively (p = 0.0006). Diastolic FFR identified hemodynamic relevance in five patients, whereas mean FFR did so in only one patient. The discrepancy between mean FFR and diastolic FFR increased with dobutamine challenge: the ratio of mean FFR/diastolic FFR was 1.03 at baseline and 1.09 after dobutamine (p = 0.02). During the administration of dobutamine, the discrepancy was inversely related to the systolic pressure gradient (r = 0.58, p = 0.04).

CONCLUSIONS
Physiologic assessment of MB should include dobutamine challenge. Because the overshooting of systolic pressure interferes with and is a cause of error in FFR measurements based on mean pressures, diastolic FFR appears to be the technique of choice for MB assessment, whereas mean FFR should be used with caution. (J Am Coll Cardiol 2003;42:226–33) © 2003 by the American College of Cardiology Foundation

Although myocardial bridges (MB) are commonly found in normal human hearts (1,2), their association with anginal chest pain or abnormal noninvasive tests often constitutes a important clinical issue. Myocardial bridges have been associated with stable and variant angina, sudden death, and myocardial infarction (1–10), a variety of coronary syndromes with the twofold substrate of the disturbed coronary hemodynamics (9), and endothelial dysfunction (11) caused by extravascular vessel compression. Although surgical treatment of MB was seldom performed (12), the widespread use of coronary stenting has led to a more aggressive treatment approach of MB (9,13–20). Although stenting can be hemodynamically effective in MB (9,19), the availability and ease of coronary stenting probably constitute key factors for its growing use in MB, even though its long-term results remain unclear (20).

In this scenario, adequate identification of MB with hemodynamic relevance is of paramount importance to avoid unnecessary interventions. As in fixed stenoses, intracoronary physiology techniques might constitute a valuable alternative to coronary angiography (21), hampered as a diagnostic tool by the complex hemodynamics, cyclic changes in luminal dimensions and noncircular lumen morphology. Furthermore, because they are dynamic stenoses dependent on the degree of extravascular compression and intramyocardial tension (22,23), their invasive assessment should not be limited to rest conditions, which might leave unidentified the hemodynamic relevance of MB only during exercise or situations of increased inotropism.

We report our experience of angiographic and physiologic evaluation of MB using pressure guide wires and dobutamine challenge. Two pressure-derived indexes of coronary reserve were obtained and compared: conventional fractional flow reserve (FFR) calculated from mean pressures over the complete cardiac cycle (24), and diastolic FFR calculated from diastolic pressures only (25). Dobutamine was chosen as the inotropic challenge because it is compatible with FFR studies (26). Finally, diastolic FFR was compared with mean FFR because intracoronary systolic pressure overshooting occurs in MB (9,19) and potentially

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could interfere with measurements based on mean pressures. The study was not designed as a validation against noninvasive tests for detection of ischemia, and its aim was the comparison of two already validated intracoronary physiology indices.

**METHODS**

**Study population.** We studied 12 patients with angina in whom the only relevant angiographic finding was a compression of the mid segment of the left anterior coronary artery by an MB causing a >50% reduction in systolic vessel diameter, as visually assessed. All patients had abnormal noninvasive tests and/or electrocardiogram (ECG) changes during or immediately prior to admission that were suggestive of myocardial ischemia. None of the patients presented concomitant coronary stenoses or any present or previous cardiac events. Echocardiography ruled out hypertrophic cardiomyopathy in all patients. Informed consent to catheterization and physiologic assessment was obtained in all patients. Demographic data, including age, gender, and cardiovascular risk factors, were recorded.

**Catheterization procedure.** Beta-blockers were interrupted five days prior to cardiac catheterization in two patients receiving these drugs. A right femoral artery approach was used. After administration of 5,000 IU of unfractionated heparin and 200 μg of intracoronary nitroglycerin, baseline coronary angiograms were obtained in several angiographic views. The two views showing a better visualization of the MB were chosen for further angiographic runs, which were performed at a speed of 25 frames/s for detailed analysis of systolic coronary compression.

**Translesional pressure measurements.** Aortic pressure was obtained by using a 6F to 8F guiding catheter without side holes, connected to a pressure transducer (B/Braun, Braun, Melsunger, Germany) and to a Horizon 9000 computerized polygraph (Horizon 9000, Mennen Medical Inc., Haifa, Israel). After calibration, a 0.014-inch micromanometer-tipped guide wire (PressureWire, Radi Medical Systems, Uppsala, Sweden) connected to its interface and to the polygraph was advanced under fluoroscopy, distal to the MB. The pressure sensor was located approximately 3 cm distal to the MB in order to avoid its entrapment and direct compression by the bridge. Selected pressure tracings and angiographic runs were recorded during this procedure according to the following scheme.

1. **Baseline measurements.** Following intracoronary administration of 200 μg of nitroglycerin, baseline pressure measurements were obtained during hyperemia induced by a 20 μg intracoronary adenosine bolus. Coronary angiography was then performed.

2. **Measurements during dobutamine challenge.** Intravenous infusion of 5 μg/kg/min dobutamine was given for 5 min. Then, after a bolus of 100 μg of nitroglycerin, a new set of pressure measurements were performed during hyperemia, repeating a 20 μg intracoronary adenosine bolus. Coronary angiography was then repeated to document changes in the severity of systolic vessel compression. Dobutamine was then increased in 5 μg/kg/min doses, and identical sets of measurements, as described above, were repeated after 5 min. This scheme was repeated until a maximum dose of 20 μg/kg/min dobutamine was reached or until the patient developed symptoms. Because it is the first study, to our knowledge, to combine intracoronary instrumentation of MB and enhanced inotropism, higher doses of dobutamine were not intended as a precaution. At the end of the procedure, the persistence of the guide wire calibration was checked.

**Digital acquisition and post-processing of physiologic data.** Continuous digital acquisition and storage of the ECG, aortic, and intracoronary pressures were performed using a 12-bit resolution analog-to-digital converter (DI-200 PGL, DataQ Instruments, Akron, Ohio) controlled by dedicated software (WinDaq 200, DataQ Instruments) in a personal computer. The sampling rate was 114 Hz per channel. After the procedure, off-line analysis was performed using the WinDaq and Advanced Codas software (DataQ Instruments), allowing the calculation and display of instantaneous pressure gradients as waveforms. Relevant data intervals were selected and transferred to a Macintosh Power PC 8500 computer for further statistical analysis (StatView 5.0, SAS Institute Inc., Cary, North Carolina).

All measurements were performed during maximal hyperemia, which was identified as the interval with a peak instantaneous pressure gradient (ΔP) across the MB after adenosine administration. Diastole was identified as the interval between the dichrotic notch in the aortic pressure tracing and the following R-wave peak in the ECG. Average (mean) and diastolic components of aortic pressure (Pa), distal intracoronary pressure (Pd), and ΔP were calculated.

**Estimation of FFR.** Fractional flow reserve was defined as the ratio between pressures measured distal to and proximal to the MB during maximal hyperemia. For study purposes, two indexes of FFR were used. Conventional FFR was calculated using mean or average pressures during the whole cardiac cycle (mean FFR = mean Pd/mean Pa) (24). The cutoff point of 0.75, with reported sensitivity and specificity of 88% and 100%, respectively (25), was used to detect hemodynamic relevance. Diastolic FFR was calculated using
only diastolic pressures. The cutoff value of 0.76 for the detection of hemodynamic relevance in the left anterior descending artery, with reported sensitivity and specificity of 96% and 100%, respectively (25), was used.

**Quantitative coronary angiography.** Cineangiographic frames were analyzed using an automated edge-detection quantitative angiography system (QCA-CMS Medical Imaging Systems, Leiden, The Netherlands). The filmed catheter tip was used as a scaling device. Measurements were performed at the point of maximal systolic coronary compression by the MB at baseline and at the end of each stage of dobutamine challenge. Bifurcations were used as landmarks for segment analysis. Edge detection was automatically detected using the gradient field transform feature included in the QCA-CMS for vessels with irregular intraluminal morphology. From the diameter function obtained by the system, the interpolated reference diameter, minimal luminal diameter, stenosis length (mm), and percent diameter stenosis (%DS) were calculated.

**Statistical analysis.** For all continuous variables, mean and standard deviation were calculated. Linear regression analysis was performed using a least-square approach. Comparison of mean values was performed using Student’s t test (pair or unpaired, as required) or one-way analysis of variance. For comparison of percentages in discrete variables the chi-squared test was performed. A p value of <0.05 was considered significant.

**RESULTS**

The study population was composed of 12 patients with an age of 53 ± 13 years, 11 (91%) were male, 3 (25%) presented diabetes mellitus, 3 (25%) hypercholesterolemia, 4 (33%) systemic hypertension, and 5 (42%) had a history of smoking. Nine patients presented an abnormal noninvasive test suggesting myocardial ischemia (seven by means of exercise tolerance test, two by means of MIBI SPECT). The remaining three patients were admitted with unstable angina and reversible ECG changes suggestive of anterior wall myocardial ischemia. The study was successfully accomplished according to the protocol described earlier in all patients without complications. In four patients the target dose of dobutamine (20 μg/kg/min) was reached. In five patients dobutamine infusion was prematurely interrupted due to chest pain that was described as being similar to previous episodes, and in three due to anxiety and discomfort judged to be unbearable by the patient.

**Angiographic findings.** Figure 1 shows the effect of dobutamine challenge on the angiographic features of MB. Systolic %DS increased from 46.09 ± 10.50 to 68.72 ± 17.95 (p < 0.0001), and systolic minimal luminal diameter decreased from 1.52 ± 0.39 to 0.82 ± 0.44 mm (p = 0.001). A twofold increase in stenosis length, as automatically quantified by the quantitative angiography system, occurred after dobutamine challenge: at baseline the compressed segment was 12.40 ± 9.05 mm in length, increasing to 24.04 ± 9.17 mm in length in response to dobutamine (p = 0.0005) (Figs. 1 and 2).

**Hemodynamic changes.** Dobutamine infusion caused an increase in the double product from 8,884 ± 2,239 at baseline to 13,788 ± 3,287 at the maximal dose reached (p < 0.0001). Hyperemic mean pressure gradient through the MB was 8.93 ± 4.90 mm Hg at baseline, reaching a maximum of 13.89 ± 8.35 mm Hg during dobutamine challenge (p = 0.06). The hyperemic systolic gradient through the bridged segment was 6.40 ± 4.81 mm Hg and 5.13 ± 7.47 mm Hg at baseline and during dobutamine challenge, respectively (p = NS). In six patients (50%), the systolic gradient decreased in response to dobutamine infusion, and in four (33%) it reached negative values, meaning that as a result of the compressive effect of the MB on the vessel, during systole the average coronary pressure distal to the MB was higher than the aortic pressure (Fig. 3). During diastole, a significant increase in pressure gradient through the bridged segment was observed in response to dobut-
amine infusion (increasing from 9.69 ± 5.16 mm to 17.26 ± 8.53 mm Hg, p = 0.002). When displayed as a waveform, the instantaneous diastolic gradient typically followed a peak-and-plateau morphology that closely resembled a characteristic flow pattern documented by Doppler guide wires in MB by other authors (1,7–9,14,27) (Fig. 3), with a predominant early diastolic pressure gradient.

Before dobutamine mean FFR was 0.90 ± 0.04, in all cases higher than the cutoff value of 0.75 used with this technique. Although mean FFR significantly decreased to 0.84 ± 0.06 during dobutamine challenge (p = 0.0008), only one patient presented an FFR <0.75 (Fig. 4). Diastolic FFR was 0.88 ± 0.05 and 0.77 ± 0.10 at baseline and in response to dobutamine infusion, respectively (p = 0.0006). Conversely, to mean FFR, a diastolic FFR value of <0.76 was already documented in one patient at baseline, and in five patients during dobutamine infusion (Fig. 4). The MB with associated diastolic FFR ≤0.76 presented a higher angiographic severity in response to dobutamine challenge (minimal luminal diameter 0.59 ± 0.11 mm, %DS 74.00 ± 18.18%) than those with associated diastolic FFR >0.76 (minimal luminal diameter 0.98 ± 0.21 mm, %DS 64.33 ± 18.14%), although these differences were not statistically significant. A higher rate-pressure product was reached by patients with diastolic FFR ≤0.76 than by those with diastolic FFR >0.76 (16,413 ± 1,586 vs. 11,914 ± 2,879 mmHg·s, respectively, p = 0.01). At baseline three of the patients with diastolic FFR ≤0.76 had unstable angina and reversible ECG changes suggestive of anterior wall myocardial ischemia, and two had positive exercise tolerance tests.

The discrepancy between FFR based on mean as opposed to diastolic pressures was expressed as the ratio of mean FFR to diastolic FFR. This ratio increased significantly from 1.03± 0.02 at baseline 1.09 ± 0.09 during dobutamine challenge (p = 0.02). Because the difference between diastolic and mean FFR is related to systolic events, the relationship between the ratio of mean FFR to diastolic FFR and the pressure gradient documented during systole was investigated using linear regression analysis (Fig. 5). A significant inverse relationship between the systolic gradients and diastolic FFR overestimation, absent at baseline, developed during dobutamine challenge. This finding indicates that the decrease or negativization of the systolic pressure gradient across the MB was a major determinant of the discrepancies between the two methods, contributing to the inability of mean FFR to identify an MB in which the ischemic threshold had been reached according to diastolic FFR criteria.

Based on the lack of evidence concerning the long-term outcome of stenting in the presence of an MB at the time of inclusion in the study, long-term treatment with beta-blockers was followed in all patients with hemodynamic relevance of MB. At one year clinical follow-up, all these patients remained asymptomatic and free of cardiac events.

**DISCUSSION**

The main conclusions of this study are: 1) the angiographic and functional severity of some MB are demonstrated only after inotropic stimulation; 2) the development of significant diastolic pressure gradients demonstrates that MB influence diastolic hemodynamics; 3) diastolic FFR identifies a significant proportion of hemodynamically relevant MB that are left unidentified by conventional FFR; and 4) the superiority of diastolic FFR over conventional FFR relies on the exclusion of systolic pressure gradients, char-
characteristic of MB hemodynamics. These aspects and their implications are discussed in detail in the following paragraphs.

Although angiographic evidence of MB is accepted as a harmless variant of normal human coronary circulation (1), a potential link between MB and various coronary syndromes (1–6) has been strengthened by direct demonstration, using intracoronary techniques, of decreased coronary flow reserve (7–10,14,19,27–30). These data have also revealed two hemodynamic features that are specific to MB

Figure 3. Intracoronary hyperemic pressure measurements at baseline and during dobutamine challenge. The graph shows the recorded electrocardiogram (EKG), aortic pressure (Pa), and intracoronary pressure distal to the myocardial bridge (Pd) as well as the instantaneous pressure gradient resulting from the difference between the two pressures. These tracings are shown as recorded at baseline and during dobutamine challenge (note the differing scaling of the pressure tracings). The overshooting of Pd over Pa noted during dobutamine challenge contributes to the characteristic negative systolic and positive protodiastolic pressure gradients, which mimic the Doppler flow velocity pattern described previously (1,9). At baseline mean fractional flow reserve (FFR) was 0.90 and diastolic FFR was 0.87; during dobutamine challenge mean FFR was 0.80 and diastolic FFR was 0.72.

Figure 4. Fractional flow reserve (FFR) values obtained at baseline and at peak dobutamine challenge using either mean or diastolic FFR. The combination of dobutamine challenge and diastolic FFR allows identification of the largest number of patients in whom the optimal cutoff value for detection of hemodynamic relevance was reached.
and not present in fixed stenoses and that have relevance to our study. First, the “milking” of blood in the compressed epicardial segment against a highly resistive microcirculation (systole) causes premature overshooting of intracoronary over aortic pressure, resulting in a negative systolic pressure gradient across the MB (9,19). Second, systolic MB compression is followed by a delayed gain in luminal dimensions during early diastole, which may impair diastolic blood flow (8,30).

Because MB are dynamic stenoses, we believe that their assessment should not be limited to a baseline situation but should also include inotropic challenge. Intravenous dobutamine was used in this study because along with the positive inotropic-effect increases coronary blood flow it causes (31), it does not modify epicardial vessel or stenotic dimensions (32), and it facilitates maximal coronary hyperemia (32). An intermediate dose (20 μg/kg/min) was used for safety reasons and to limit its effect to increasing extravascular compression (33), not aimed to induce the heterogeneity of coronary flow, as in noninvasive imaging tests.

Furthermore, unlike coronary flow velocity reserve, pressure-derived FFR is not influenced by dobutamine administration (26,32). The widespread acceptance of FFR also means that it is easy to perform, requiring only two mean pressures to be obtained during maximal hyperemia (24). Although the use of mean pressure constitutes a major simplification of the shifting hemodynamics during the cardiac cycle, the introduction of diastolic FFR and its elegant validation by Abe et al. (25) supports the idea that in fixed stenoses, the difference between mean and diastolic values is not significant. However, for the study of MB, diastolic FFR presents two theoretical advantages over conventional FFR. First, the restriction of measurements to diastole avoids the influence of systolic negative intracoronary gradients on overall pressure measurements (9,19). Second, it allows identification and quantification of the effect of the MB on the diastolic coronary blood flow.

Our results demonstrate the usefulness and safety of combining dobutamine challenge with diast FFR in the presence of MB. At baseline, only one patient was found to have a hemodynamically significant MB using diastolic FFR. During dobutamine challenge, five patients were identified by diastolic FFR and only one by conventional FFR. As shown in Figure 5, the discrepancy between the two FFR modalities is related to the inclusion of systolic translesional gradients in conventional FFR and to increase during dobutamine challenge. Therefore, when using conventional FFR, a negative result, even after dobutamine challenge, does not preclude the possibility of a false negative, and should be interpreted with caution.

We found that a relationship between the degree of inotropic stimulation and the degree of positivity of the test might exist, because the patients who registered a diastolic FFR <0.76 were found to have reached a higher rate-pressure product than the others. Based on our results, higher doses of dobutamine should be encouraged in future studies in clinical practice if diastolic FFR remains >0.76 with intermediate doses of dobutamine. It is foreseeable that

![Figure 5. Influence of the intracoronary systolic pressure gradients on the discrepancy between mean and diastolic fractional flow reserve (FFR) measurements, expressed as the ratio mean FFR/diastolic FFR. At baseline the discrepancy between the techniques is minimal and is not influenced by systolic gradients. Conversely, during dobutamine challenge a significant inverse relationship between intracoronary systolic gradient and the defined discrepancy develops, being maximal in those patients who developed negative systolic intracoronary pressure gradients.](image-url)
even at higher doses of dobutamine, diastolic FFR will remain a more sensitive technique than conventional FFR for the detection of hemodynamic relevance. Although calculation of diastolic FFR is currently cumbersome, the development and implementation of algorithms for its automatic calculation in pressure guide wire interfaces is technically feasible and might be fostered by our results.

In agreement with Diefenbach et al. (22), we found that the angiographic severity of MB is modified by dobutamine. However, as has been documented in cases of fixed stenoses (21), the angiographic severity of MB did not correlate well with its functional relevance. If treatment by coronary stenting is planned, dobutamine challenge may help in sizing the stent length so as to avoid incomplete coverage of the MB, which can be hazardous (16,34,35). The length of the compressed segment may also provide clues to the anatomic characteristics of the MB. In our population, the mean length (24.04 mm) was found to fall between that of the more commonly observed superficial, and potentially harmless, bridges found in necropsy studies (15.3 mm) (36) and that of the less common, deep MB (39.5 mm), which theoretically may cause significant vessel compression or twist (36).

**Study limitations.** This study was not designed for comparison of FFR with noninvasive tests in the detection of ischemia. The performance of an intracoronary study to ascertain the physiologic relevance of the MB was deemed justified only in the presence of abnormal noninvasive tests or chest pain with reversible ECG changes, so patients with no evidence of ischemia were excluded. In those who showed no documented pathologic FFR, the results of noninvasive tests might be regarded as being false positive or, as discussed earlier, as being a failure to reach a maximal rate-pressure product. The observations obtained in this regard will facilitate the performance of future studies. Although intravenous administration of adenosine may be superior to intracoronary administration, maximal coronary hyperemia was also facilitated by the hyperemic effect of dobutamine in our study (32).

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