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CLINICAL PRESENTATION OF THE NON-ATHEROSCLEROTIC CORONARY LESIONS. MORPHOLOGICAL EVALUATION OF THE MYOCARDIAL BRIDGE

PhD thesis

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List of Abbreviations

CABG	Coronary artery bypass graft
CCTA	Coronary CT angiography
EF	Ejection fraction
FFR	Fractional flow reserve
HR	Hazard ratio
IVUS	Intravascular ultrasound
LAD	Left anterior descending artery
LAD-MB	Left anterior descending artery – Myocardial Bridge
LAD-MB^{neg}	Left anterior descending myocardial bridge without another significant atherosclerotic coronary lesion group.
LAD-MB^{pos}	Left anterior descending myocardial bridge with another significant atherosclerotic coronary lesion group.
MB	Myocardial Bridging
MRI	Magnetic resonance imaging
OCT	Optical coherence tomography
PCI	Percutaneous coronary intervention
QCA	Quantitative coronary angiography
Qp/Qs	Pulmonary-systemic flow ratio
SD	Standard deviation
VSR	Ventricular septal rupture

1. Introduction

1.1. Myocardial bridge: definition, epidemiology

Coronary arteries that could be made visible in vivo mainly run in the epicardial space. If – during ontogenesis - a segment tunnels through the myocardium refer to myocardial bridging (MB). The "bridge" itself is the myocardium that belts completely or partially (incomplete MB) the vessel (Figure 1.). In the case of partial encasement, the vessel courses within a gorge formed by the myocardium while in the case of complete MB the myocardium surrounds the coronary segment. Depending on the imaging method, MB is a frequently detected congenital anomaly. According to a meta-analysis, the prevalence in autopsy reports is 30-55%, evaluated with computed tomography: approximately 22% and with invasive coronary angiography: 5-8% (1). MB involves mainly (82%) the middle segment of the left anterior descending (LAD) with a mean length of 19-20 mm. If the myocardium is hypertrophic (e.g., due to hypertension or hypertrophic cardiomyopathy) the phenomenon might be more pronounced and described more often (2). The dispersion in prevalence is caused not only by the different modalities, but MB itself (and its clinical relevance) may vary in the same subject. For example, in elderly people -as hypertension evolves-, the myocardium becomes hypertrophic and degenerative changes may be more severely expressed, that might result in fibrotic replacement. Although these factors may lead to symptomatic MB as the compression forces increase during systole, overall MB has been considered a benign anomaly, which might remain hidden during lifetime.

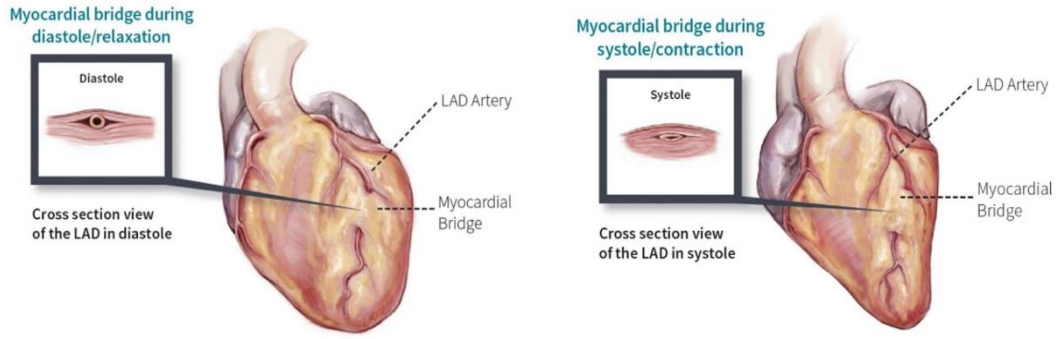

Figure 1. Schematic figure of a Myocardial Bridge on the left anterior descending (LAD) artery. When the heart is in diastole it allows blood to flow freely through, but when the heart is in systole the myocardial bridge overlying the LAD also contracts, trapping the artery by limiting blood flow Source: https://med.stanford.edu/ctsurgery/clinical-care/adult-cardiac-surgery-services/myocardial-bridge-unroofing.html.

1.2. Pathophysiology

MB is a unique non-atherosclerotic coronary lesion in two aspects. On the one hand it causes dynamic stenosis, compared to other forms like for example vasospasm which is a persistent narrowing of the vessel. Theoretically, most of the coronary flow occurs during systole. So, at rest, when the heart rate is low and there is sufficient time for the artery to fill (the diastole is long enough), the MB might not provoke symptoms. However, during physical effort or mental stress – when the heart rate increases and the diastolic filling time shortens - symptoms can occur. Its pathological relevance is more complex: beyond anatomic features like the MB's length, depth, the surrounding muscle thickness, also other factors could play a role, including concomitant vasospasm, the number of side branches that arise from "tunneled" part, the presence of atherosclerosis, or the micro- and macro-dissections which may occur in a twitching artery (3). Moreover, the compression of epicardial coronary artery might extend into diastolic phase, causing impairment of early diastolic myocardial perfusion, that would aggravate the supply-demand mismatch.

On the other hand, it is considerable that – according to several studies – the affected part is free from atherosclerosis, but the proximal segment from the bridge is

more exposed due to the sheer stress caused by turbulent blood flow (4,5). The prior issue is explained by the lack of epicardial adipose tissue and vasa vasorum here. These pathophysiological factors play an important role in the pathogenesis of coronary artery disease. The epicardial adipose tissue is a source of inflammation's mediators which affect paracrine and endocrine pathways. Proinflammatory nature of epicardial adipose tissue were observed irrespectively of plasma concentrations of circulating biomarkers (6,7). This mechanism is assisted by the lack of vasa vasorum, which forms the passage of inflammatory cells and cytokines from the perivascular adipose tissue. (8). All these factors might contribute to lessening atherosclerosis in bridged segment of coronary vessels.

1.3. Clinical relevance of Myocardial Bridge

The factors above act together with the given patient's clinical characteristics. The age, the concomitant diseases, left ventricular dimensions and function, the actual blood pressure might influence the manifestation of the symptoms (9). Our knowledge about the pathological and prognostic role of MB is still limited, however multiple case reports were published where MBs caused symptoms through myocardial ischemia. These ischemic events are thought to be the result of coronary spasm, thrombosis, coronary dissection, or the development of focal atherosclerosis immediately proximal to the MB. As a clinical consequence of the MB-related ischemia, stable angina pectoris and myocardial infarction, significant arrhythmias (both ventricular and supraventricular) or even sudden cardiac death may occur (10-14). However, in the most cases, symptomless MB has been revealed as a secondary, stochastic finding.

1.4. Diagnostic test of Myocardial Bridge

Although several invasive and non-invasive diagnostic tests are available for diagnosing MB, there is no gold standard test that evaluates every aspect of the bridge.

1.4.1. Non-invasive assessment

MB is most frequently described during coronary angiography or CT which has been performed due to chest pain. As we mentioned before the cardiac CT angiography is a more sensitive modality as the rate of detection of MB has been reported even up to

58%. The diagnostic accuracy of coronary CT angiography has been reported to be comparable with invasive intravascular ultrasound (IVUS) imaging. Although CCTA provides anatomic evidence of bridging it is unable to assess the functional significance of the bridged segments (15). That is why it is much more difficult to demonstrate the causality between the lesion and the symptoms. Ischemia provocation might help to reveal the role of revealed MB. The traditional ECG exercise test is even less sensitive than it is in atherosclerotic coronary artery disease. Proper physical stress or dobutamine stress echocardiography used the most commonly among the available non-invasive assessments to provoke ischemia in the MB related myocardial segments. Assessment of septal longitudinal strain during stress suggests decreased values compared to controls. This mid-septal ischemia might distinct between MB and fixed LAD stenosis (16). Myocardial perfusion imaging also might help to assess the hemodynamic significance of MB by the detection of perfusion defects. In a study 39 patients free from atherosclerotic lesion, with LAD-MB (previously evaluated with coronary angiography) were enrolled. Using myocardial perfusion imaging, 8 patients (20.5%) were found to have perfusion defects in the anterior wall. The difference in the mean systolic narrowing of bridging segments was statistically significant between patients with and without ischemia. However, there was no significant difference either between the mean length of the tunneled artery in patients with and without abnormal perfusion test. In conclusion the incidence of perfusion defects with MB depends on the morphological severity of MB (17). A new approach is the CT-FFR which is already validated – although it was a retrospective comparison -. by perfusion computer tomography. 75 patients (mean age: 62.7 years; 48 males) with LAD-MB and without concomitant obstructive stenosis were included. The change in CT-FFR across myocardial bridging (ΔCT-FFR, defined as the difference in CT-FFR values between the proximal and distal ends of the myocardial bridging) in different cardiac phases were measured to study myocardial bridging-related myocardial ischemia using CT myocardial perfusion imaging as the reference standard. ΔCT-FFR calculated in the systolic phase) was higher in patients with versus without myocardial bridging-related myocardial ischemia in contrast, ΔCT-FFR calculated in the diastolic phase did not differ significantly. ΔCT-FFR systolic had the highest sensitivity: 91.7% and negative predictive value: 97.8%. ΔCT-FFR diastolic had the highest specificity: 85.7% for the diagnosis of MB related ischemia. Myocardial bridging

showing positive CT-FFR results requires further evaluation. (18). CT-FFR has a high negative predictive value regarding ischemia provoked by LAD-MB, therefore the role to rule-out the hemodynamically significant MB is important.

1.4.2. Invasive assessment

In the last two decades we have been able to perform functional evaluations also in the catheterization laboratory, due to the fast development and spread of technology. These allow dissociation between clinically relevant and non-relevant MBs. The gold standard, classical method is coronary angiogram when we study selectively the anatomical features of concerned segments as the length, the diameter and the maximal thickening in end-systole (narrowing). Indeed, coronary angiography using multiple planes and using the view showing largest systolic narrowing is one of the simplest invasive methods for evaluation of bridging: bridged segment of coronary arteries has 71% to 83% reduction in mean luminal diameter. Although further clinical symptoms or functional assessment should be associated to interpret the results. The use of intracoronary nitroglycerin affects better visualization (19), but on the other hand it can provoke ischemia. The fractional flow reserve (FFR) measurement and the intravascular ultrasound (IVUS) are the most widely used modalities for anatomical and functional assessments. IVUS can be used to assess systolic compression (characteristic echo lucent "half-moon phenomenon") and it is also helpful to detect atherosclerotic plaque in segments proximal to bridge. Although this technique is not capable to gain functional information. During classical FFR measurement we confront the intracoronary pressure distal to the aorta of the lesion during maximal hyperemia (induction of vasodilation by using adenosine). In the case of MB, the generally accepted cutoff FFR value is 0.75 (Pd/Pa), below this value, the thickening should be kept hemodynamically significant. Hakeem and co-authors pointed out that FFR measurement with administering increasing dose of dobutamine could indicate more sensitively the significant lesion (20). This was called ("FFR paradox") which cannot be observed in fixed coronary stenoses. The phenomenon is explained by the positive inotropic effect of dobutamine in the fibers that cover the tunneled segment. Integrating the previous results in another study diastolic–FFR during dobutamine provocation was suggested even more accurate (21). A third workgroup as a synthesis compared the classical adenosine-induced FFR with diastolic-

FFR during dobutamine provocation (22). In their prospective study 60 symptomatic patients were involved where the systolic compression exceeded 50 per cent diameter stenosis at coronary angiogram. Each patient underwent stress echocardiography and both types of FFR measurements. Of 60 patients, 19 (32%) had a positive exercise test. The traditional FFR showed similar results also with adenosine and dobutamine, but diastolic-FFR revealed a lower threshold at peak dose of dobutamine (0.76±0.08 versus 0.79±0.08, P=0.018). Furthermore, diastolic-FFR in dobutamine effect showed a significantly lower result in those patients where the reference exercise test was positive compared with exercise test negative persons (0.70±0.07 versus 0.79±0.06, P<0.001). Among physiological indicators, diastolic-FFR was confirmed as an independent predictor of ischemia with $\leq$ 0.76 cutoff value. During angiography the mean diameter measured in systole was more severe, and the mean lumen diameter was smaller in the exercise positive group. Use of modern techniques (such as iFR) in functional evaluation of MB needs to be validated in further studies.

Diagnostic imaging modalities for MB are summarized in Table 1.

Table 1. Diagnostic imaging modalities for evaluation of Myocardial Bridging (MB). Source: Sternheim et al. 2021 (23).

Imaging Modality	Description	Diagnostic Criteria	Advantages	Disadvantages	Functional Information
Invasive techniques					
Coronary angiography	Selective catheterization of coronary arteries with contrast	Milking effect	-Frequently used anatomic assessment -Quantification of systolic compression	- Invasive - No physiological value	No
Intravascular ultrasound	Selective with insertion of a probe across the lesion of interest; 3D visualization	Half-moon sign	-Identifies proximal plaque -Quantification of compression, MLA -Identifies remodeling	- No physiological value -Underestimate the length of a bridge if rapid pullback	No
Optical coherence tomography	Insertion of a fiberoptic probe across the lesion	Fusiform, signal poor border with systolic compression	- Identifies plaques -Identifies neo atherosclerosis -Quantification of MB arc thickness	- High pullback velocity risk misidentifying MB edges - Not widely used	No
Intracoronary Doppler wire	Selective, insertion of a pressure wire across the lesion of interest	Fingertip sign	-Assessment of microvascular disease - Can simulate dynamic systolic obstruction - Endothelial function testing	-Pharmacotherapy required - Longer procedural time - No standardized cutoffs	Yes
Fractional flow reserve	Selective, insertion of a pressure wire across the lesion of interest	FFR $\leq$ 0.75	- Functional evaluation of dynamic lesions - Widely available	- Longer procedural time Pharmacotherapy required - Diastolic FFR not commonly accessible	Yes
Instantaneous free wave ratio	Selective, insertion of a wire across the lesion of interest	iFR $\leq$ 0.85	- Diastolic-specific index - Functional evaluation of both fixed and dynamic lesions - Adenosine not mandatory	- Longer procedural time	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.

Table 1. (continued) Diagnostic imaging modalities for evaluation of Myocardial Bridging (MB). Source: Sternheim et al. 2021 (23).

Imaging Modality	Description	Diagnostic Criteria	Advantages	Disadvantages	Functional Information
Noninvasive techniques					
Coronary 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 atherosclerosis. Sensitive	Over detection of minor MB may lead to unnecessary testing. Relation of symptom severity to depth of MB unclear	Yes
Computed tomographic fraction flow reserve	Contrast-enhanced CT with computational fluid dynamics to estimate stenosis	FFR <0.75 (Gray Zone 0.75-0.80)	Functional assessment of ischemia at rest	Tested only in patients with proximal MB. Requires contrast.	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. 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. Radioactive tracer injection	Yes
Stress transthoracic 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.

1.5. Therapeutic strategy

There are distinct therapeutic strategies for treatment of patients with symptomatic MB. As MB has basically been declared a prognostically benign anomaly, we must always keep in mind the principle “primum non nocere” regarding treatment. It is important to follow up regularly our patient with the revision of symptoms (especially angina pectoris). Concomitant conditions, like coronary artery disease, diabetes mellitus, hypertension, atrial fibrillation, myocardial hypertrophy can affect choice of treatment for these patients. Beta blockers are the first line choice of therapy, which have negative inotropic and negative chronotropic effects (prolongation of the diastolic perfusion). Indeed, beta-blocker therapy provided symptomatic relief in 89% of patients with hemodynamically significant MB (24). Other medications that can decrease heart rate could be an option too, such as non-dihydropyridine calcium channel blockers or ivabradine if beta-blockers are contraindicated or should be complemented. At first sight nitrates seem favorable with their vasodilator effect, however hemodynamic evaluations confirmed that nitrates will increase the percentage diameter stenosis of MB compared to proximal reference diameter (narrowing). More the early diastolic relaxation delays which lead to further ischemia. Except that the reflex tachycardia caused by nitrates could also provoke ischemia (19).

Coronary intervention looks like a good solution as intracoronary stent placement might provide stability against external compression. However, the first results of coronary interventions due to MBs often ended with severe complications such as stent thrombosis (25), coronary perforation (26) or early restenosis (27). Even so, coronary intervention may be attempted in selected cases with refractory angina pectoris (in patients whose are not surgical candidates). Our group published an interventional case with long-term success (28, see later in details).

The surgical approach may be myotomy or surgical revascularization (CABG). Competitive flow is a practical and theoretical consideration against CABG which brings forth early graft occlusion (graft failure). An interesting new technique has been developed, when the LIMA graft is led to the proximal and distal end of the MB. (29). According to the authors, this results in better hemodynamic outcome and longer graft patency. The computer simulation was followed by a successful operation. More data is

needed about this possibility. Myotomy (surgical unroofing) can be another option in case of persistent symptoms: performed through median sternotomy and can be done off-pump or with cardiopulmonary bypass. Detailed planning with CT and operator experience are mandatory for such a surgery to avoid possible complications (ventricular injury, vessel perforation, aneurysm formation, bleeding). There is no evidence of survival benefit after unroofing the MB, therefore it should be considered only for relief of angina symptoms (30).

1.6. Unresolved questions regarding Myocardial Bridge

Despite this data, the prognostic factors and the clinical evaluation of MB has remained limited. Key questions remain unresolved and wait for answers:

- How can we model dynamic obstruction? There is a lack of validated mechanical (in vitro) or animal (in vivo) models.
- Can myocardial bridge cause symptoms per se or only with other concomitant factors (triggers)?
- If MB is a congenital anomaly, why do patients develop symptoms typically after the age of 40?
- What is the role of MB in plaque burden and morphology in the coronary which is concerned by the anomaly?
- How can the benign and malignant type be differentiated morphologically and functionally?
- If once symptomatic, should it be treated medically or invasively?

Our group aimed to approach these questions. In the dissertation I present a retrospective, high-number population-based clinical study we aimed at describing the anatomical differences between symptomatic and non-symptomatic LAD myocardial bridges found on coronary angiography and to investigate the influence of clinical and bridge morphological factors on long-term mortality. I also present data from a case – control study driven by coronary CT angiography, where we evaluated the plaque morphology beneath the tunneled segment.

2. Objectives

2.1. Aims of our study

As it was described in the previous chapter, there are plenty of unanswered questions about MB. We had only sporadic case presentations which demonstrate LAD-MB as a non-atherosclerotic coronary lesion that can cause ischemia with its consequences.

First, we would investigate the relation of long-term outcome and coronary morphology in a numerous MB population. We looked for the characteristics of morphological factors detected by angiography, those may be associated with angina pectoris. We aimed to compare the life expectancy among patients with LAD-MB only and patients who had LAD-MB and significant atherosclerotic disease together. We also aimed to study whether these morphological factors influence long-term mortality.

Secondly, in a retrospective case control study we investigated the plaque morphology beneath the myocardial bridge by CT angiography.

Finally, we aimed to present an own case where LAD-MB led to ischemia, myocardial infarction and ventricular septal rupture (Case I.).

In another case report, we show in a case where the treatment choice of a symptomatic, therapy refractory LAD-MB was revascularization, percutaneous coronary intervention (Case II). This case refers as an example that the mode of revascularization may result in a long-term success in the treatment of significant MBs.

3. Methods

3.1. Invasive, morphological study

For our retrospective study we investigated a large number patient population in our primary cardiac center. A total of 11,385 diagnostic coronary angiographies were performed. Indications were defined according to the current European guidelines: high risk patients for coronary artery disease based on pretest probability and patients with Acute coronary syndrome were also evaluated.in our cardiology center, at the Heart and Vascular Center of the Semmelweis University of Budapest between 25 March 2009 and 12 March 2011. Ethical approval (of enrolled patients) was obtained from the Central Ethics Committee of Hungary, with all the participants completing informed consent forms, which were in conformity with the WMA Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects.

We enrolled a total of 203 patients (1.78%) with a clear presence of MBs (defined as a clearly visible alteration of vessel caliber between systole and diastole, recognized by the investigator). To obtain a more consistent study group, we excluded patients with MBs affecting arteries other than the LAD and where any other obvious cause of angina pectoris was presented (n = 57), see Figure 2. The remaining patients (n = 146) were divided into two groups according to accompanying coronary artery disease. Seventy-eight patients were referred for angiography because of typical angina pectoris, and, except for LAD-MB, no other underlying, epicardial coronary disease was found (LAD-MBneg group). Sixty-eight patients were also referred for angiography because of angina pectoris, but in this group significant coronary artery disease was also revealed in addition to the LAD MB (LAD-MBpos group). In the LAD-MBpos group coronary plaque was considered significant if lumen narrowing (>50% in diameter) of significant epicardial coronary arteries (>1.5 mm diameter) was observed, and we provided therapy according to current guidelines. Ad-hoc percutaneous coronary intervention was performed in 23 (34%) of these patients, with indications according to current guidelines. For a better understanding, the design of the study and the selection of the patients are shown in Figure 2.

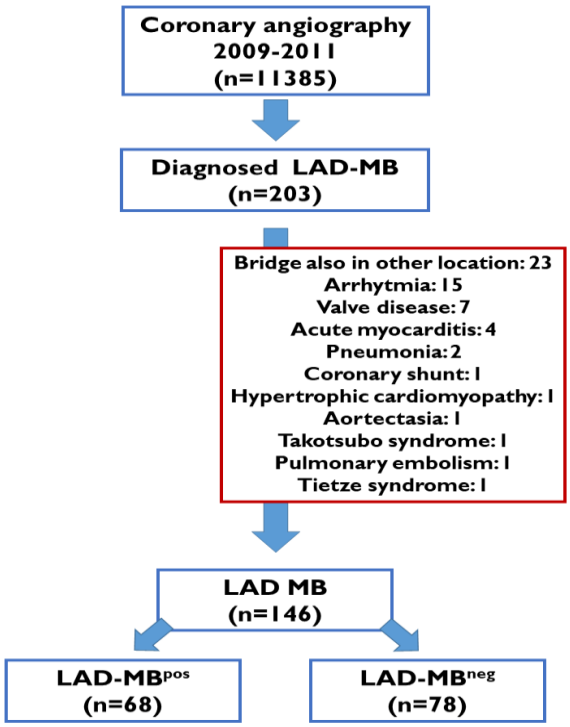

Figure 2. The design of the study and the selection of patients. LAD-MB: Myocardial bridge of left anterior descending coronary artery; LAD-MBpos: Left anterior descending myocardial bridge with another significant atherosclerotic coronary lesion group; LAD-MBneg: Left anterior descending myocardial bridge. Source: Bárczi G et al. 2022 (47).

Quantitative angiography was performed according to our standard clinical practice. Vessels and lesions were analyzed using a computerized quantification system (Innova 2100, General Electric Medical Systems, Milwaukee, WI, USA). Measurements were obtained with digital calipers. All the MBs were measured in lateral view (angulation of the "C" arm left lateral, LAO: 90 degrees, caudal: 0 degrees) in end-systole and end-diastole by an expert interventionist (Figure 3.). Four main parameters were measured:

(1) length of the MB, defined as the distance from the most proximal point to the most distal point of the LAD, where the systolic narrowing phenomenon could be observed.

(2) reference diameter of the MB, defined as the diameter of the vessel immediately proximal to the point where the systolic narrowing started; and

(3) minimal diameter of the MB, measured also in end-systole at the point where the thickening was the most prominent. Additionally, from these parameters we calculated.

(4) minimal diameter to reference diameter, the ratio between minimal stenosis and reference diameter in percentage to characterize shortening of bridge for each patient.

In addition to these data, we also recorded height, weight, sex of patients and presence of main cardiovascular risk factors, such as diabetes mellitus, hypertension, and dyslipidemia. We collected information about the patients' mortality by phone visit and we also checked data on survival status (according to the Hungarian National Database) in 1. April 2020.

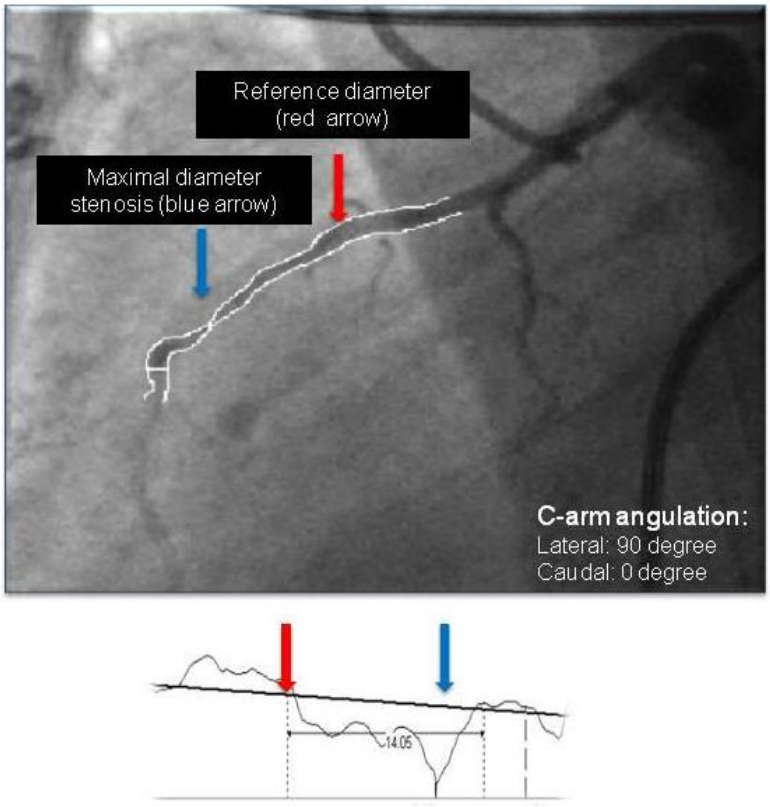

Figure 3. Representative image of a measurement process in lateral view (end-systole) by quantitative coronary angiography (QCA). Bárczi G et al. 2022 (47).

3.2. Non-invasive CCTA Study

In another patient group we quantified plaque volumes proximal to the MB and beneath it in patients with MB and in the equivalent coronary segments in patients without MB. We searched for patients' data who underwent coronary CCTA due to suspected coronary artery disease in our cardiovascular center (Semmelweis University Heart and Vascular Center) between April of 2016 and May of 2017 May. We selected patient records with LAD-MB where image quality was sufficient for further evaluations. Patients with established cardiac disease as history of acute myocardial infarction, coronary intervention, coronary artery bypass surgery, heart transplantation or stroke were not selected. The control group also had an excellent image quality of coronary CTA but without LAD-MB. The controls were matched for the variables listed below: age (±10% range), gender, body mass index (±10% range) and the presence of typical cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidaemia, smoking) and for scan parameters.

In our center we used a 256-slice multidetector row computed tomography (CT) scanner (Brilliance iCT 256; Philips Healthcare, Best, the Netherlands). We analyzed coronary CTA scans using a semi-automated plaque quantification software (Angiocath Research Edition, version 3.1.0.1, Medis Medical Imaging Systems, Leiden, The Netherlands) After the manual tracing of the vessel centerline, the software reconstructed the straight multiplanar view of the segmented vessel. For the control patients, we extracted two corresponding segments with equal length as their matched pairs' segments. The software calculated the total plaque volume and the plaque composition according to predefined density ranges based on Hounsfield unit (HU) categories: −100 to 30 HU necrotic (low attenuation non-calcified) core, 31 to 130 HU fibrofatty (mid attenuation noncalcified) plaque, 131 to 350 HU fibrous (high attenuation noncalcified) plaque, and > 350 HU calcified plaque component were identified. We separately analyzed the entire segment and a ~ 20-mm-long subsegment immediately proximal to MB.

3.3. Statistics

2020. Statistics GraphPad Prism (version 6, GraphPad Software, San Diego, CA, USA) and SPSS (version 22, SPSS Inc., Chicago, IL, USA) were used for the statistical analysis.

In the invasive study we compared the LAD-MBneg and LAD-MBpos groups directly. In the case of normal distribution of continuous data, the unpaired t-test was used. In the case of non-normal distribution, the Mann–Whitney U-test was utilized. To compare parameters with binomial outcomes (sex, hypertension, hyperlipidemia and diabetes mellitus), the Chi-square test was performed. Mortality rate was summarized by constructing Kaplan–Meier curves, and the distributions of the groups were compared by a log-rank test. For this analysis, median values were used to dichotomize continuous variables (MB length, reference diameter, minimal diameter and minimal diameter to reference diameter). Single variable Cox regression analysis was used for the search of predictors of death from the data of the patients (age, sex, BMI, hypertension, hyperlipidemia and diabetes mellitus). All variables associated with a p value <0.15 by single variable analysis were entered into the multiple variable Cox regression analysis with the parameters of myocardial bridge (MB length, reference diameter, minimal diameter and minimal diameter to reference diameter). Hazard ratio was given with 95% CI interval and p value was provided for the significance of different parameters on clinical outcomes. Continuous data are expressed as means with standard deviation.

In the non-invasive, CCTA study we compared the “Patients with myocardial bridge” and “Patients without myocardial bridge” groups directly. In the case of normal distribution of continuous data, the unpaired t-test was used. In the case of non-normal distribution, the Mann–Whitney U-test was utilized. Data were expressed by providing interquartile range (IQR).

A p value <0.05 was considered significant for all tests.

4. **Results.**

4.1. Results of the invasive, morphological study

Demographic and clinical data and LAD-MB morphological data are summarized in Table 2. The total number of analyzed patients was 146, and 64% were male with no differences of sex ratio between LAD-MBpos and LAD-MBneg groups regarding sex. LAD-MBpos patients were characterized by older age, increased presence of type 2 diabetes mellitus, while there was no statistical difference between the presence of hypertension or hyperlipidemia and BMI.

MB morphological data is also presented in Table 2. According to our results, LAD-MBneg group was characterized with more severe morphological features. The shortening of MB (minimal diameter to reference diameter) significantly decreased, while the length and reference diameter showed a strong tendency towards decreased value in the LAD-MBneg group compared to LAD-MBpos group. The minimal diameter showed no differences between our groups.

Table 2. The distribution of the data of patients presenting with angina pectoris and with a myocardial bridge detected in the left anterior descendent artery (n = 146) and comparison of LAD-MB neg and LAD-MB pos population. Data is shown as mean (SD). LAD-MB: Left anterior descendent myocardial bridge; LAD-MB pos: Left anterior descendent myocardial bridge with other significant atherosclerotic coronary lesion; LAD-MB neg: Left anterior descendent myocardial bridge without another significant atherosclerotic coronary lesion. Bárczi G et al. 2022 (47)

	Overall population n = 146	**LAD-MB^{neg} n = 78**	**LAD-MB^{pos} n = 68**	**LAD-MB^{neg} vs. LAD-MB^{pos}**
Mean age (years)	**60.6 (12.7)**	**57.6 (12.4)**	**64.5 (11.5(**	***0.001***
Male sex	**94 (64%)**	**50 (64%)**	**43 (64%)**	**0.99**
Hypertension	**105 (72%)**	**57 (73%)**	**48 (72%)**	**0.87**
Type 2 diabetes mellitus	**36 (25%)**	**13 (17%)**	**24 (36%)**	***0.008***
Hyperlipidemia	**77 (53%)**	**37 (47%)**	**40 (60%)**	**0.14**
Body mass index (kg/m^2)	**27.6 (3.8)**	**27.2 (3.4)**	**28.2 (4.3)**	**0.11**
LAD-MB length (mm)	**21.4 (8.2)**	**23.4 (8.3)**	**20.0 (7.7)**	***0.05***
Reference diameter (mm)	**2.18 (0.46)**	**2.23 (0.42)**	**2.09 (0.41)**	**0.06**
Minimal diameter (mm)	**1.10 (0.41)**	**1.02 (0.36)**	**1.11 (0.38)**	**0.39**
Minimal diameter to reference diameter (%)	**49.5 (15.5)**	**54.5 (13.1)**	**46.5 (16.4)**	***0.006***

Long term follow-up: the average follow-up period of this patient population was 3115±249 days, almost ten years. When we checked survival status, we found that mortality was 16.4% in the overall population. Eight persons died in the LAD-MBneg group; thus, the all-cause mortality rate in this population was 10.3% for this follow-up period. We searched for differences between the two prespecified subgroups: the Kaplan-Meier analysis revealed significant disparity in mortality between LAD-MBneg and LAD-MBpos groups (Figure 5.).

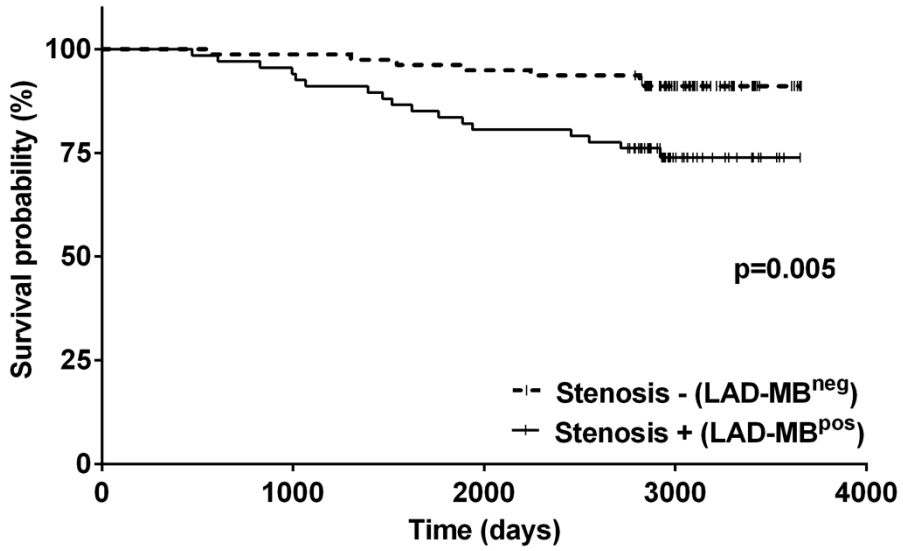

Figure 4. Kaplan–Meier curve of the long-term follow-up comparing LAD-MBpos (left anterior descendent myocardial bridge with another significant atherosclerotic coronary lesion) and LAD-MBneg (left anterior descendent myocardial bridge without another significant atherosclerotic coronary lesion) group. The LAD-MBpos group was associated with higher mortality. Bárczi G et al. 2022 (47).

We also searched for factors that could influence long-term mortality both in overall population and LAD-MBneg group. As a first step, we determined factors from the demographic and clinical data using single variable Cox regression. In the overall population the presence of coronary stenosis, diabetes mellitus and older age were associated with increased mortality, while in the LAD-MBneg group only age influenced survival outcome. To determine the role of morphological parameters, a multiple variable Cox regression was performed with the morphological parameters (MB length, reference

diameter, minimal diameter, minimal diameter to reference diameter) and influencing factors from single variable analysis. Our results show that none of the morphological parameters influence long-term mortality (Table 3).

Table 3. Summary of univariate and multivariate Cox regression analysis of overall survival in overall population and LAD-MBneg group. LAD-MB: Left anterior descendent myocardial bridge; LAD-MB^{neg}: Left anterior descendent myocardial bridge without another significant atherosclerotic coronary lesion group. HR: hazard ratio. Bárczi G et al. 2022 (47).

	Overall population n = 146		**LAD-MB^{neg} n = 78**	
	Single variable analysis	**Multiple variable analysis**	**Single variable analysis**	**Multiple variable analysis**
Stenosis	**0.005 HR:3.45**	**0.11 HR:2.14**	**NA**	**NA**
Mean age (years)	**< 0.001 HR:1.08**	**0.001 HR:1.08**	**0.03 HR:1.07**	***0.03*** **HR:1.09**
Male sex	**0.77 HR:0.89**	**NA**	**0.42 HR: 0.56**	**NA**
Hypertension	**0.62 HR:1.26**	**NA**	**0.93 HR:1.07**	**NA**
Type 2 diabetes mellitus	**0.06 HR:2.14**	**0.251 HR:1.62**	**0.73 HR:0.69**	**NA**
Hyperlipidemia	**0.36 HR:0.69**	**NA**	**0.55 HR:0.64**	**NA**
BMI (kg/m^2)	**0.86 HR:1.01**	**NA**	**0.95 HR:1.01**	**NA**
LAD-MB length (mm)	**NA**	**0.83 HR:1.01**	**NA**	**0.15 HR:1.07**
Reference diameter (mm)	**NA**	**0.48 HR:2.73**	**NA**	**0.51 HR:6.30**
Minimal stenosis (mm)	**NA**	**0.77 HR:0.45**	**NA**	**0.50 HR:0.02**
Minimal stenosis to reference diameter (%)	**NA**	**0.70 HR:0.98**	**NA**	**0.59 HR:0.94**

This result was also confirmed by Kaplan-Meier analysis, when median values were used to dichotomize variables of MB morphology: more severe morphological characteristics were not associated with increased mortality (Figure 6.).

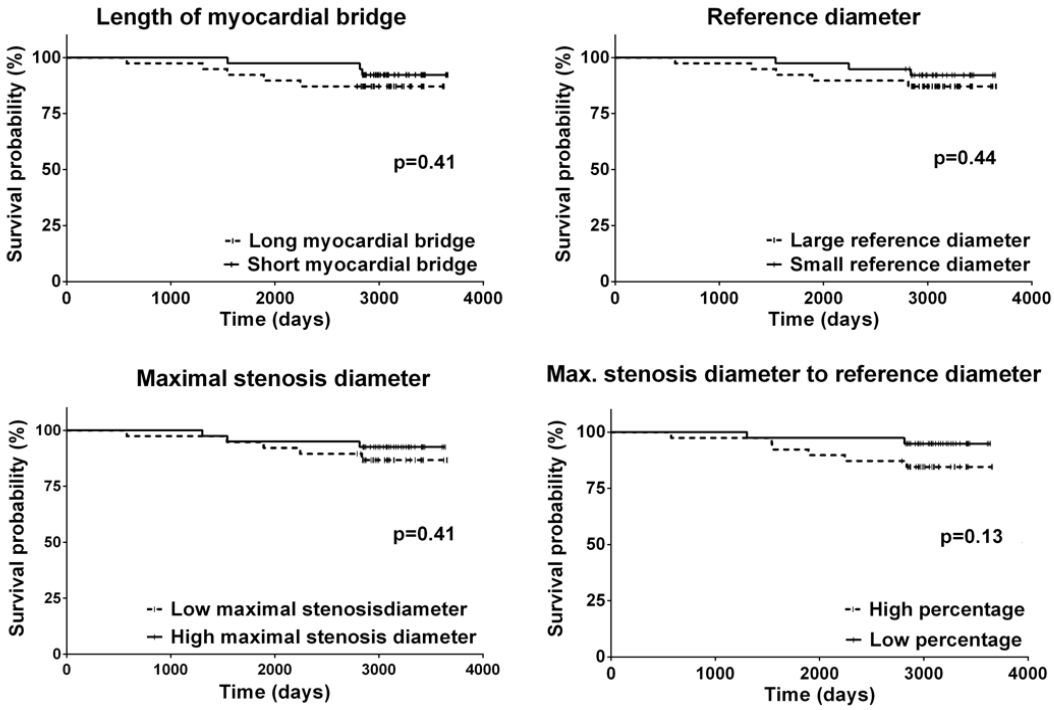

Figure 5. Kaplan–Meier curve of the long-term follow-up comparing morphological features of the myocardial bridge in LAD-MBneg (left anterior descendent myocardial bridge without another significant atherosclerotic coronary lesion) group. For this analysis, median values were used to dichotomize continuous variables. None of the morphological characteristics influenced the mortality rate. Bárczi G et al. 2022 (47).

4.2. Results of the non-invasive, CCTA study

There were not significant differences regarding different plaque components in segments proximal to the MB. Fatty plaque and necrotic core volumes were smaller or negligible in coronary segment beneath MB than in controls (0.07 mm3 [IQR: 0.005-0.27 mm3] vs. 12.7 mm3 [IQR: 7.4-24.4 mm3]) and 0.00mm3 [IQR: 0.00-0.04 mm3] vs. 0.06 mm3 [IQR: 0.03-2.8 mm3], respectively ($p<0.001$). (Table 4.)

Table 4. Plaque characteristics of left anterior descending coronary artery segments beneath myocardial bridge in cases and those of corresponding coronary segments in controls (median values with interquartile range [IQR]). Papp S, et al. 2021 (4).

	Patients with Myocardial bridge n = 50		**Patients without Myocardial bridge (controls) n = 50**		**p**
	Median	**IQR**	**Median**	**IQR**	
Segment length (mm)	**19.6**	**14.1-24.7**	**19.4**	**14.0-24.3**	**0.95**
Vessel volume (mm^3)	**110.9**	**61.5-154.6**	**146.4**	**114.3-203.7**	***<0.001***
Lumen volume (mm^3)	**93.3**	**48.8-128.9**	**112.62**	**94.5-160.2**	***0.002***
Total plaque volume (mm^3)	**16.2**	**12.6-25.8**	**21.1**	**14.0-42.4**	***0.03***
Necrotic core volume (mm^3)	**0.00**	**0.00-0.04**	**0.06**	**0.03-2.8**	***<0.001***
Fatty plaque volume (mm^3)	**0.07**	**0.007-0.27**	**12.7**	**7.4-24.4**	***<0.001***
Fibrosus plaque volume (mm^3)	**12.8**	**5.4-18.3**	**14.3**	**10.0-26.5**	**0.07**
Calcified plaque volume (mm^3)	**1.1**	**0.4-3.2**	**1.1**	**0.2-2.9**	**0.82**

4.3. Case I. Ventricular septal rupture caused by Myocardial bridge, solved by interventional closure device.

An 88-year-old female patient was admitted due to chest pain which lasted for 20 hours. Her ECG showed a presumably new left bundle branch block. In her previous medical history, we revealed gastro-esophageal reflux disease with hiatus hernia, duodenal ulcer, bronchial asthma, mammary fibroadenoma, vertebrobasilar syndrome, cervical and lumbar spondylosis, fibromyalgia, osteoporosis and psychiatric disorders such as dysthymia. In her young age she was a successful fencer. Coronary artery stenosis was ruled out with immediate coronarography and a myocardial bridge 19.1 mm in length was described on the mid third of the left anterior descending coronary artery. The bridge's minimum systolic lumen diameter was 0.91 mm, and the maximum systolic lumen reduction compare with the diastolic diameter was 82.8%. Due to the lack of fixed atherosclerotic stenosis as a possible target of stent implantation, an intervention was not performed. Laboratory results revealed positive cardiac necro enzymes with the highest creatine kinase-MB being 77 U/L. Echocardiography showed a 22×15 mm aneurysm on the distal third of the anterior septum, in which 8-mm wide VSR jet was detected (with a peak gradient: 100 mm Hg). A few pericardial fluids were described as well. The positive biomarkers and the detected signs led to the diagnosis of a myocardial infarction. The left ventricular systolic function was maintained with an ejection fraction: 60 per cent. To clarify the relation between the infarction and the lesion we carried out MRI, which demonstrated colocalization of the late contrast enhancement and the VSR (Figure 4.). A dilated right ventricle and the preserved left ventricular systolic function were also confirmed.

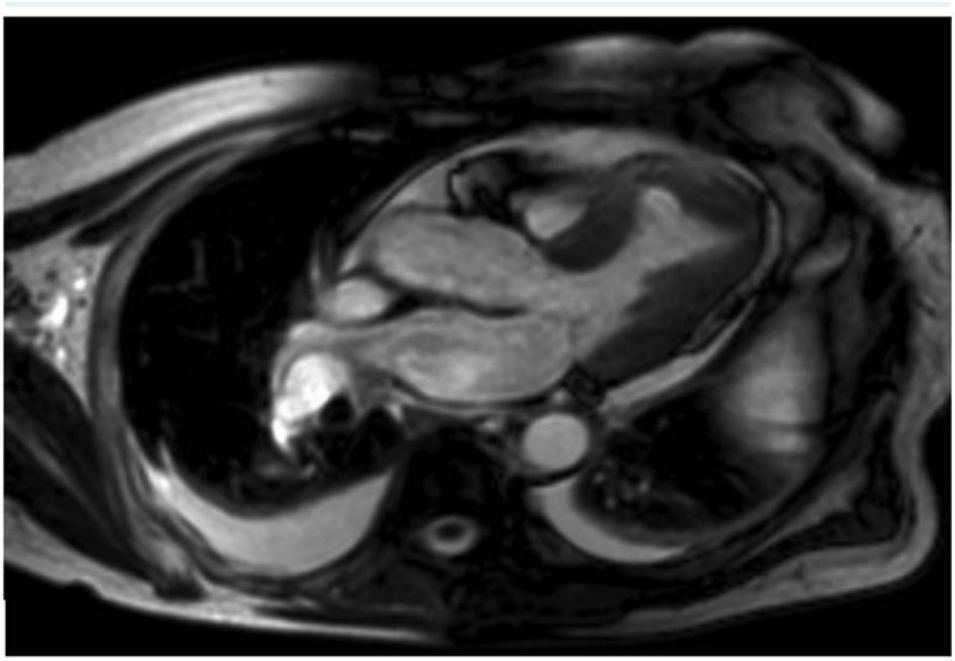

Figure 6. The aneurysm containing the rupture can be seen on the distal septum (MR) Zóka A, et al. 2012 (12).

Taking into consideration the discrepancy between the right and the left ventricular cardiac output Qp/Qs:1.75, we decided to close the rupture. As open-heart surgery was contraindicated because of the woman's age and concomitant diseases, a transcatheter closure approach was decided upon. The left ventricular angiography was carried out from right femoral artery approach. A Terumo guidewire (Terumo Europe N.V, Leuven, Belgium) was driven through the ventricular septal defect into the right ventricle, right atrium, and vena cava superior. An arteriovenous loop was formed with a Multisnare (pfm medical ag, Köln, Germany) catheter and 9F sheath was inserted from the right jugular vein through the defect. Through the sheath the defect was closed with a 12 mm AMPLATZER® (AGA Medical Corporation, North Plymouth, MN, USA) muscular ventricular septal defect occluder. Despite the right ventricular disc misalignment, the position of the device was stable. The intervention was successful and after the procedure only minimal residual blood flow was detected through the device. Echocardiography also excluded any mechanical complications. The patient was discharged with regular medical therapy. For one year follow-up did not occur any adverse event.

4.4. Case II. Fractional flow reserve guided stenting of a Myocardial bridge.

A 52-year-old man was admitted with chest pain provoked by emotional stress. Laboratory tests and transthoracic echocardiography were within normal range. An exercise treadmill test was indicated according to Bruce protocol that demonstrated ischemia, significant ST segment depressions on ECG at 125 Watts workload. As the first, therapeutical step, beta-blocker was up titrated (bisoprolol from 2.5 to 10 mg daily). Despite the medical therapy, the patient remained symptomatic. Coronary angiography showed MB in the mid left anterior descending artery with lumen compression (minimal lumen diameter: 0.26 mm, reference vessel diameter: 2.6 mm, and lesion length: 25.4 mm). Atherosclerotic lesions were not detected. FFR measurement proved relevant myocardial ischemia (Pd/Pa=0.69). After FFR measurement, the lesion was stented with a 3.0×38 mm paclitaxel eluting stent (Promus Premier, Boston Sci, US) at 14 atm. Control angiography showed good results, and final FFR (Pd/Pa=0.96) verified improved hemodynamics. Following the intervention the patient remained asymptomatic and at the 18-months control multislice CT angiography excluded the restenosis or any other procedure-related complications.

5. Discussion

In this thesis we would characterize long-term outcome of MB in a relatively large, single-center population and provide unique cases, where MB was associated with different clinical features.

Above we also provided a retrospective, single-center study using long-term follow-up, with a moderate number of patients, to investigate anatomical symptomatic LAD myocardial bridges and to determine the role of clinical, demographic and morphological features in the long-term survival of the patients with relevant LAD-MB. Although myocardial bridging has been intensively investigated since it was recognized by autopsy and coronary angiography, the exact potential effect on cardiovascular mortality is still unknown. Coronary angiography remained the gold standard for detecting MB; however, it has recently been more frequently revealed by MDCT (3.5–58%) than by angiography (0.4–15.8%) (32-34). Angiography detects bridging at rates from 0.5% to 12%, most frequently localized on the middle segment of the LAD artery. The prevalence of LAD-MBs (1–2%) in our population was similar compared to the findings in other large-volume centers, detected by routine coronary angiography (Figure 2.) (1). The morphological parameters of these bridges, measured by quantitative coronary analysis (both the length and reference diameter values), are also comparable with the data from literature (Table 2.) (1, 35,36). We utilized QCA, that gave us the opportunity to measure simple parameters describing the LAD bridge and might be utilized routinely and promptly during invasive measurements (Figure 3.). There are more sophisticated invasive methods to characterize a bridge in detail; however, they need temporal and material sacrifice. Invasive imaging and functional assessment of the severity of MBs is possible with angiography, IVUS, OCT and FFR measurement (37-39). IVUS demonstrated characteristic systolic compression of the bridge segments (the so-called half-moon phenomenon) (40). Recently, there have been some reports of the usefulness of OCT in the evaluation of the internal coronary artery wall of myocardial bridges and MBs investigated by OCT, and they were found to be longer, but the diameter stenosis was lower than with angiography-based measurements (38)**.** The use of FFR is controversial because MB is a dynamic stenosis, and FFR has not been validated in MB; however, some reports exist of FFR-guided coronary intervention in MB (39). Clinical adjudication of myocardial bridges is often difficult. On the one hand, there is an essential

discrepancy between the high prevalence of the phenomenon accompanied with excellent prognosis (which was also observed in this study) and between the numerous case reports describing serious clinical significance to tunneled arteries, mostly without detailed anatomical descriptions of these MBs. On the other hand, the proof of functional significance–linkage with clinical symptoms–is challenging with either invasive or non-invasive tests. Large, controlled clinical trials are very limited in this field mainly because of the suspected benign nature of this unique coronary anomaly, moreover the model of MB has not been successfully established in experimental models either. It would be essential to clarify which tunneled arteries are potentially symptomatic and which are potentially life-threatening, and this might even cause sudden cardiac death.

We divided our population with angina pectoris, where obstructive coronary disease (>50% coronary stenosis) was also present, to examine whether in this population–where myocardial bridge might be only an accidental finding–there are different clinical factors and bridge features compared to patients with isolated LAD-MB (Table 2). The cut-off of 50% diameter stenosis on epicardial vessels for defining obstructive CAD is based on studies on what degree of stenosis is flow limiting and may cause ischemia under stress (41). It is not surprising that the LAD-MBpos patients were older and could be characterized by an increased prevalence of type 2 diabetes mellitus and were associated with higher mortality compared to the LAD-MBneg group (Figure 4)**.** From another view, age and diabetes mellitus were the only risk factors that showed significant differences in the prevalence between the two groups. The high prevalence of hypertension (Table 2) despite much younger patients in the LAD-MBneg group–suggests that elevated arterial pressure might play an important role in the development of symptoms in the case of LAD bridge, which was not observed in previous studies (42). Indeed, hypertension-induced cardiac hypertrophy might worsen the symptoms in patients with coronary myocardial bridge. Symptomatic, isolated LAD bridges were associated with more severe lumen narrowing, longer bridge segments and increased reference diameter (Table 2). The first-line treatment for symptomatic MB is medical therapy by providing beta and calcium channel blockers, which was provided to our patients (3). The placement of metal stents in MB might be associated with stent fracture and edge restenosis; therefore, it should only be considered in patients with bridging

refractory to medical therapy (28). Except the provided case report, there was no need to implant stent in such quite large number of LAD-MB population.

Isolated myocardial bridging is generally considered to be a benign condition. Besides appealing, unique clinical cases (10-14), studies with long-term follow-up suggest that bridging might be associated with negative clinical outcomes, such as myocardial infarctions and arrhythmias (43). Long bridges were associated with these complications. The 10.2% 10-year mortality in the LAD-MBneg group is comparable with 1.1% average yearly mortality in 45–59 years old men and women in Hungary (WHO statistics, 2014). Therefore, we investigated in the LAD-MBneg group whether the anatomical parameters measured by QCA might influence long-term mortality (Figure 5). We found that patients in the isolated myocardial bridging group were associated with low mortality and none of the anatomical factors or morphological severity influenced long-term (a follow-up of approximately 10 years) mortality **(**Figure 5, Table 3). Our data also suggest that more severe bridge anatomical characteristics are not associated with worse long-term outcomes, suggesting the benign nature of myocardial bridges independently from the severity of anatomical features.

The main limitations of the study were the retrospective design of the study and the lack of non-invasive assessment of MB anatomy with MDCT and invasive imaging techniques, such as IVUS or OCT. Although these measurements, which are not routinely used, would be more precise to describe bridge morphology, they require more financial and medical effort and are associated with increased radiation time. We also emphasize that no healthy control group was investigated to compare mortality directly to these individuals.

In the other retrospective study, where CCTA was used to investigate , we proved that there are significant differences between cases and controls regarding total plaque volumes and compositions in the corresponding coronary segments (Table 4.). These data suggest a protective mechanism of plaque formation in tunneled segment of LAD that may be the consequence of altered pressure and flow due to the bridge. It has been already described that epicardial adipose tissue may play a role in the plaque formation of epicardial coronary arteries (44, 45). Indeed, a few studies documented that epicardial adipose compartment should be considered as a source of inflammatory mediators that might influence coronary arteries via paracrine and endocrine routes (7). The involved

coronary segment beneath MB is tunneled by the surrounding myocardium and adipose tissue might be absent and therefore, no local deleterious atherogenic effect from local adipose tissue might be expected (46). In our study we found a reduced plaque volume with a more favorable plaque composition beneath LAD-MB corroborating former observations about the protective role of MB in the development of coronary plaques.

In our first case (Case I.) a clear pathological or pathophysiological condition underlying the myocardial infarction and the ventricular rupture was not established. We found no visible atherosclerotic plaques and no vasospasm was noted during coronary angiography. Some data suggest proximal clot formation as a mechanism for bridge obstruction, even postulating its transient repetition followed by spontaneous lysis (12). Nevertheless, in this case the diagnostic procedures showed only myocardial bridge anatomy and aneurysm containing the rupture. We also considered the possibility of this VSR being a congenital defect. However, there are a few arguments against this theory:

- A long lasting 1.75 times higher right ventricular cardiac output would have caused visible ventricular hypertrophy, which was not found.
- Although the distal septal area is a possible localization for a congenital defect, this wall segment showed characteristics typical of ischemia: hypokinesis, normal thickness, and delayed contrast hyperenhancement.
- A congenital jet normally crosses the wall perpendicularly, while in our case it crosses the wall diagonally.
- It is well known that small congenital defects affecting the muscular septum tend to close spontaneously until the age of seven, but the one presented in our study remained open despite its small size (31).

These arguments, the lack of significant fixed stenosis or any other visible coronary anomaly, the localization of the infarction, and the normal left ventricular ejection fraction led us to the conclusion that the myocardial bridge played a significant role in the patient’s ventricular septal rupture. However, it is still unclear why this bridge did not cause any disruption before the patient's advanced age. Indeed, according to our knowledge, angina associated with MB might be more pronounced by age, which can be explained to the age-related remodeling of the heart.

In case II. drug eluting stent implantation with a longer stent than the visible bridge was safe and effective in this patient during the follow-up period. PCI seems a reasonable treatment in symptomatic MBs; however, patient selection and procedural aspects remain unclear in the absence of comparative clinical trials. Angina pectoris-like symptoms could be caused by several reasons beyond atherosclerotic coronary disease. To hold the MB responsible for the symptoms, its pathological role must be proved. In a recent publication by Hakkem (20), the FFR measurement was done with dobutamine provocation in the symptomatic bridge. The most severe hemodynamic alteration was found in diastolic FFR; therefore, the authors suggested using this value in the MB patients. Dynamic compression caused by the MB is unique and this kind of coronary lesion differs from other atherosclerotic lesions. The high incidence of procedural failures like stent thrombosis (25), coronary perforation (26), and early restenosis (27) suggest that the stents' mechanical properties, diameter, and length are the determining factors for a successful intervention. High inflation pressures may be required for optimal stent implantation despite the higher risk of coronary perforation. Basically, the stent recoil means the percentage by which the diameter of a stent decreases from its expanded diameter (when the balloon is inflated at nominal pressure) to its relaxed diameter (when the balloon is retrieved from the stent). We must calculate with a dynamic stress component as well, which is caused by the myocardium mass above the lesion. The given device's resistance to this permanent, cyclic force can make a difference between various stent types. On the contrary e.g., the push ability seems to be a less important feature when preparing for stenting a MB on the mid segment of the LAD.

We have started further prospective research to study the correlation between morphology detected by angiography and functionality (FFR) and myocardial fibrosis. Also, an important topic is the coronary stent's different property against dynamic compression.

6. Conclusions

In this dissertation first, we provided a retrospective, single-center study using long-term follow-up. We looked for the characteristics of morphological factors measured by angiography that may provoke angina pectoris. We proved that the isolated, symptomatic bridges are longer, and the systolic caliber indecision is more prominent. Morphological parameters of angina-associated, isolated LAD bridges were more severe compared to bridges that were accidentally found in patients with obstructive coronary disease. Our ten-year long follow-up period showed that morphological parameters measured with QCA did not influence long-term mortality outcomes; therefore, it suggests that anatomical differences might not predict long-term outcomes. Our data underline the benign nature of myocardial bridge.

In another patient group we quantified plaque volumes proximal to the MB and beneath it in patients with MB and in the equivalent coronary segments in patients without MB. This case control, retrospective study was driven by CCTA.

Thirdly, we presented two cases where LAD-MB, a non-atherosclerotic coronary lesion, led to ischemia, myocardial infarction and ventricular septal rupture. The mechanical complication of the myocardial infarction was successfully treated invasively with a closure device. In another case report, we show a patient, in whom the treatment decision of a symptomatic LAD-MB was revascularization, percutaneous coronary intervention. This case demonstrated that even this choice could be successful and may result in long-term event free survival. Here we pointed out the importance of the stent structure and the mode of deployment.

The main conclusions of the dissertation:

- Isolated, symptomatic LAD-MB (associated with angina pectoris) are longer, with a more expressed systolic caliber variation. Those patients who have significant arteriosclerosis besides MB have a worse prognosis.
- The morphological features of LAD-MB do not influence long-term (10 years) survival. This result and the all-over mortality of LAD-MBneg group suggest benign nature of isolated LAD-MB.
- Fatty plaque and necrotic core volumes were smaller or negligible in coronary segment beneath LAD-MB compared to controls. This finding suggest that MB might hold a protective role against plaque rupture.

- LAD-MB can cause significant ischemia, that can lead to myocardial infarction and its mechanical complications (Case I.).
- Percutaneous coronary intervention and stent implantation might be an option in medical therapy refractory cases of LAD-MB (Case II).

7. Summary

Although myocardial bridging (MB) has been intensively investigated using different methods, the effect of bridge morphology on long-term outcome is still doubtful. We aimed at describing the anatomical differences in coronary angiography between symptomatic and non-symptomatic left anterior descendent (LAD) myocardial bridges and to investigate the influence of clinical and morphological factors on long-term mortality. In our retrospective, long-term, single center study we found relevant MB on the LAD coronary artery in 146 cases during a two-year period, when 11,385 patients underwent coronary angiography due to angina pectoris. Patients were divided into two groups: those with myocardial bridge only (LAD-MBneg) and those with associated obstructive coronary artery disease (LAD-MBpos). Clinical factors, morphology of bridge by quantitative coronary analysis and ten-year long mortality data were collected. The LAD-MBneg group was associated with younger age and decreased incidence of diabetes mellitus, as well as with increased minimal diameter to reference diameter ratio, while there was a tendency towards longer lesions and higher vessel diameter values compared to the LAD-MBpos group. The LAD-MBpos group was associated with increased mortality compared to the LAD-MBneg group. The analysis of our data showed that morphological parameters of LAD bridge did not influence long-term survival, either in the overall population or in the LAD-MBneg patients. Therefore, morphological parameters of the LAD bridge might not influence long-term mortality outcomes.

In another case control, retrospective study by coronary computed tomography angiography, we proved that there are significant differences between MB coronary segments and matched controls regarding total plaque volumes and compositions in the corresponding coronary segments. Fatty plaque and necrotic core volumes were smaller or negligible in coronary segment beneath MB than in controls. Therefore MB might hold a protective role against vulnerable plaque formation.

In two related cases we confirmed that some MBs can cause symptoms even with severe complications and demonstrated that symptomatic MBs can be treated successfully with stent implantation. However, several questions wait for an answer regarding symptomatic MBs and proper treatment.

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9. Bibliography of the candidate's publications

9.1. Publications directly related to the dissertation:

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