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Efficacy of calcium channel blockers in the treatment of the Myocardial Bridging: a pilot study

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Abstract. – *Background:* **Myocardial Bridging (MB) is defined as a segment of a major epicardial coronary artery, the "tunnelled artery", that goes intramurally through the myocardium beneath the muscle bridge.**

Matherials and Methods: **A 69-year-old male patient with a story of arterial hypertension and dyslipidemia in treatment with converting enzyme inhibitors (ACE-I), antiplatelet therapy and HMG-CoA reductase inhibitors and calcium channel blockers, presented with anginal-like chest pain and dyspnea. The coronary angiography showed a myocardial bridging and no hemodynamically significant coronary artery disease.**

Results: **On admission in our Department, the exercise cyclo ergometer test was significant for > 3 mm ST segment depression in the anterior and lateral leads (V3, V4, V5, V6) associated with chest pain. The coronary angiography revealed a 40% stenosis of the distal tract of the right coronary artery (RCA), a 30% stenosis of the proximal tract of the left anterior descending artery (LAD) and 40% of the proximal tract of the first diagonal branch. A 30% stenosis in the middle tract of the left circumflex coronary artery (LCX) was then detected. A marked systolic localized narrowing (90%) on the middle tract of the LAD, after the second diagonal branch (a myocardial bridge) was also detected.**

After eight months, the exercise cyclo ergometer test using a standard Bruce protocol was normal and, after sixteen months, no significant coronary artery disease (< 50%) and no myocardial bridging were detected by the coronary 64-multislice spiral computed tomography.

Two years later, the patient was readmitted to our Department because of angina-like chest pain during light exertion in the last two months. The coronary angiography of the right system revealed a 30% stenosis of the proximal tract and a 50% stenosis of the distal tract of the RCA. The coronary angiography of the left system showed a 30% stenosis of the proximal tract of the LAD and 85% of the middle tract of the first diagonal branch. A 40% stenosis in the middle tract of the left circumflex coronary artery (LCX) was then detected. No MB of the middle tract of the LAD was detected, and a bare metal stent (Presillion 2.5 x 12 mm) was deployed in the middle tract of the first diagonal branch.

Conclusions: **After 2 years, the administration of the calcium channel blockers has been effective in the treatment of the MB but no effect on the atherosclerotic plaque growth has been demonstrated.**

Key Words:

Myocardial bridging, Calcium channel blockers, Myocardial ischaemia, Coronary angiography.

Introduction

Myocardial bridging (MB) is defined as a segment of a major epicardial coronary artery, the "tunnelled artery", that goes intramurally through the myocardium beneath the muscle bridge[1]. It is a non-atherosclerotic disease but a congenital anomaly of the coronary tree distribution[2] and the middle and distal tract of the left anterior descending (LAD) coronary artery are mostly involved[2]. During systole, the tunnelled artery is continuously squeezed, undergoing calibre narrowing (the milking effect[2]) that may cause an abnormal region blood flow to the area perfused by the bridged vessel. However only 15% of coronary blood flow occurs during systole, and because myocardial bridging is only a systolic event, its clinical significance and relevance have been questioned. Even though coronary flow is mainly diastolic, recent quantitative angiographic and intravascular ultrasound studies demonstrated that vessel compression is not limited to systole but rather persists into diastole, and an arterial compression with over 70% arterial lumen reduction has been described as a possible cause of myocardial ischaemia[2-5].

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Then, the clinical relevance of MB is debated[4,6,7]: even if it is generally considered a benign condition, some Authors[3,8] have considered this anomaly as cause of tachyarrhythmias (including supraventricular and ventricular tachycardia[9]), ischaemia and acute coronary syndromes[10-12], coronary spasm[12-14] and ventricular septal rupture[15]. The MB is the only abnormality found out in 4% of sudden cardiac death reports of an otherwise normal coronary tree[3].

It is a very frequent coronary disease (MB is found out in 85% of autopsies[15-19]), it affects men more than women (2:1 ratio) and manifests clinically over 40 years of age[3-6]. Symptoms range from a typical oppressive to an atypical chest pain, inconstantly related to physical or psychic stress[3,4,6]. Despite the high rate of autoptic findings, the MB is hard to diagnose: it could be shown only in 16% of patients undergoing coronary angiography[15-19].

Pharmacological approaches that have been attempted for the MB therapy include β-blockers and calcium channel blockers[20]. The β-adrenergic blockers are the first choice for relieving angina on symptomatic myocardial bridging treatment[20]. In patients with refractory angina despite medical therapy, coronary stenting[21-26], minimally invasive coronary artery bypass grafting[27] (CABG) and surgical myotomy[28] can be considered as an alternative treatment.

In the present report, we describe herein a myocardial ischaemia associated with a subtotal systolic narrowing of the LAD by a myocardial bridge treated with calcium channel blockers.

Case Presentation

A 69-year-old male patient with a story of arterial hypertension, dyslipidemia, chronic obstructive pulmonary disease (COPD) and renal failure, presented with anginal-like chest pain and dyspnea which initially started during mild exertion. There was a story of exertional chest pain associated with dyspnea over the past four months that was progressive. His drug therapy comprised converting enzyme inhibitors (ACE-I), antiplatelet therapy and HMG-CoA reductase inhibitors. On admission in our Department, physical examination was normal. The arterial pressure was 130/90 mmHg. The electrocardiogram (ECG) showed sinus rhythm at the rate of 95 with a normal axis, a first grade atrioventricular block and nonspecific ST-T changes.

Laboratory tests showed high LDL-cholesterol (140 mg/dl) and fatty acids (298 mg/dl) levels. Fasting plasma glucose (98 mg/dl) and 24 hours glucose monitor were normal. Initial creatine phosphokinase and MB fraction, Troponin I and Myoglobin were normal. Subsequent electrocardiograms were unchanged and cardiac enzymes were not raised. The Chest X ray was normal. The transthoracic echocardiogram (TTE) revealed a left ventricle concentric hypertrophy (IVS=PW=12 mm) without outflow tract obstruction, a preserved overall contractility without wall motion abnormalities, an altered relaxation filling pattern, a right ventricle slightly enlarged with maximal systolic pulmonary artery pressure 45 mmHg. The exercise cyclo ergometer test using a standard Bruce protocol was significant for > 3 mm ST segment depression in the anterior and lateral leads (V3, V4, V5, V6) associated with chest pain. For this reason he was taken to the cardiac catheterization laboratory.

The coronary angiography revealed a 40% stenosis of the distal tract of the right coronary artery (RCA), a 30% stenosis of the proximal tract of the left anterior descending artery (LAD) and 40% of the proximal tract of the first diagonal branch. A 30% stenosis in the middle tract of the left circumflex coronary artery (LCX) was then detected. A marked systolic localized narrowing (90%) on the middle tract of the LAD, after the second diagonal branch (a myocardial bridge) was also detected (Figure 1).

We administered angiotensin receptors blockers (Irbesartan 300 mg/day), dual antiplatelet therapy (Aspirin 100 mg/day and Ticlopidine hydrochloride 250 mg/day), HMG-CoA reductase inhibitors (Atorvastatin 20 mg/day) and calcium channel blockers (Diltiazem hydrochloride 240 mg/day). We excluded β-blockers for the story of COPD.

The patient was discharged and followed as outpatient every three months, reporting a good state of health and no anginal-like chest pain. After eight months, the exercise cyclo ergometer test using a standard Bruce protocol was normal and, after sixteen months, no significant coronary artery disease (< 50%) and no myocardial bridging were detected by the coronary 64-multislice spiral computed tomography (64-MSCT).

Two years later, the patient was readmitted to our Department because of angina-like chest pain during light exertion in the last two months. On admission, physical examination was normal. The arterial pressure was 130/80 mmHg. The electrocardiogram (ECG) showed sinus rhythm at the rate of 55 with a normal axis, a first grade

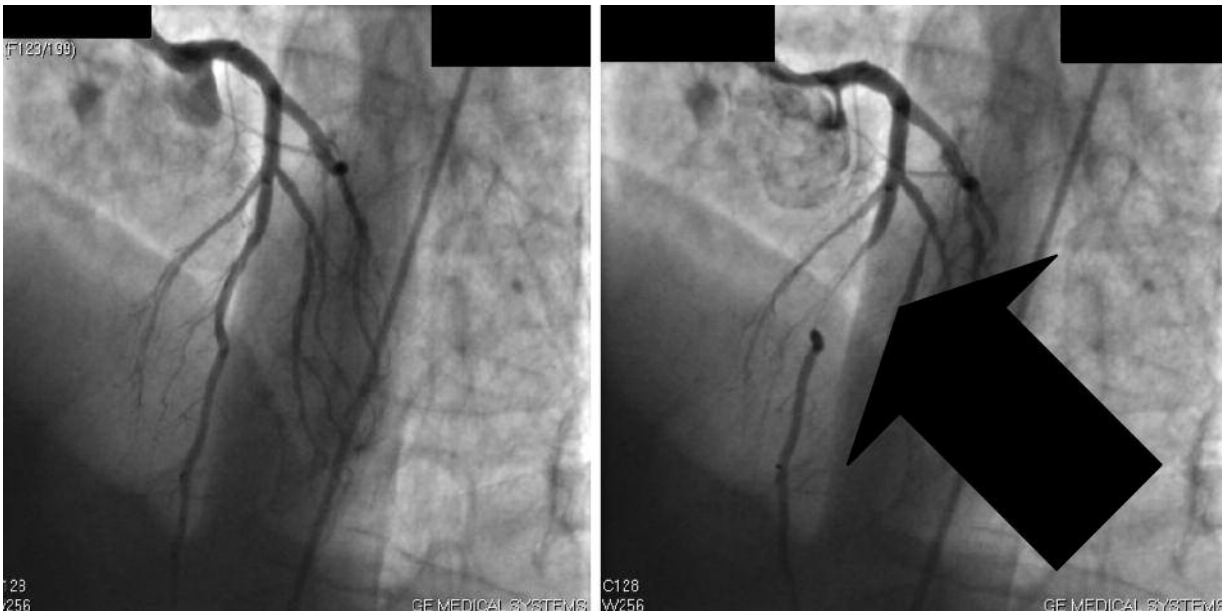

Figure 1. Selective coronary angiography of the left system showing a myocardial bridge of the middle tract of the LAD.

atrioventricular block and patological negative T waves in V4-V5-V6 leads. Laboratory tests showed normal LDL-cholesterol (93 mg/dl) and fatty acids (111 mg/dl) levels. Fasting plasma glucose was normal (98 mg/dl). Initial and subsequent electrocardiograms were unchanged and cardiac enzymes were not raised. The Chest X ray was normal. The transthoracic echocardiogram (TTE) revealed a leftventricle concentric hypertrophy (without outflow tract obstruction), a preserved overall contractility without wall motion abnormalities, an altered relaxation filling pattern, a right ventricle slightly enlarged with maximal systolic pulmonary artery pressure 40 mmHg. According to its clinical history, the patient was taken to the cardiac catheterization laboratory. The exercise cyclo ergometer test using a standard Bruce protocol was significant for > 3 mm ST segment depression in the anterior and lateral leads (V3, V4, V5, V6) associated with chest pain. For this reason he was taken to the cardiac catheterization laboratory.

The coronary angiography of the right system revealed a 30% stenosis of the proximal tract and a 50% stenosis of the distal tract of the RCA. The coronary angiography of the left system showed a 30% stenosis of the proximal tract of the LAD and 85% of the middle tract of the first diagonal branch. A 40% stenosis in the middle tract of the left circumflex coronary artery (LCX) was then detected. No MB of the middle tract of the LAD was detected, and a bare metal stent (Presillion 2.5 × 12 mm) was deployed in the middle tract of the first diagonal branch (Figure 2). Thus, the patient was discharged and treated with angiotensin receptors blockers (Irbesartan 300 mg/day), dual antiplatelet therapy (Aspirin 100 mg/day and Clopidogrel 75 mg/day), high dose of Atorvastatin (80 mg/day) and calcium channel blockers (Diltiazem hydrochloride 240 mg/day).

Discussion

The myocardial bridging is generally considered as a benign condition in most cases, and treatment is required only for symptomatic ones[29], although hard evidence for a favourable effect on morbidity and mortality is missing. However, although infrequent, myocardial ischaemia or infarction, left ventricular dysfunction, ventricular arrhythmia, and sudden death may occur. Because of these serious adverse events, controversy exists on the appropriate therapeutic approach for symptomatic patients and the correct management of patients with MB has not been systematically established yet[29]. Although MB is only a systolic event, it affects blood flow in both systole and diastole, and it produces significant hemodynamic changes in coronary blood flow[2-5,29]. The hemodynamic fea-

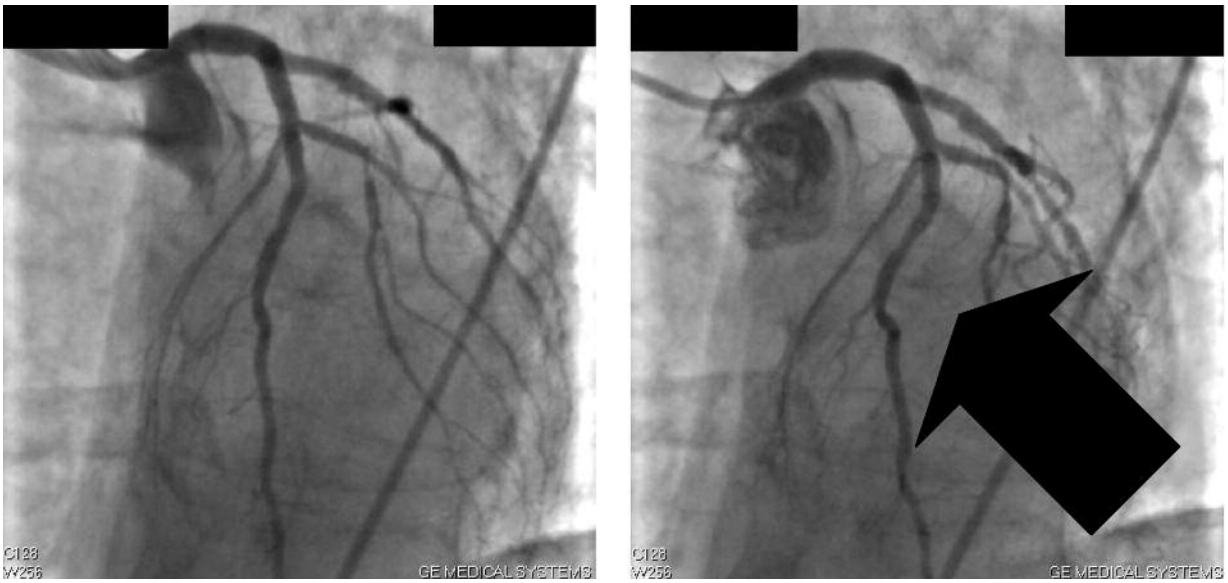

Figure 2. Selective coronary angiography of the left system after medical therapy.

tures were characterized by phasic systolic compression with a localized peak pressure, a persistent decrease in diastolic diameter, an increase in blood flow velocities and retrograde flow, and a reduced flow reserve[1]. On the basis of the above mechanism of ischaemia, 3 treatment strategies have been thought: (1) pharmacological treatment, (2) stenting of the tunnelled segment[26] and (3) surgical myotomy and/or coronary bypass grafting[29]. Medication is considered first-line therapy and should be initiated only for symptomatic patients to improve their quality of life. Negative inotropic and/or negative chronotropic agent, such as β-blockers[19] and calcium antagonists[20] can be used. βeta-blockers are generally considered the first choice of treatment, because these agents (1) by decreasing both systemic and intramural pressures, reduce compression of the coronary artery segment, (2) by reducing heart rate, they lengthen diastolic filling time and ensure vessel patency and (3) they reduce systolic-diastolic time ratio, which leads to reduction of symptoms by reduction of systolic compression time. Although the administration of β-blockers or calcium channels blockers should be beneficial in patients with MB, additional randomized controlled trials are needed to evaluate the long-term efficacy of this pharmacological approach. Nitrates generally should be avoided in patients with MB because they increase the angiographic degree of systolic narrowing and can lead to worsening of the symptoms[30]. In the 1995, Stables et al[25] first reported coronary stenting as an interventional approach to severe MB refractory to medication. Normalization of the pathological coronary flow profile, the reduced coronary flow reserve, and symptoms after stent deployment promised successful use of stents in these patients[23]. Then, despite a favorable long-term outcome at 2 years of follow-up, the rate of restenosis and severe complication, such as coronary perforation, has been too high to generally recommend this approach in symptomatic patients[6]. In subjects refractory to medication and not eligible for coronary stenting, surgical treatment (myotomy and/or CABG) should be considered[31,32]. In 1975, Binet et al[31] observed that the dissection of the overlying myocardium is associated with an increase in coronary flow, abolishes clinical symptoms and improve the quality of life. At present, good clinical results have been reported in a small series of patients, although serious complications, such as right ventricular perforation and left ventricular aneurysm, are possible[32]. According to the high risk of severe complication, surgical treatment with myotomy should be limited only to patients with symptoms that persist despite medical treatment[2].

On the basis of the serious complication of coronary stenting and surgery, medication should be considered the first-line therapy of patients with MB. The effect of β-blockers administration on the tunnelled artery has been well established in clinical studies, although the long-term efficacy of β-blocker therapy has not been studied in randomized controlled trials. Calcium channel

blockers are generally considered for MB therapy thanks to their negative inotropic and chronotropic effect even if, to our knowledge, their efficacy has not been evaluated in large clinical trials.

In our report, β-blockers should not been used for the story of COPD and we chose for Diltiazem, a benzothiazepine not-dihydropyridine calcium channel blocker[33]. In our report, Verapamil was initially administered according to its strong negative inotropic and chronotropic effect, but it was early stopped for hypotensive symptoms (asthenia and dizziness)[33,34].

Ultimately, we can underline the following key points:

- The first coronary angiography showed a MB of the the middle tract of the LAD and a no hemodynamically significant (< 50%) coronary artery disease and, according the our experience, the administration of Diltiazem was the first choice pharmacological treatment[33].
- After 16 months of follow-up, the MSCT confirmed the absence of hemodynamically significant coronary stenoses, but no MB was detected
- After 2 years, the coronary angiography showed a hemodynamically significant coronary artery disease but no MB, emphasizing how the calcium channel blockers have no benefit on the progression of the coronary atherosclerosis (a negative effect of the calcium channel blockers on the atherosclerotic plaque growth was been hypothesized)[35].
- The calcium channel blockers are effective in the treatment of the MB for their good negative inotropic and chronotropic effects and the reduction in vascular resistance with an improvement in blood flow, but no effect on the atherosclerotic plaque growth has been demonstrated[33].

To our knowledge, this is the first work that stresses the inefficacy of the calcium channel blockers on the atherosclerotic plaque growth but shows their role in the treatment of MB.

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