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Old unsolved problems: when and how to treat silent ischaemia

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Silent myocardial ischaemia (SMI) is defined as objective evidence of ischaemia without angina (or equivalent symptoms) in the presence of coronary artery disease, differing from silent coronary artery disease. Silent myocardial ischaemia represents the majority of episodes of myocardial ischaemia at Holter monitoring. During transient myocardial ischaemia, the symptoms appear after the contraction anomalies of the left ventricle and after the ECG changes. The cause of silent myocardial ischaemia is still not well established. The severity and duration of ischaemia have been theorized as important elements in the SMI mechanism. Another possible mechanism responsible for SMI is represented by changes in the perception of painful stimuli with an increased pain threshold. Finally, a neuronal dysfunction of the diabetic, in post-infarction or a cardiac neuronal 'stunning' could play a role in SMI. In the present era, the SMI was associated with a worse prognosis. In patients with diabetes mellitus, SMI seems to be more represented because autonomic dysfunction is present in this category of patients. In conclusion, SMI is more frequent than symptomatic ischaemia. However, despite the presence of countless studies on the subject, it is not clear today whether medical therapy has equalized the risk and what the real prognosis of SMI is.

Silent myocardial ischaemia (SMI) is defined as the presence of objective evidence of ischaemia in the absence of angina or equivalent symptoms (dyspnoea, nausea, diaphoresis, etc.).

The objective evidence of SMI can be obtained in different ways, by means of non-invasive diagnostic tests (exercise stress test, Holter-ECG, SPECT/PET imaging, Eco-stress) or more recently by invasive tests during catheterization with the use of coronary pressure (FFR, iFR, and other non-hyperaemic indices).

Silent myocardial ischaemia represents an important public health problem and to date the extent of this phenomenon is largely unknown. Since it was first recognized as a relevant part of the spectrum of ischaemic heart disease in the early 20th century,[1] episodes of asymptomatic ischaemia have been estimated to occur in a percentage ranging from 25% to 50% of the patients with ischaemic heart disease and that this occurs, with respect to symptomatic episodes, with a ratio greater than 20:1.[2]

The classification of silent myocardial ischaemia involves three categories of patients:

- Type I: this is the least common form, and occurs in completely asymptomatic patients with chronic ischaemic heart disease (which can be severe) in the absence of angina symptoms.
- Type II: this type occurs in patients with previous and documented myocardial infarction.
- Type III: this is the most common form and occurs in patients with the classic forms of chronic stable angina (stable, unstable angina, and Prinzmetal's angina).

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The mechanisms of transient myocardial ischaemia

During ischaemia induced by a reduced flow, the systolic thickening of the left ventricle depends almost exclusively on the level of available subendocardial flow. Therefore, there is a 'matching' or tight coupling between substrate and oxygen supply (reflected by regional coronary flow) and regional myocardial oxygen consumption (indicated by the level of contractility at steady state) (perfusion–contraction matching).

Numerous studies have shown that during ischaemia the perfusion level of the internal part of the myocardium plays a fundamental role in determining the transmural systolic ventricular function. During a gradual reduction in coronary flow, changes in systolic function correlate almost linearly with a reduction in subendocardial flow and not with subepicardial flow[3,4] (*Figure 1*).

The pathophysiology is attributable to stable coronary artery disease, alone or combined with a greater demand for oxygen by the myocardium. In fact, thanks to studies conducted with Holter-ECG and ambulatory blood pressure monitoring, it was observed that most of the episodes of ischaemia during daily activities were preceded by significant increases in heart rate and blood pressure; moreover, episodes of silent ischaemia were more frequent in the morning in conjunction with the physiological increase in heart rate and systolic blood pressure, in a manner dependent on sympathetic hypertone.[5,6] In addition, numerous studies have shown that patients undergoing coronary artery bypass surgery usually have a higher incidence of SMI episodes detected by 24-h Holter-ECG monitoring. *Figure 2A* shows an episode of symptomatic changes on the left, and on the right an asymptomatic episode in which the patient had the same changes of the recording but of shorter duration.

Diabetes mellitus is a significant risk factor for coronary heart disease and correlates with a higher incidence of SMI. Autonomic cardiac dysfunction is the main culprit in diabetic patients involving pain receptors, afferent neurons, and brain areas.[7,8] *Figure 2B* shows RR intervals in the supine position and immediately after tilting in a healthy subject (empty circles) and in a diabetic patient with asymptomatic ST-segment changes (filled circles) that highlights autonomic dysfunction in the diabetic patient.

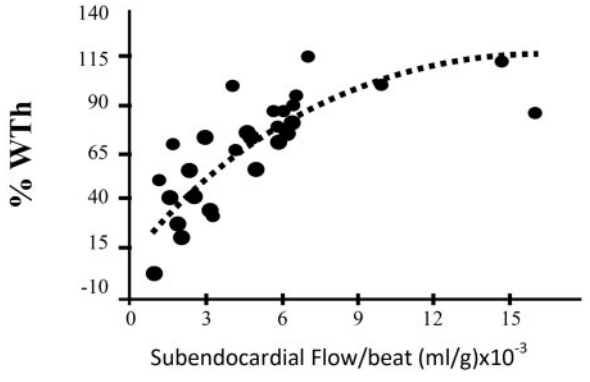

Figure 1 Relationship between subendocardial flow per beat and percentage of systolic thickening (wall thickness, % Wth). During myocardial ischaemia, changes in systolic function correlate almost linearly with the reduction in subendocardial flow. (Modified from Indolfi, *Circulation*, 1989).

Prognostic value of silent myocardial ischaemia

Numerous studies have shown that the presence of silent myocardial ischaemia is associated with an increased risk of adverse events both in asymptomatic patients with no history of coronary artery disease and in those with various manifestations of coronary artery disease. In the Multiple Risk Factor Intervention Trial, in 12 866 asymptomatic middle-aged subjects with two or more coronary risk factors, 12.5% had evidence of silent myocardial ischaemia at the transthoracic echocardiogram.[9]

Similarly, in 2682 subjects without known coronary heart disease who participated in the Kuopio Ischaemic Heart Disease study, exercise-induced silent ischaemia was associated with an increased risk of death and acute coronary events [relative risk (RR) of 5.9 and 3.0 in smokers, 3.8 and 1.9 in hypercholesterolaemic subjects and 4.7 and 2.2 in hypertensive patients, respectively].[10]

Although the presence of silent myocardial ischaemia (*Figure 3*) is related to an unfavourable prognosis, several studies have shown that the extent or severity of ischaemia could be a more important predictor of adverse events.[11,12]

A further critical issue is represented by technological evolution in the cardiovascular diagnostic field. In fact, the introduction of functional assessment indices of the severity of coronary stenosis is uncovering a Pandora's box that is leading the Cardiologist to insidious therapeutic junctions when facing significant coronary artery disease or extensive ischaemia in the absence of symptoms. Furthermore, one of the dilemmas, currently with no clear answer, is whether screening should be performed in asymptomatic patients at high risk for myocardial ischaemia, but especially when and how to treat them.

Angioplasty or optimal medical therapy in the patient with chronic coronary syndrome?

As demonstrated in randomized clinical trials, the benefit of revascularization compared to medical therapy and the selection of the type of revascularization [percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG)] are clearly influenced by the anatomical position, the extent of coronary artery disease, the symptoms, and the degree of ischaemia.

The COURAGE study[13] showed that, at an extended follow-up of up to 15 years, there is no difference in survival between an initial approach with PCI plus medical therapy compared to medical therapy alone in patients with stable ischaemic heart disease. In addition, a substudy examined a small group of patients ($n = 314$) who had performed SPECT at baseline and 6–18 months after randomization during the COURAGE study. The primary

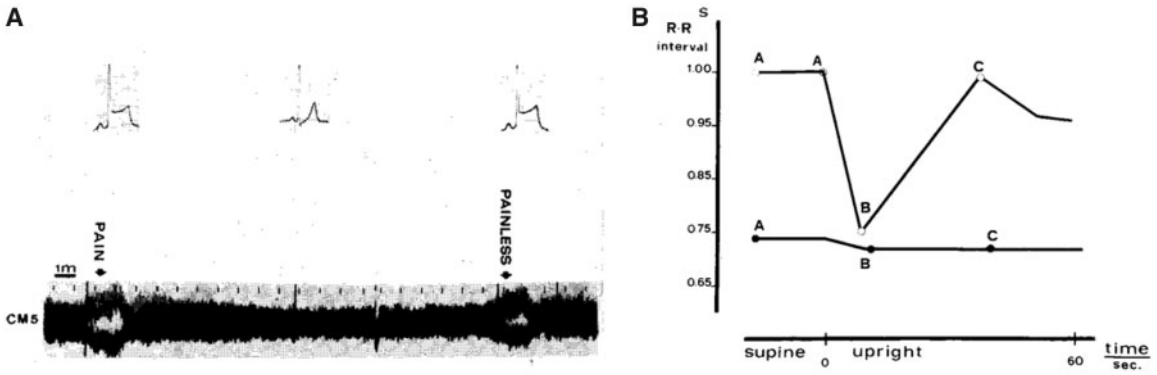

Figure 2 (*A*) Compact Holter-ECG recording showing two episodes of myocardial ischaemia in the same diabetic patient. The episodes of ST elevation are represented by the 'white' window inside the 'black' band. (*B*) R-R intervals in the supine position and immediately after tilting in a healthy subject (empty circles) and in a diabetic patient with asymptomatic ST tract changes (full circles) which highlights the autonomic dysfunction in the diabetic patient.

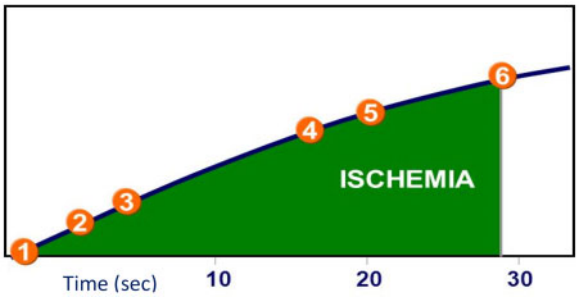

Figure 3 Time-course of the ischaemic cascade. (1) Coronary occlusion; (2) diastolic abnormalities; (3) systolic abnormalities; (4) Haemodynamic changes; (5) ECG abnormalities; (6) angina.

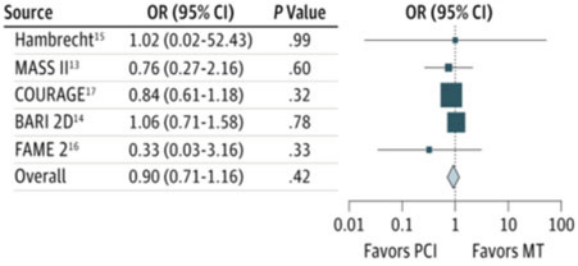

Figure 4 Meta-analysis on mortality that does not show any difference between patients undergoing PCI and those in whom optimal medical therapy was given.

endpoint was the 5% reduction in ischaemic myocardium at follow-up. At follow-up, the reduction in ischaemic myocardium was greater in patients treated with PCI + medical therapy than in medical therapy alone. This effect was greater in patients with moderate to severe baseline ischaemia (78% vs. 52%; $P = 0.007$).[14] These data were considered as evidence that patients with a large ischaemic load could benefit from revascularization. However, this effect was no longer significant if appropriate to the risk and, as clearly stated by the authors, the study did not have adequate statistical power. More recently, the FAME 2 study demonstrated how FFR-guided coronary angioplasty results in a 34% reduction in the incidence of IMA ($P = 0.05$), but no difference in 5-year mortality compared to medical therapy alone in patients with stable chronic ischaemic heart disease.[15]

In addition, several meta-analyses were conducted on the topic that analysed the issue using slightly different methodologies but with substantially similar results. Using data from five randomized trials and 5286 patients, Stergiopoulos *et al.*[16] found no reduction in mortality when comparing invasive therapy vs. medical therapy (*Figure 4*).

The study by Pursnani *et al.*[17] which included 7182 patients from 12 randomized trials and demonstrated an insignificant reduction in mortality and acute myocardial infarction. Recently, the ISCHEMIA study[18] was presented at the 2019 American Heart Association Congress. This study, which included a good number of patients with silent ischaemia, failed to demonstrate that routine invasive therapy was associated with a reduction in adverse ischaemic events greater than optimal medical therapy in patients with stable coronary artery disease and moderate ischaemia. Patients with stable ischaemic heart disease and moderate to severe ischaemia were randomized to routine invasive therapy ($n = 2588$) compared to medical therapy ($n = 2591$). In the routine invasive therapy group, subjects underwent coronary angiography and PCI or CABG, as appropriate. The primary outcome of cardiovascular death, myocardial infarction, resuscitated cardiac arrest, or hospitalization for unstable angina or heart failure at 3.3 years occurred in 13.3% of the invasive routine group compared to 15.5% of the medical therapy group ($P = 0.34$). The results were the same in multiple subgroups. There was also no benefit from invasive therapy with regards to all-cause mortality or cardiovascular mortality/myocardial infarction. These results have also been surprisingly found in patients three-vessels coronary artery disease.

Pharmacological treatment of transient ischaemia

The drugs for the treatment of myocardial ischaemia are traditionally catalogued, according to the effects on cardiovascular haemodynamics, in drugs that reduce the

demand for O_2, or that increase the supply of O_2 through an increase in myocardial flow.

Among the various determinants of ventricular function that can be manipulated during myocardial ischaemia, heart rate seems to be of primary importance. The decrease in heart rate produces a large change in the oxygen demand per minute in the ischaemic zone (as well as increases the absolute subendocardial flow per beat, as will be described later). The mechanisms of the increase in subendocardial flow per beat (and therefore the availability of O_2 per beat) induced by beta-blockers are linked to the reduction of heart rate, blood pressure, and myocardial contractility with consequent reduction of the consumption of in the external portion of the myocardium (epicardium) by reducing the flow demand in this region. This increases coronary resistance in the epicardium by reducing transmural steal and increases subendocardial flow ('reverse steal').

The mechanisms of redistribution of ischaemic myocardial flow induced by bradycardia can occur transmurally (endocardium/epicardium) or in different geographical areas of the myocardium (left ventricle/right ventricle) having different vascular resistances with reduction of the regional myocardial flow in the right ventricle ('reverse steal' of the right ventricle). The ultimate effect is always an increase in subendocardial flow in the ischaemic area with an increase in the regional contractile function. Therefore, in addition to the conventional mechanism attributed to the action of β-blockers (reduction of ischaemia and angina due to reduction of the myocardial demand for O_2), another action of this category of drugs should be added, i.e., an increase in intake of O_2 to the subendocardium in the ischaemic zone.

In conclusion, in light of current and recent evidence, the treatment of SMI must be personalized based on the patient's clinical characteristics, symptoms, the degree of ischaemia, and the extent of coronary artery disease. Today, we have terrific drugs for primary and secondary prevention of coronary heart disease. An invasive approach can be safely recommended in patients with left main disease or with moderate to severe ischaemia and proximal coronary artery disease for improved symptoms when patients with SMI also have typical angina. On the contrary, an aggressive conservative strategy, mainly based on anti-ischaemic and lipid-lowering drugs, can be considered a reasonable approach in asymptomatic patients with good left ventricular function.

Conflict of interest: none declared.

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