

The risk of acute coronary events in microvascular disease

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KEYWORDS

Coronary microvascular dysfunction; myocardial infarction with non-obstructive coronary arteries

The microvascular disease represents a widespread clinical entity in the general population, especially among women. The dysfunction of the microcirculation is often responsible for myocardial ischaemia and angina in the absence of significant stenosis of the epicardial district, while in other cases it can represent a contributing cause of angina even in the presence of coronary artery disease, cardiomyopathies or heart failure. The cardiovascular risk factors of people with microvascular disease are similar to those who develop epicardial atherosclerotic disease. However, the prognostic significance of microvascular disease remains a matter of debate. An element to be clarified, in fact, is whether subjects with dysfunction of the microcirculation and coronary tree without significant stenoses present an increased risk of myocardial infarction and sudden death. In recent years, several studies seem to confirm an association between microvascular disease and progression of coronary epicardial atherosclerosis. The prognosis of microvascular disease would therefore not be benign as was previously believed, but associated with an increased risk of cardiovascular events including revascularization, heart attack, and cardiac death.

Introduction

According to a definition recently accepted by the international community, the impaired function of the microcirculation (coronary microvascular dysfunction, CMD) requires signs and/or symptoms of myocardial ischaemia in the absence of significant obstructive coronary artery disease.¹

CMD is therefore responsible for myocardial ischaemia and in some cases angina in the absence of significant stenosis of the epicardial district. In other cases, CMD can be a contributing cause of angina even in the presence of coronary heart disease, cardiomyopathies, or heart failure.

It is important to remember that the cardiovascular risk factors of people with CMD are similar to those who develop epicardial atherosclerotic disease.

It is legitimate to ask whether the microcirculation can be called into question for the most fearful complication of ischaemic heart disease: myocardial infarction.

Concepts of pathophysiology

To understand CMD, notions of anatomy and pathophysiology are important. Two microcirculatory compartments are identified; the pre-arteriolar one consisting of vessels with a diameter >100 microns and capable of exerting resistance to flow, and the distal one with vessels having a caliber <100 microns and characterized by intramural arterioles that respond to the local concentration of metabolites.²

CMD can be caused by functional or structural changes. Functional CMD can be endothelium dependent; in these cases, the reduced production or increased degradation of NO (Nitric Oxide) can cause a vasospasm, in the most proximal compartment of the microcirculation or an

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alteration of the vasodilation mechanisms. There is also a non-endothelium-dependent CMD although the mechanism is less well known.¹

The structural causes of CMD include luminal narrowing of the arterioles, perivascular fibrosis or rarefaction of the capillaries, where there is an increase in the mass of the left ventricle.¹

Several invasive and non-invasive techniques are available to analyse the functional state of the coronary microcirculation.^{3,4} In patients with epicardial vessels free from significant lesions, the coronary flow reserve (CFR) provides a reliable estimate of the function of the microcirculation. CFR is defined by the relationship between coronary flow at baseline and in conditions of maximal hyperemia obtained following infusion of adenosine (endothelium-dependent vasodilation) or acetylcholine (endothelium-independent vasodilation). The flow can be evaluated invasively through the use of a Doppler guide placed distally in the coronary artery.⁵ A CFR <2 is indicative of significant CMD. A further invasive index of microcirculation analysis is the index of microvascular resistance (IMR).⁶ The IMR exploits the thermo-dilution principle and can be easily determined through an intra-coronary pressure and temperature guide. Corresponds to the product of distal coronary pressure and mean transit time of a bolus of 3 cc of saline solution repeated three times at room temperature during maximum hyperemia. An IMR > 25 is an expression of impaired microvascular perfusion. IMR also offers the considerable advantage of not being influenced by haemodynamic conditions and epicardial stenosis.⁷

Among the non-invasive techniques, transthoracic echo-colour-Doppler certainly represents the most immediate and low-cost method, although often hampered by the intrinsic difficulty in obtaining an optimal coronary Doppler signal. The Doppler ultrasound allows the calculation of CFR by measuring the diastolic peak flow rate during adenosine infusion and at baseline.⁸ Furthermore, a reduction in eco-stress CFR with dipyridamole in the absence of alterations in regional kinetics is also indicative of CMD. The functional state of the microcirculation can also be investigated by cardiac magnetic resonance imaging (CMR), an instrument used in particular to study the phenomenon of no-reflow caused by obstruction of the microcirculation after restoration of the patency of the epicardial vessel responsible for infarction. Stress CMR with perfusion study allows the calculation of the myocardial perfusion reserve index (MPRI), surrogate of the CFR. It has been shown how MPRI correlates with CFR evaluated with invasive techniques.⁸ The investigation using positron emission tomography (PET), due to its ability to reliably quantify the blood flow per gram of myocardium, currently represents the gold standard among the imaging methods for the study of the microcirculation. The blood flow at baseline and after pharmacologically induced hyperemia, quantified through the use of radioactive tracers such as ammonia labelled with ¹³N, water labelled with ¹⁵O or rubidium82, allows a reliable determination of the CFR. PET, however, is limited by cost and low availability.

CMD as a cause of myocardial ischaemia or angina

In many cases, CMD simply causes exertion or resting ischaemia in the absence of angina. Similar to people with epicardial coronary artery disease, patients with CMD may experience typical angina pectoris, as well as atypical symptoms or exertion dyspnea. According to some studies, the angina symptom is observed in a percentage of cases that can reach 40%.⁹

Furthermore, angina in subjects with CMD can also appear at rest, especially in those who have a vasospastic mechanism or an increase in the tone of the small vessels. CMD is more common in women and it is no coincidence that many studies have been conducted in women.^{2,10}

There is no doubt that angina due to CMD worsens the quality of life.⁷ According to Taqueti *et al.*,¹¹ the use of a strategy aimed at identifying subjects with CMD and the mechanisms that are responsible for them translates into an improvement in the quality of life.

Furthermore, CMD can modulate the ischaemic threshold in patients with stable obstructive coronary artery disease. Pupita *et al.*¹² observed in patients with angiographic evidence of chronic total occlusion of a coronary artery and the presence of collateral circulation, a wide variability of the ischaemic threshold in the absence of spasm of the epicardial vessels, related to vasoconstriction phenomena of the microcirculation.

CMD and risk of acute coronary events or cardiac death

An element to be clarified is whether subjects with CMD and coronary tree without significant stenoses have an increased risk of major cardiovascular events, including myocardial infarction and sudden death.

Johnson *et al.*¹³ studied 673 women with precordial pain and suspected myocardial ischaemia. In 412 cases, there was no significant coronary disease while in the remaining 261 coronary angiography showed significant narrowing. In the group without coronary artery disease, 189 subjects had angina and were considered to have CMD.

In the group without obstructive disease, the composite event of non-fatal myocardial infarction, stroke, heart failure and cardiovascular death was observed in 16.6% of women with CMD vs. 5% of women with normal coronary artery tree (control group) ($P=0.03$).

The incidence of events was lowest in women in the absence of symptoms and significant obstructive lesions (control group) and highest in the group with significant obstructive lesions and CMD. The role of precordial pain in predicting a composite cardiovascular event had an HR of 1.89 in women with CMD and no obstructive coronary artery disease ($P=0.03$) and dropped to 1.17 in those with obstructive coronary artery disease ($P=0.49$). The presence of significant coronary stenosis therefore had a great prognostic impact, while the presence of CMD contributed in predicting the prognosis to a lesser extent.

Pepine *et al.*¹⁴ studied 189 women with suspected ischaemia using CFR. The authors noted a significant

association between CFR alteration (indicating CMD) and major cardiovascular events (death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure). Reduced CFR was associated with a risk of major adverse cardiovascular events (MACE) of 1.16 ($P=0.009$). The incidence of cardiovascular events was as follows: myocardial infarction 1.7%, stroke 4.2%, heart failure 3.2%, angioplasty 6.4%, bypass 0.5%, angina 19%.

It is interesting to underline how the diagnosis of major cardiovascular CMD events (reduced CFR) improved the ability to predict cardiac events even in subjects with coronary heart disease. The work did not specify the percentage of cases with normal coronary trees (smooth coronaries). However, 51% had stenoses below 20%. In this subgroup of patients, an altered CFR identified subjects with a worse prognosis.

Gulati *et al.*¹⁵ studied 540 women with CMD (suspected ischaemia and no obstructive coronary disease) in the Women's Ischaemia Syndrome Evaluation (WISE) registry and compared them with 1000 female subjects in the St James Women Take Heart (WTH) registry, which included asymptomatic patients with no history of coronary heart disease. Women with CMD, belonging to the WISE registry, had a higher prevalence of obesity, family history of ischaemic heart disease, hypertension, and diabetes mellitus. The 5-year annual incidence of cardiovascular events was 16% in women with CMD and non-significant coronary artery disease, 7.9% in women with CMD and a completely normal coronary artery tree, and 2.4% in asymptomatic women without ischaemia of the WTH register ($P\leq 0.002$). The analysis was performed after adjustment of the coronary risk variables. Cardiovascular events were also more frequent in women with at least four coronary risk factors; the risk of cardiovascular events at 5 years was 25.3% in the WISE group with coronary artery disease, 13.9% in the WISE subjects with completely normal coronary artery tree, and 6.5% in the WTH control group of asymptomatic women.

More specifically, the incidence of myocardial infarction was 3.9% in the group with non-significant coronary artery disease, 0.9% in the group with normal coronary arteries and 0.7% in the WTH group of asymptomatic women. The incidence of stroke was 5.2%, 2.4%, and 1.0%, respectively, while cardiac death occurred in 4.4%, 1.5%, and 0.6%, respectively.

Bugiardini *et al.*¹⁶ published in 2004 an interesting prospective study on 42 female subjects, with chest pain, ischaemia to Single Photon Emission Computed Tomography and the absence of coronary heart disease. The CMD study with acetylcholine identified endothelial dysfunction in 22 subjects (52.4%). After 10 years, 13 subjects continued to experience precordial pain and in all cases the formation of new coronary stenosis in the epicardial district was highlighted.

The mechanism of the association between endothelial dysfunction and cardiovascular events

Studies on this particular aspect show that the prognosis in women with endothelial dysfunction and complete

absence of coronary atherosclerosis is not benign, as was initially believed.

It is difficult to understand whether the microcirculatory disease should be considered as distinct from the atherosclerosis of the epicardial district or whether it predicts its development in the period following the diagnosis. The perspective observation of Bugiardini *et al.*,¹⁶ relating to the ability of CMD to predict the development of obstructive coronary artery disease, supports the second hypothesis.

There are also two confounding elements. As a first aspect, CMD can be associated with cardiovascular events during the follow up due to less careful secondary prevention than in patients with epicardial atherosclerotic disease. As a second observation, angiography does not always detect atherosclerotic lesions since it allows us to study only the lumen and not the initial coronary lesions, identifiable with CT scan or intra-coronary imaging methods. Epicardial disease could therefore be underestimated.

Uncertainties remain about the mechanism of the association between endothelial dysfunction and cardiovascular events. However, it is likely that endothelial dysfunction is a disorder that precedes and promotes vascular alterations of the atherosclerotic type. Endothelial dysfunction can be considered from this pro-atherosclerotic and pro-thrombotic perspective.

The progression of coronary heart disease by Bugiardini *et al.*¹⁶ is associated with the observation by Pepine¹⁴ according to which in a high percentage of cases with CMD (19%) angioplasty is necessary in the follow-up period up. The CMD would therefore identify those patients at risk of developing a more aggressive atherosclerosis in the epicardial area; the progression of the disease of the great vessels seems to be the element that most influences the prognosis.

On the other hand, it is difficult to believe that the microcirculatory infarction plays an important role. It is possible that in some cases of non ST-segment elevation myocardial infarction-type infarction, the cause may be microcirculatory, with secondary or primary ischaemic mechanisms. The spasm of the microcirculation could, for example, be responsible for ischaemia with increased level of cardiac enzymes.

However, there are no data in the literature, and at the same time observations that arise from clinical experience, which support a microcirculatory genesis of ST elevation myocardial infarction (STEMI)-type infarction. Excluding Tako-Tsubo syndrome, which cannot be classified as a CMD, the STEMI-type heart attack is attributable to an epicardial disease. The latter does not always have significant stenoses; in a significant percentage the STEMI heart attack can be classified as myocardial infarction with non-obstructive coronary arteries (MINOCA). Lysis of the thrombus on an ulcerative or erosive basis, spontaneous dissection, embolism and finally epicardial spasm are the pathogenetic mechanisms that can be called into question.

Conclusions

The prognosis of endothelial dysfunction in the absence of coronary atherosclerosis is not as benign as previously

believed. The disease is associated with an increased risk of cardiovascular events which include revascularization, acute coronary events, and cardiac death.

The mechanism of the association between endothelial dysfunction and cardiovascular events is unclear; however, endothelial dysfunction appears to be a disorder that precedes vascular alterations of the atherosclerotic type.

Conflict of interest: None declared.

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