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REVIEW

Coronary microvascular dysfunction

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ABSTRACT

Patients with coronary microvascular dysfunction (CMVD) represent a widespread population and despite the good prognosis, many of them have a poor quality of life with strong limitations in their daily activities because of the angina symptoms. This work summarizes the most frequent clinical presentation pictures like stable and unstable microvascular angina. Main risk factors are discussed, followed by the last updates on the subject about different pathogenic hypotheses, diagnosis and treatment. Not very well understood microvascular alterations, like slow flow phenomenon and no reflow are discussed and both prognosis and the impact of the disease in the quality of life are analyzed.

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Coronary microvascular dysfunction is extremely widespread, considering that 20-30% of patients, mainly women undergoing coronary angiography for stable angina, have normal coronary arteries and a microvascular dysfunction.[1] This condition can be defined as primary microvascular angina (PMVA), to distinguish it from microvascular angina forms in which coronary microcirculation dysfunction (CMD) is related to the presence of a specific diseases.[2]

TABLE I.—*Clinical pictures of coronary microcirculatory dysfunction.*

Clinical picture	Features
Stable microvascular angina	Physical stress chest pain Positive exercise stress test Free stenosis coronary angiography
Unstable microvascular angina	Physical stress chest pain Positive exercise stress test Free stenosis coronary angiography
Acute microvascular dysfunction	Clinical and EKG picture similar to acute coronary syndrome with free stenosis coronary angiography (Takotsubo Syndrome)

CMVD affects prearterioles, those vessels that have a diameter between 300 and 600 microns, with a primary involvement of the endothelial function.[3]

Recently many studies tried to understand much more about the disease and to identify some typical pathological patterns. Currently the PMVA can be distinguished in stable and acute (kind of microvascular dysfunction related to the Takotsubo syndrome)[4, 5] (Table I).

Despite many obscure points, little by little we begin to have evidences that underline the importance of some risk factors compared to others and other evidences that lead to alterations in endothelial function. About therapy and prognosis, the debate is still open.

Clinical pictures: stable and unstable microvascular angina

Stable microvascular angina (SMVA) is the most studied form of PMVA. It is characterized primarily by stress angina and can be identified with the condition commonly called cardiac X syndrome (CSX), characterized by the classically triad; stress angina, positive stress test for myocardial ischemia and angiographically normal coronary arteries.[4]

Mechanisms responsible for SMVA are likely to be multiple. Some studies have shown structural abnormalities of small coronary vessels, but other studies have failed to highlight such alterations. A wider consensus exists, however, on the presence of functional alterations of the coronary microcirculation, which are mainly expressed with a reduction of the vasodilator response, but also with an increase in vasoconstriction of the small coronary vessels.[5-7] The prognosis of PMVA patients is generally good, however, 20-30% of patients show a progressive worsening of symptoms. The primary goal of PMVA treatment is to control the angina symptoms. Traditional anti-ischemic drugs are the first choice, but often they are not sufficiently effective. Some studies have reported a greater benefit of beta-blocker compared to calcium antagonists, for this reason they could be administered first, especially if there is the evidence of an increased adrenergic tone.

We can define, instead, unstable microvascular angina (UMVA) an acute condition with acute onset, mostly at rest, characterized by a significant aggravation of a pre-existing angina, that can simulate an acute coronary syndrome (ACS) due to an alteration of the coronary flow caused by a dysfunction of the coronary microcirculation. The "coronary slow flow phenomenon" is a typical angiographic alteration of these patients, characterized by delayed opacification of the distal vessels in the absence of obstructive disease of the subepicardial coronary arteries. Case-control and observation studies were conducted to determine the association between clinical features and prognosis. In one of these studies during a 21-month average follow-up of 64 patients with slow flow, 84% had recurrent chest pain. Based on these results and on other similar and previous ones, it is hypothesized that the "coronary slow flow phenomenon" is a new entity of the disease characterized by acute, but recurrent, alterations of microvascular function.[8] Moreover, the picture of UMVA differs significantly from both a clinical and physiopathological point of view from SMVA, with frequent admissions for resting pain and a higher incidence of death and acute myocardial infarction.[9, 10]

SMVA patients have evidence of myocardial ischemia with an abnormal responsiveness to endothelium-dependent and -independent stimuli. In these patients, some studies have demonstrated a higher oxygen with evidence of anaerobic metabolism.

These data support the idea that SMVA patients have microvascular dysfunction with subsequent production of lactate and metabolic markers of myocardial ischemia.

In slow flow phenomenon patients with UMVA, resting resistances are abnormally high; because of this reason coronary flow at rest is slow. In contrast with SMVA, microvessels respond to vasodilators. This pattern of abnormal microvascular function justifies the observation that UMVA, in contrast to patients affected by SMVA, have a normal CFR[11] (Table II).

TABLE II.—*Diagnostic key steps for microvascular dysfunction.*

1. Typical symptoms of myocardial ischemia:
   - angina at rest and during exercise;
   - angina equivalents (*i.e.* dyspnea)
2. Absence of coronary obstructive disease (stenosis inferior than 50%) o FFR<0.8 demonstrated by:
   - coroCT;
   - angiography
3. Evidence of myocardial ischemia demonstrated by:
   - ischemic variation on the ECG at rest or during chest pain;
   - positive ECG or ECO stress or cardiac scintigraphy
4. Evidence of impaired coronary microvascular function demonstrated by:
   - reduction in coronary flow reserve (CFR<2);
   - microvascular coronary spasm defined by evidence of symptoms or ECG modifications during acetylcholine test in the absence of epicardial coronary spasm;
   - abnormal coronary microvascular resistance index (IMR>25);
   - presence of coronary slow flow (TIMI frame count >25).

Role of cardiovascular risk factors on pathogenesis: between consolidated and new evidence

The specific role of cardiovascular risk factors in coronary microangiopathy is not yet clear. Numerous studies have analyzed the association between cardiovascular risk factors and microvascular coronary dysfunction, although their results are still conflicting. Some studies show that patients with microvascular angina have a lower frequency of all conventional cardiovascular risk factors than patients with obstructive CAD, while other ones show that these two categories of patients (microvascular angina and obstructive CAD) have a similar risk profile. Below a brief summary of the main alterations related to risk factors.

Hypertension

The pathogenic mechanisms underlying angina pectoris in patients with essential hypertension, in the absence of obstructive coronary disease, are still unknown. These patients report various pathophysiological abnormalities including endothelial dysfunction, increased sympathetic tone, microvascular spasm, estrogen deficiency and increased pain sensitivity.[12, 13]

The presence of endothelial dysfunction in patients with hypertension and microvascular angina has been suggested because of the presence of a reduced coronary flow in response to acetylcholine or atrial pacing and inappropriate vasoconstriction activity, mainly mediated by endothelin-1 production (ET-1).[14]

In fact, the ET-1 plasma concentration increase has been found in patients with microvascular angina (cardiac X syndrome - CSX) in many studies. Furthermore, it was observed that ET-1 increases in response to atrial pacing in the coronary circulation of patients with CSX. However, other studies have shown a vasoconstriction of the coronary microcirculation in response to endothelium-independent stimuli, such as adenosine, dipyridamole and papaverine, suggesting the presence of primary abnormalities of vascular smooth muscle cells that can lead to vasodilatory dysfunction and vasospasm[15, 16]

Type 2 diabetes mellitus

Several studies have shown a reduced vasodilatation capacity of the coronary microcirculation both endothelium dependent and endothelium independent in patients with type 2 diabetes, even in the absence of lesions of the large epicardial branches. A recent study showed a potential mechanism to demonstrate the endothelium dependent vasodilatory function alterations. ADMA (asymmetric dimethylarginine), a competitive endogenous inhibitor of nitric oxide synthase, increases its plasma concentration in direct proportion to insulin resistance in non-diabetic patients, while it increases in direct proportion to glycaemia in diabetic patients. The accumulation of ADMA can result from the inhibition of its catabolism caused by the reduction of dimethylarginine synthase.[17]

In a study conducted in our institute we tried to evaluate the impact of diabetes on the function of the coronary microcirculation in patients with chest pain and stenosis free coronary arteries. The analysis of the microcirculation carried out through the Gibson indexes (Timi Frame Count - TFC and Myocardial Blush Grade - MBG) and performed in the two populations of patients with chest pain and stenosis free coronary arteries, with and without diabetes, allowed us to state that patients with diabetes have a greater disruption of the microcirculation than non-diabetic ones.[18]

Metabolic syndrome

Usually, studies concerning the impact of metabolic syndrome (MetS) on the coronary microcirculation address their attention to atherosclerosis and endothelial dysfunction of large caliber arteries; in fact, an increasing number of trials suggest that the components of the metabolic syndrome (MetS) could also negatively affect the coronary microcirculation through different mechanisms. Microvascular remodeling, in the course of MetS, is multifactorial and includes changes in transmural and luminal pressure, changes in the renin-angiotensin-aldosterone system, increased products of advanced glycosylation (AGE), increased inflammation and activation of the TGF-β signaling pathway. Furthermore, the metabolic syndrome determines,

in the microcirculation, the expression of a different receptorial pattern respect to large-caliber vessels and AGEs may be partly responsible for the hypertrophic remodeling of the resistance microvessels and for the discordant expression of the components of the extracellular matrix. However, even more interest comes from the data showing the effects of statins in myocardial perfusion in patients with MetS who have perfusion abnormalities attributed to microvascular dysfunction in the absence of obstructive coronary disease. In these patients, statin therapy produces significant improvements in myocardial perfusion abnormalities. In addition, rosuvastatin treatment is associated with a reduction in myocardial fibrosis and diastolic dysfunction in patients with MetS; this antifibrotic effect is mediated by AMP-protein kinase (AMPK) at the fibroblast level. According to their cardioprotective effects, statins have been associated with a reduction in cardiac tissue remodeling thanks to the downregulation of TGF-B1, a fundamental fibrosis mediator inhibited by AMPK.[19, 20]

Pathogenic hypotheses

There are numerous pathogenic hypotheses that have been proposed in recent years to explain the alterations that involve not only the endothelium structure but also its function.

Recent studies have highlighted new pathogenic mechanisms.[12]

The endothelium luminal surface is covered by a thin layer called glycocalyx, which is strongly involved in the regulation of blood flow (transmission of shear stress). In fact, the structural degradation of glycocalyx leads to a reduced shear stress dependent, NO-mediated, arteriolar vasodilation.[21] Glycocalyx can be easily degraded by toxic oxygen radicals, ischemia and inflammation.[22, 23] The degradation of the superficial layer could therefore be involved in the dysfunction of the coronary microcirculation.

In order to maintain an adequate flow and oxygen distribution to the microvascular network is necessary that signals originated by vascular, metabolic and hemodynamic growth factor are transmitted upstream along the vessel wall, through the gap junctions.

If this transmission is compromised a functional shunt would develop and the distribution of the flow and oxygen would then become very irregular. While the regulation of vascular connections is not known in detail, there are studies that relate the expression of connesins with aging, hypertension and ischemia/reperfusion, making plausible again that altered signal transmission may contribute to the dysfunction of the coronary microcirculation.[24-26]

Vascular responses to metabolic signal molecules released from different sources are necessary to associate the local blood flow with tissue demand. The main effects of impaired metabolic signaling would be an increase in the heterogeneity of spatial perfusion in the resting state and a reduced perfusion in conditions of increased demand, for example during exercise.[27, 28] Metabolic feedback signaling could be compromised at any stage of the overall signaling chain, including oxygen detection, production of signaling molecules or the activity of the respective receptors. Reduced red blood cell (RBC) capacity to produce NO in patients with PMVA has been reported, probably reflecting a compromised RBC metabolic signaling.[29] (Figure 1).

Very interesting is the role of microvascular dysfunction in aortic stenosis. TAVI or aortic valve replacement have been associated with improved coronary blood, probably due to an increased aortic diastolic pressure and/or a decrease in left ventricular diastolic pressure.[30]

Microvascular dysfunction has been described as a possible pathophysiological mechanism underlying Takotsubo syndrome (TTC). Several studies have confirmed the involvement of coronary microvascular abnormalities in the pathogenesis of TTC, but authors were not sure if mi-

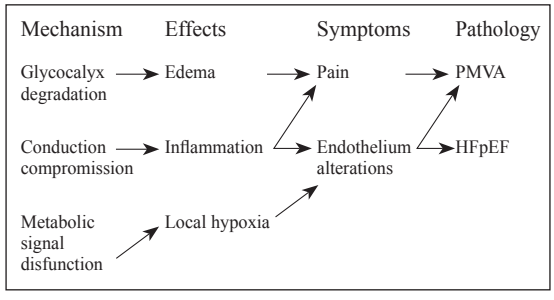

Figure 1.—New pathogenic hypotheses.

crovascular dysfunction was the primary cause or a secondary phenomenon. Very interesting is the description of the usefulness of adenosine in the acute phase of TTC, that led to rapid improvement both of myocardial perfusion and left ventricular ejection fraction, both probably related to relief from microvascular disfunction.[31]

Slow flow phenomenon in UMVA has to be differentiated to no-reflow phenomenon after-percutaneous coronary intervention where, despite reestablishing epicardial coronary vessel patency, the flow to the previously ischemic myocardium is markedly reduced. When it occurs, it reduces the effect of reperfusion therapy. The possible mechanisms under the no reflow phenomenon could be related both to alterations in the microvascular circulation and thrombus embolization. The clinical presentation in useful to differentiate the two entities. In the STEMI setting in much more appropriate thinking to a thrombus migration, though a concomitant microvascular dysfunction cannot be simply excluded, while in an UMVA setting the presence of a thrombus in unlikely after the demonstration of normal coronary arteries.[32]

The role of coronary microvascular dysfunction in heart failure with preserved ejection fraction

In a recently published work, *Paulus et al.* hypothesize that, at the base of heart failure with preserved ejection (HFpEF), there is an endothelial dysfunction at the level of the coronary microcirculation that can alter the cross-talk paracrine signaling pathway between the coronary microcirculation and the cardiomyocyte, through a reduction of the bioavailability of nitric oxide (NO) and downstream of both cyclic guanosine monophosphate (cGMP) and protein kinase G (PKG) activity. It has been shown that in these patients, because of the increase in interstitial fibrosis and the hypertrophy of cardiomyocytes, there is a decrease of the left ventricle compliance (LV).[33-35]

Recent researches suggest that endothelial inflammation, at the level of the coronary microcirculation, is associated with coronary microvascular rarefaction, with a consequent reduction in capillary density that may compromise the coronary flow reserve, causing left ventricular diastolic dysfunction.[36]

Based on recent literature data that showed endothelial inflammation at the coronary microcirculatory level in patients with HFpEF, a retrospective study was conducted in our department. Our test sample consisted of a population of 286 patients that we divided into two groups: 155 patients with HFpEF and 131 patients without HFpEF (with EF>50%, in the absence of dyskinesia). The objective of this study was to evaluate if there was a major dysfunction of the coronary microcirculation in patients with microvascular angina and HFpEF, compared to those who did not have HFpEF. Criteria for the inclusion of the study were the presence of chest pain, positive stress test and free-stenosis coronary arteries. All patients underwent an echocardiogram before coronary angiography. Patients who had positive biomarkers for myocardial infarction upon arrival in the hemodynamics room or during hospitalization and patients with EF<50% were excluded. From the analysis of the microcirculation, performed by the Gibson indexes (TFC and MBG), in patients with HFpEF we concluded that the population with HFpEF has a greater involvement of the coronary microcirculation compared to patients without HFpEF.[37]

Current imaging techniques for the study of microcirculation

Several methods have been proposed for the analysis of the functional state of the coronary microcirculation. The evaluation of coronary microvascular function presents, however, many problems. CMVD can be identified only indirectly through measurements of changes in coronary blood flow (CBF) and coronary vascular resistance in response to particular stimuli.[38-41]

Several methods have been proposed to evaluate CMV function in these patients, including invasive methods such as thermodilution and intracoronary Doppler which represent the gold standard.[42] However, in recent years, technological advances have led to the development of several non-invasive imaging techniques that allow sufficiently reliable measurements for the assessment of CMVD.

Transthoracic echocardiogram

Transthoracic eco-Doppler (TTED) allows to measure the coronary flow velocity and is considered an indirect measurement of coronary flow (CBF). The CMV function can normally be evaluated in the left anterior descending coronary artery (LAD) and it is easier to visualize than other coronary arteries.[43, 44]

Coronary flow reserve (CFR) is measured as the ratio of the diastolic peak flow rate, during vasodilator infusion (mainly adenosine), and basal flow velocity. A ratio of less than 2.0 is considered diagnostic of a dysfunction of the coronary microcirculation.

A significant reduction in the CFR has been documented with TTDE in patients with cardiovascular risk factors, idiopathic dilated cardiomyopathy (IDCM) or hypertrophic cardiomyopathy and finally in patients with PMVA or takotsubo syndrome.[45] Worthy of note is the fact that the TTDE was also used to document changes in the vasodilatory capacity of the coronary microcirculation in response to drug therapy, particularly in patients with hypertension.[46, 47] A relationship between reduced CFR, assessed by TTDE, and clinical outcome was observed in preliminary studies in patients with dilated or hypertrophic cardiomyopathy.[48, 49]

Another useful method to identify a coronary microcirculatory disease is represented by the echo-stress with dipyridamole, which allows to distinguish an epicardial coronary stenosis from an isolated coronary microvascular dysfunction: the first, in fact, shows a reduction of the CFR associated with alteration of the wall during dipyridamole infusion, while in case of an alteration of the coronary microcirculation, during the infusion of dipyridamole we will have a reduction of the CFR in the absence of alterations of the regional kinetic.[50]

Contrast myocardial echocardiography (CME) has often been used to evaluate the status of the coronary microcirculation in patients with acute myocardial infarction (AMI) after successful recanalization of the affected vessel.[51, 52]

The assessment of myocardial perfusion, after percutaneous coronary intervention (PCI), aims to establish the real effectiveness of the procedure. In fact, it is now clear that an optimal recanalization of the coronary artery is not always followed by an effective restoration of CBF at the microvascular level.[53] The CME helped to clarify some important pathophysiological aspects of no-reflow, in particular, it has been shown that this is a process characterized, in part, by structural and irreversible damages of the coronary microcirculation and, in part, by functional anomalies that can be resolved. in time.

Recently, the CME has allowed to capture some particular characteristics on the pathophysiological condition of the syndrome of takotsubo. The CME evaluation of myocardial perfusion, during the acute phase, revealed large transmural perfusion defects in the dysfunctional zone.[54]

Finally, the CME also helped to confirm coronary microcirculatory dysfunction in patients with the stable form of PMVA. In fact, the CFR assessed both through CME and through TTDE, was significantly reduced in these patients compared to control, with a high correlation between the two methods.[55]

Myocardial scintigraphy

Myocardial scintigraphy is a diagnostic test that is used to assess the presence of possible abnormalities in myocardial perfusion.

In a study conducted at our institute we examined a population of 208 patients who experienced a strong chest pain and with coronary artery without stenosis. We studied the correlation between Total Myocardial Blush Score (TMBS), predictive index of microcirculation alteration and scintigraphic positivity, noting that patients with positive scintigraphy, undergoing a coronarographic study, had a TMBS worse than patients with negative scintigraphy, with a high statistical significance.[56]

Cardiac magnetic resonance

The assessment of myocardial perfusion, using cardiac magnetic resonance (CMR), is based on changes in the intensity of myocardial gadolinium signal, an extracellular contrast agent.[57]

CMR has been used to evaluate coronary microcirculatory dysfunction in different clinical conditions. CMVD has also been documented by CMR in patients revascularized with coronary artery disease, in patients with takotsubo

syndrome and in patients with hypertrophic or dilated cardiomyopathy.[58] Significant alterations of the coronary microcirculation have also been documented by CMR in patients with PMVA.

Panting *et al.* demonstrated a reduction in subendocardial CBF in response to adenosine. Lanza *et al.* subsequently revealed important perfusion defects during stress tests with dobutamine in 56% of patients with PMVA, correlated with a reduction in CBF in response to adenosine, as assessed by TTDE in the anterior descending coronary artery.[59]

Finally, CMR has become the method of choice to identify and characterize areas of microvascular obstruction ("no-reflow") in patients with AMI who undergo recanalization of the coronary artery related to the infarct.

The role of the angiographic indexes: TIMI frame count and myocardial blush grade

The TIMI frame count (TFC) is a quantitative index that allows the coronary flow to be evaluated as a continuous quantitative variable. It consists of the number of frames necessary to the contrast medium, injected during the coronographic examination, to reach and opacify a predetermined distal "landmark". The TFC value is probably closely related to the characteristics of the coronary microcirculation given that, at this level is concentrated almost all the resistance of the coronary tree even in physiological conditions.[60]

The TFC correlates closely with the measurement of the coronary flow reserve obtained with the Doppler guidewire. It is clear that the use of the TFC offers the possibility to easily investigate the coronary flow. In a patient with a dysfunction of the coronary microcirculation, the coronary flow will be considerably slower, due to the obstruction downstream and this method is an indirect measure of the compromise of the coronary microcirculation: more the microcirculatory dysfunction will be serious, higher the number of frames necessary for the contrast medium to opacify the landmark will be.[61]

The Myocardial Blush Grade is an angiographic measure of the level of tissue perfusion, in fact the "Blush" (redness) indicates the capacity that the coronary microcirculation has to be opacified by the contrast agent and the speed of the wash out from the coronary microcirculation. Gibson hypothesizes the existence of four degrees of MBG ranging from a 0 degree in case the contrast agent is not able to opacify the coronary microcirculation, to a degree four in the case of the opacification and the wash out occur within the third cardiac cycle after opacification.[62]

Treatment

Given the good prognosis, the primary endpoint of PMVA treatment is represented by the control of angina symptomatology. The therapeutic strategy in these patients aims to improve the function of the microcirculation and to reduce the perception of chest pain, trying to act on the two main pathophysiological mechanisms of the disease: CMD and altered cardiac nociception.

Beta blockers, calcium antagonists, ACE inhibitors and nicorandil

According to the ESC 2019 guidelines, anti-ischemic drugs remain the therapy to be used as first approach: beta blockers and calcium antagonists have an indication of class I, ACE inhibitors and nicorandil instead have an indication class IIb.

Unfortunately, most of the treatments have been evaluated on small numbers of patients, and often these are uncontrolled trials, making difficult to establish their real effectiveness. Unfortunately, in many cases, satisfactory results are not achieved requiring a personalized therapy with the introduction of different alternative forms of therapy.

Ivabradine

Ivabradine inhibits If current, an important current involved in generating the early stage of spontaneous diastolic depolarization in pacemaker cells, reducing the frequency of action potential and lowering heart rate. It reduces myocardial oxygen demand, with no effect on blood pressure, myocardial contractility and conduction time; this is translated into a reduction of anginal symptomatology and of sublingual nitrate intake. The use of ivabradine resulted in a reduction in major cardiovascular adverse events (cardiovascular mortality, hospitalization for fatal and non-fatal myocardial infarction and heart

failure), coronary revascularization for patients with stable CAD, limiting angina and systolic dysfunction left ventricular.[63]

Trimetazidine

Trimetazidine has been shown to decrease the amount of angina attacks, as well as silent myocardial ischemia episodes; it has reduced the needs for short-acting nitrates and has been shown to improve quality of life.[64]

Ranolazine

Ranolazine is a relatively new anti-ischemic drug that acts, on the one hand, by inhibiting the late current of Na + in the myocardiocytes, with favorable effects on cardiac relaxation, and on the other one by intervening on the diastolic function and on the subendocardial coronary flow.

In patients with PMVA, Ranolazine has been tested in a recent study, showing favorable effects on anginal symptoms and quality of life, which is why it appears to be a promising therapeutic option in patients with microvascular angina, although the data will be confirmed in further studies.[65]

Prognosis and quality of life

The prognosis of PMVA patients has always been recognized to be good, with mortality rates and major cardiac events not significantly different from those seen in the general population.

Unlike the excellent prognosis, patients with microvascular angina may have a compromise in their quality of life. In 10-20% of cases, the angina symptoms progressively worsen during follow-up, becoming more frequent and prolonged, appearing for lower workloads or arising even at rest and becoming less sensitive, or even refractory, to drug therapy.

Suwaidi *et al.* found that 14% of patients with severe endothelial dysfunction (assessed by intracoronary acetylcholine infusion) had cardiac events during a follow-up of 28 months, compared to patients with mild or moderate endothelial dysfunction who had no events cardiac.[66]

In the WISE study, which included 189 women with signs and symptoms of ischemia in the absence of obstructive CAD, endothelium-independent dysfunction, characterized by reduced CFR, was also significantly associated with major adverse effects with a mean follow-up of 5 years.[67]

A comparison of cardiovascular events and mortality rates in the WISE study and in the St. James Women Take Heart (WTH) study showed a more than ten-fold increase in heart failure rates and a 5-fold increase in major cardiovascular events in patients symptomatic of the WISE study compared to patients in the asymptomatic WTH Study.[68]

More recent studies have used PET to calculate the CFR and build a risk stratification. Patients with CFR<1.5 were associated with an increased risk of cardiac death of 5.6 times compared to those with CFR>2.5.[69]

There are several results from a recently published study that followed a population of 250 patients with microvascular angina, with the aim to evaluate the percentage of major adverse cardiac-vascular events (MACE). The data from this study showed an excellent long-term prognosis of these patients, with fatal event rates in the very low risk range (<1% per year). In contrast to previous studies, moreover, the results emerged from this study showed that the majority of patients reported reduction of episodes of angina.[70] The attention that only in recent years has been had towards microvascular angina requires further studies to clarify the real prognosis in this cluster of patients.

Conclusions

CMVD occurs both in patients affected by specific cardiac or systemic diseases and in patients without other diseases. The pathogenesis is still uncertain, though evidences suggesting a role for certain risk factors rather than others are gradually emerging, along with the demonstration of new alterations of endothelial function. About therapy and prognosis the debate is still open.

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