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RESEARCH ARTICLE

The Role of Coronary Microvascular Disease in Cardiomyophaties

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ABSTRACT

Coronary microvascular disease (CMD) makes reference to the anatomically and functionally disorders affecting vascular compartments (<400 mm diameter), covering a broad range of clinical conditions in which the structure and function of the coronary microcirculation is affected. CMD is characterized by an impaired coronary flow reserve (cut-off values of 2.0-2.5) or an abnormally index of coronary microvascular resistance (IMR >25) and/or focal or diffuse vasoconstriction during acetylcholine challenge, with an important role in myocardial perfusion. The aim of this work is to review CMD, definition, clinical manifestations, diagnosis method (non invasive and invasive approach) and the role of CMD in the main cardiomiophaties, such as Hypertrophic cardiomiopathy, none idiomatic dilated cardiomiopathy and infiltrative miocardiophaty.

1.- Introduction

Heart disease has been defined as obstructive atherosclerosis involving the epicardial coronary arteries. There is acknowledgement that structural and functional disorders affect the whole coronary circulation, serve as mediators of patient symptoms in what might more accurately be called Ischemic Heart Disease (IHD). (1)

Coronary microvascular disease (CMD) makes reference to the anatomically and functionally disorders affecting vascular compartments (<400 mm diameter), covering a broad range of clinical conditions in which the structure and function of the coronary microcirculation is affected. CMD is characterized by an impaired coronary flow reserve (cut-off values of 2.0-2.5) or an abnormally index of coronary microvascular resistance (IMR >25) and/or focal or diffuse vasoconstriction during acetylcholine challenge, with an important role in myocardial perfusion. (2) Coronary microcirculation is responsible for the regulation of blood flow distribution to cover the metabolic demands of the myocardium. (3) Significantly more women (65%) than men (32%) had no obstructive Cardiovascular Artery Disease (CAD). (4)
In individuals without epicardial atherosclerosis increases in myocardial metabolic demand are met by progressive vasodilation of coronary arterioles, which can normally induce a five-fold increase of coronary blood flow. (5)

The endothelial layer lining the interior of blood vessels is directly exposed to hemodynamic forces. Coronary blood flow remains constant over the range of coronary perfusion pressures through dynamic changes in vessel tone. These changes result from a number of mechanisms including adrenergic stimuli, changes in local oxygen tension, and the response to changes in transmural pressure. High blood pressure accelerates the development of atherosclerotic plaques in large epicardial coronaries and endothelial dysfunction of heart microvessels. CMD decreases coronary flow in response to stress, which can lead to a mismatch between supply and demand, and can cause subclinical or clinical myocardial ischemia. (6)
Small vessel disease does not include atheroma of the epicardial arteries; however, it is probably magnified by the presence of atherosclerosis, especially in patients with cardiovascular risk factors. These changes lead to microvascular obstruction with luminal narrowing of intramural arterioles and capillaries, frequently in the context of increased Left Ventricular (LV) mass. Evidence of microvascular remodeling has been reported in some but not all studies, and is consistently associated with risk factors including diabetes, hypertension, and kidney failure, or evidence of diffuse epicardial atherosclerosis. (7,8)

The vascular endothelium plays a fundamental role in the modulation of smooth muscle function through the release of vasoactive substances. A normal vascular endothelium causes vasodilation of the epicardial microvascular and coronary circulation in the presence of acetylcholine and physical stimuli, resulting in increased coronary blood flow and myocardial perfusion. In the presence of cardiovascular risk factors and atherosclerosis, the vascular endothelium becomes dysfunctional and the vasodilator response to pharmacological and physiological interventions is attenuated, resulting in decreased coronary blood flow or vasoconstriction with reduced coronary blood flow. (9)
The treatment of CMD has been empirical because its pathophysiology is multifactorial, with overlapping phenotypes that often coexist, may be the primary abnormality in some patients and a secondary pathological feature in others. (10)

2.- Risk factors in Coronary microvascular disease

Risk factors for CMD do not vary from those for epicardial macrovascular arterial disease, including hypertension, diabetes mellitus, hyperlipidemia, obesity, smoking and age.
Hypertension enhances CMD through functional and structural changes in the microcirculation. Clinical studies provide evidence that microvascular hallmarks of hypertension are inward remodeling of resistance arteries and microvascular rarefaction, determinants of microvascular resistance reducing myocardial blood flow.(11)

CMD in diabetes is characterized by decreased Nitric Oxide (NO) activity, increased Reactive Oxygen Species (ROS) production, increased endothelin synthesis, reduced endothelial barrier function, and increased inflammatory activity. . Diabetes is a multiorgan endocrine disease, and consequently, diabetes-associated DCM has been detected in multiple organs, including the heart, retina, kidneys, and skin. (12)

Dyslipidemia is an important risk factor for microvascular dysfunction, especially hypercholesterolemia, which has a clear correlation with reduced Coronary Flow Reserve (CFR). Plasma levels of total cholesterol and LDL-C are inversely correlated with Fractional Flow Reserve (FFR) and Index of Microvascular Resistance (IMR), regardless

of the severity of coronary atherosclerosis or the number of diseased vessels. (13)
Smoking is a well-established cardiovascular risk factor in CMD for both sexes, but it increases significantly in young women who combine smoking with the use of oral contraceptives. (14)

3.- Coronary microvascular disease definition and classification:

3.1.- Coronary microvascular disease definition

Microvascular angina in the context of CMD is defined as symptoms of myocardial ischemia, absent obstructive CAD, and abnormal CFR with cut-off values below 2.0-2.5 depending on the methodology or microvascular spasm to acetylcholine. (9) Hemodynamic indexes, CFR and IMR, have been shown to be the most reliable to assess coronary microcirculation. (15)

Coronary vascular function is assessed by infusion of a vasoactive substance such as acetylcholine or ergonovine (16) The physiological alterations to vascular tone following intracoronary infusion of these substances are determined by the relative functions of the endothelium and smooth muscle cells Vasodilatation reflects a dominant response of healthy endothelial cells, opposite to the constrictor effects of vascular smooth muscle cells, vasoconstriction reflects a dominant smooth muscle cell effect over impaired endothelial cell mediated vasorelaxation (vascular dysfunction). (17)

Endothelial dysfunction is associated with epicardial vasoconstrictor response after intracoronary acetylcholine infusion with adverse cardiovascular events. Acetylcholine-induced epicardial or microvascular spasm has been reported in approximately 50% of patients with stable chest pain and no evidence of obstructive CAD. Coronary microcirculation remains the main culprit as assessed by measurements of coronary blood flow, suggesting a concurrent involvement of functional abnormality. (18)

3.2.- Coronary microvascular disease Classification

Coronary microvascular disease and atherosclerosis

In 2007, Camici and Crea proposed 3 categories of CMD including the documentation of non-atherosclerosis and non-obstructive or obstructive atherosclerosis. The interplay of CMD, CAD, and cardiovascular risk factors is clinically relevant and may guide us for appropriate therapeutic strategies in CMD. (1)

3.2.1.- Coronary microvascular disease without atherosclerosis

CMD without atherosclerosis, more common in women, refers to a heterogeneous clinical condition with multiple potential causes that are not always apparent, where atherosclerosis plays little or no role in its pathogenesis. It plays a crucial role documenting the presence of CMD in patients with arterial hypertension and non-ischemic cardiomyopathies to establish the association of CMD as an etiology or secondary cause in the different heart diseases. (19)

3.2.2.- Coronary microvascular disease with non-obstructive atherosclerosis

Most patients undergoing evaluation for CMD have some degree of atherosclerosis, even if no obstructive lesions are found. Some of these patients may present ischemia or acute myocardial infarction; otherwise, this subgroup represents the largest cohort of patients with CMD.

3.2.3.- Coronary microvascular disease with obstructive atherosclerosis

CMD is also prevalent in patients with obstructive CAD. This finding is not surprising because endothelial and coronary vasomotor dysfunction represents an early manifestation of atherosclerosis. (20) CMD in patients with stable obstructive CAD has several important diagnostic, prognostic, and management implications. In the presence of CMD, FFR values measured for any given stenosis are higher (and potentially pseudonormal) than when coronary microvascular resistance is normal, which can lead to underestimating the physiological severity of a stenosis. (21) . This suggests that interrogation of CMD in patients with obstructive CAD could potentially identify circumstances in which abnormalities from upstream stenoses and CMD could entail a misunderstanding of the functional significance value of coronary indexes. (22)

4.- Clinical manifestations of Coronary microvascular disease

The most frequent clinical manifestation is angina, dyspnea or heart failure; also, the combination of symptoms is common. Angina occurs in approximately 30% to 60% of patients with CMD. (23) Exceptional dyspnea may represent an ischemic equivalent caused by LV diastolic dysfunction, with an excessive increase in end-diastolic pressure leading to cardiopulmonary congestion or may also be due to a limited ability to increase cardiac output with exercise. (2)

Positive stress tests generally mirror obstructive CAD, and patients are referred to a cathlab for definitive anatomic diagnosis. If obstructive CAD is identified, those patients may be considered for revascularization, depending on the extent and severity of myocardial ischemia. Nevertheless, when there is non-obstructive disease, the result of the stress test is typically interpreted as a "false positive." However, large studies including women and men with chest pain and non-obstructive CAD found that a positive exercise stress test was neither sensitive nor specific for CMD. However, in some patients this may be the diagnosis of CMD, especially in the presence of symptoms and positive stress testing. Those patients should be considered further for direct assessments of coronary vasomotor function. There are differences in accuracy and levels of validation between the different techniques, the choice depends on local availability, clinical expertise, and patient preference. (24)

Coronary microcirculation is beyond the resolution of invasive or non-invasive coronary angiography, at this point a real challenge begins, so a direct interrogation of coronary microvascular function is necessary to establish the diagnosis of CMD. (6)

5.- Non-invasive techniques for Coronary microvascular disease.

Non-invasive diagnosis is made by measuring global and regional myocardial blood flow at rest and during stress, microvascular resistance, and CFR. CFR, calculated as the ratio of hyperemic to resting absolute myocardial blood flow, is a measure of coronary vasomotor dysfunction. Obstructive CAD and DCM can coexist, and others can manifest CMD in the absence of detectable atherosclerosis. (5)

Single-photon emission computed tomography (SPECT): this non-invasive technique has demonstrated reversible and fixed uptake defects without obstructive coronary disease on invasive coronary angiography, suggesting ischemia and scarring, respectively. The imaging protocol consists of a rest and vasodilator-stress myocardial perfusion study, each following the injection of a blood flow radiotracer (25)

Positron emission tomography (PET) is the most validated and accurate non-invasive approach for the quantitative assessment of coronary blood flow at rest and after vasodilatation, consequently, calculation of coronary flow reserve. The advantages of this technique is the accuracy of PET for quantitative non-invasive measurement of myocardial blood flow. The CFR has been extensively validated and the reproducibility of this technique is well-established, which allows the quantification of the ischemic load. The disadvantage of the nuclear imaging techniques is the exposure of patients to radiation; hypoperfusion assessed by these techniques is influenced by the presence of epicardial coronary artery stenosis, and SPECT does not allow the ischemic load to be quantified. (26)

Coronary microvascular ischemia can be evaluated by cardiac magnetic resonance, the protocol consists the former by first-pass perfusion and the latter by Late Gadolinium Enhancement (LGE). The first-pass myocardial perfusion at rest and vasodilator stress, each after injection of a gadolinium-based contrast agent. Post-processing of rest and stress images allows quantification of regional and global myocardial perfusion using semi-quantitative (myocardial perfusion reserve index) or fully quantitative (CFR) models. The advantages of CMR are to be a non-invasive and reproducible technique with high spatial resolution, which allows transmural characterization of myocardial blood flow, ischemic burden quantification, including the evaluation of fibrosis extension which is marker of poor prognosis, absence of ionizing radiation, along with the ability to perform a comprehensive assessment of cardiovascular structure and function. The disadvantages include hypoperfusion is influenced by the presence of epicardial coronary artery stenosis, badly tolerated by claustrophobic patients and contraindicated in the presence of non-MRI compatible cardiac devices. (27)

Doppler echocardiography can study coronary flow velocity after adenosine perfusion in the Left Anterior Descending (LAD) artery and in the Posterior Descending (PD) artery. Adenosine causes coronary vasodilatation by acting in adenosine A2 receptors and through release of endothelial NO. In detail, the evaluation of coronary flow velocity reserve is performed in an apical three chambers view for the LAD artery and in an apical two chambers view for the PD artery. Blood flow is identified with color Doppler and blood flow velocity is measured by pulsed-wave Doppler echocardiography in basal conditions and in hyperemia. Coronary flow velocity reserve is calculated as the ratio of hyperemic coronary flow velocity to rest coronary flow velocity. Echocardiography can also evaluate myocardial perfusion by using contrast, with the analyses based on myocardial opacification at rest and after adenosine perfusion. The advantages of this

technique are its low cost, lack of ionizing radiation, and potentially broad access. The disadvantages of this technique are that it is highly operator-dependent and requires echocardiographic visualization of the proximal coronary arteries, which can involve a significant challenge in obese adults; coronary flow velocity reserve is influenced by the presence of epicardial coronary artery stenosis. (28)

Dynamic myocardial perfusion Computed Tomography (CT) can also be used to estimate myocardial blood flow similarly to CMR perfusion imaging. Dynamic CT scanning is performed after injection of an iodinated contrast agent with prospective electrocardiographic triggering to capture the first pass of the contrast medium through the heart. These dynamic image sets are then used to produce estimates of myocardial blood flow using methodology developed for CMR. The major advantages of this technique are the superior spatial resolution of CT and the opportunity to perform accurate anatomic and functional assessments of both the myocardium and the coronary arteries within one examination. However, these benefits come at the price of a higher radiation dose to the patient. (25)

6.- Invasive techniques for Coronary microvascular disease.

In the absence of flow limiting stenosis, coronary circulation can be directly and separately assessed by Coronary Flow Reserve (CFR) for the entire coronary tree and by Index of Microvascular Resistance (IMR) for coronary microcirculation. Invasive coronary angiography has a spatial resolution of 3 mm and is not able to visualize arterioles. By combining the ability to exclude obstructive CAD with complementary catheter-based techniques to probe coronary epicardial and microvascular physiology, is an attractive approach for evaluating patients with CMD. The key functional parameters are vascular tone, vasodilator reserve, and resistance. Coronary resistance is determined mainly by intramural arterioles <400 mm in diameter. Invasive Coronary Flow Reserve (CFR) is most commonly assessed with an intracoronary wire to measure coronary blood flow velocity at rest and in response to adenosine and acetylcholine vasodilation. CFR is a global reflects of vasodilator capacity of the coronary circulation. (29)

There is no firm consensus about the approach, but the diagnostic procedure must focus on a single coronary artery to limit the duration of the procedure; the left coronary artery is generally preferred, as it better reflects myocardial mass. If the technical factors, such as tortuous coronary anatomy, avoid the instrumentation of this artery; then the circumflex must be evaluated. (6)

6.1.- Coronary pressure-flow wire

The usual approach to induce hyperemia is by using intravenous adenosine (140 mg/kg/min). Intravenous adenosine activities vascular A2-receptors, leading to predominantly non-endothelium-dependent vasodilation. Adenosine infusion is given for 2 to 3 min, and, although mild symptoms are common, it is generally well tolerated. Hemodynamic markers of coronary hyperemia are: 1) "Ventricularization" of the distal pressure waveform, 2) Disappearance of distal dicrotic pressure notch; and 3) Separation of Mean Aortic and Distal Pressures. (30) Generally, FFR of 0.80 or less is considered positive, which means that epicardial arteries lead to ischemic disease. (31) Changes in Heart Rate, Blood Pressure, and Rate-Pressure Product are less reliable measures of coronary hyperemia. (32) Intracoronary bolus injection of adenosine (up to 200 mg) or nicorandil (2 mg) is an alternative option to assess endothelium-independent vasodilatation (33)

6.2- Coronary Thermodilution in Coronary microvascular disease.

The principle of coronary thermodilution is that the transit time, derived from an intracoronary injected bolus of normal saline solution administered at room temperature to mix with blood at body temperature, represents the inverse of the coronary blood flow. (34)

The guide catheter must be coaxial with the long axis of the coronary artery to guarantee an effective supply and a mixture of saline solution.
The guidewire sensor tip is positioned at the tip of the guide catheter, and the pressure measurement from the wire is equalized with that of the guiding catheter. The sensor is advanced to the distal third of the coronary artery followed by 3 intracoronary injections of saline (3 ml) at room temperature. The mean transit time is measured with each bolus and averaged to calculate the resting mean transit time. When steady-state hyperemia is reached by pharmacological stress testing, 3 additional injections of 3 mL of saline are administered at room temperature.

CFR is calculated using thermodilution as resting mean transit time divided by the hyperemic mean transit time (abnormal CFR is defined as <2.0). (6) The index of microvascular resistance (IMR) is

calculated as the product of distal coronary pressure at maximal hyperemia multiplied by the hyperemic mean transit time; the normal range of IMR is considered to be <25. (35)

6.3.- Vasoreactivity testing

Coronary spasm is part of the spectrum of vasomotor abnormalities seen in patients with CMD. Vasotonic angina defined as diffuse epicardial coronary constriction, generally >_50% of the diameter of the lumen, confined to the distal segments of the coronary arteries and limiting the supply of blood flow to the myocardium, producing myocardial ischemia in the presence of normal smooth coronary arteries. (36)

A standard approach for vasoreactivity testing is intracoronary infusion of acetylcholine, at concentrations approximating 0.182, 1.82, and 18.2 mg/ml at 1 ml/min for 2 min using a mechanical pump. Alternative options to facilitate an easy implementation include manual infusion of 2, 20, 100, and 200 mg. When microvascular spasm occurs, coronary flow transiently decreases, while the patient generally experiences chest pain in association with ischemic changes on electrocardiography. Prompt recovery is typical, and nitrates can be administered if necessary. Epicardial coronary spasm is defined according to the COVADIS (Coronary Vasomotion Disorders International Study) criteria requiring reproduction of chest pain and ischemic electrocardiographic changes in association with ≥90% vasoconstriction. (6)

Acetylcholine could induce bradycardia, but safety is ensured by administration of half the dose (50 µm instead of 100 µm). Ergonovine may induce coronary vasospasm via serotonin receptors on vascular smooth muscle cells. Intracoronary ergonovine (20 to 60 mg) is an alternative to acetylcholine for the assessment of coronary vasospasm in some Asian countries. Nevertheless, Acetylcholine is useful for assessing macrovascular and microvascular function, is safer, and is more widely available. (37)

Selective intracoronary infusion of acetylcholine using a dedicated microcatheter may be preferred rather than infusing the acetylcholine through a guide catheter. The advantage of using a microcatheter is the subselective infusion of acetylcholine and, potentially, avoidance of pancoronary vasospasm. The disadvantage of this approach is the additional coronary instrumentation, related risks for vascular injury, and expense. (38)

7.- Role of Coronary microvascular disease in cardiomyopathies

In 1980, the World Health Organization defined cardiomyopathies as "heart muscle diseases of unknown cause" to distinguish cardiomyopathy from cardiac dysfunction due to known cardiovascular conditions such as hypertension, ischemic heart disease, or valvular disease. (39)

Cardiomyopathies are characterized by a disorder in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease sufficient to explain the observed myocardial abnormality. (40) CMD is present in various cardiomyopathies with different structural and functional mechanisms. (41)

7.1.- Coronary microvascular disease in Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is defined as an unexplained left ventricular (LV) hypertrophy The prevalence is approximately 1:500 in the general population. In some cases, the disease is inherited as an autosomal dominant trait. (42)

HCM with microvascular dysfunction and ischemia can be asymptomatic or show symptoms of angina, atypical chest pain, or dyspnea, symptoms of heart failure, syncope and sudden death due to ventricular arrhythmia. The identification of patients at risk for sudden death or progression to heart failure constitutes one of the main clinical concerns in HCM. The understanding of the impact of microcirculation in adverse events is a relevant issue, since both microvascular dysfunction and myocardial ischemia may be amenable to treatment. (43) A reduction in diastolic coronary vasodilator reserve was described in HCM patients in the absence of epicardial coronary stenosis, indicating microvascular dysfunction. (44) Otherwise, we know that when coronary flow reserve is measured during throughout the cardiac cycle, it reflects the influence of external compression forces during systole, and not only microvascular dysfunction. (45)

In most published studies, microvascular dysfunction appeared to be more pronounced in hypertrophied segments in patients with LV systolic dysfunction. This microvascular dysfunction is likely multifactorial, including reduced capillary density, vascular remodeling with arteriolar medial hypertrophy and

intimal hyperplasia, fibrosis, myocyte disarray, extravascular compression due to ventricular hypertrophy, diastolic dysfunction, and LV outflow tract (LVOT) obstruction. Intramural small coronary arteries abnormalities consist mainly in medial hypertrophy, intimal proliferation, perimysial and intra-arterial fibrosis, found in the interventricular septum (46) Beyond small vessel structural changes, functional dysfunction in coronary autoregulation has also been described, leading to blunted coronary vasodilator reserve and hypoperfusion during stress. (47)

The vessel wall remodeling impairs dilation and regulatory capacity, leading to an increment in microvascular resistance. Other architectural abnormalities in the surrounding space, including myocyte disarray and increased interstitial fibrosis, also contribute to reducing myocardial blood flow.(48) Apart from structural and functional abnormalities of the small vessels, the increased oxygen demand from the hypertrophied myocardium and the decrease in oxygen delivery as a consequence of diastolic dysfunction contribute to an imbalance between the oxygen requirement and supply, leading to further myocardial ischemia. (49) Extravascular compression of precapillary arteries during ventricular contraction produced a large backward compression wave, accounting for the retrograde coronary flow in systole. These changes were particularly evident in patients with hypertrophic cardiomyopathy with Left Ventricular Outflow Tract (LVOT) obstruction. (50)

A study by another group reported that HCM patients with identified sarcomere mutations have more severe microvascular dysfunction compared with genotype-negative patients, despite similar baseline features. Although this relationship has not been completely elucidated, there is a hypothesis that microvascular remodeling represents a maladaptive change secondary to increased left ventricular wall stress. (49) The repetitive episodes and chronic nature of ischemia due to microvascular dysfunction result in myocyte death and fibrotic replacement and consequent left ventricular remodeling with diastolic and, eventually, systolic dysfunction. (51) Finally, myocardial ischemia potentially has important clinical implications and was suggested to contribute to atrial and ventricular arrhythmia, sudden death, progressive left ventricular remodeling, and systolic dysfunction. (52)

7.2.- Coronary microvascular disease in Idiopathic Dilated Cardiomyopathy

Idiopathic dilated cardiomyopathy (IDCM) is a dilated cardiomyopathy defined as a cardiac disorder characterized by dilatation of the ventricular chambers, with impaired myocardial contractility. (53) IDCM is the third most common cause of heart failure after coronary artery disease and hypertension, and the most frequent form of primary myocardial disease. The clinical course of IDCM may be progressive, and about 50% of individuals are reported to die within 5 years of diagnosis, without transplantation. (54) The cause of death is mainly sudden death and pump failure. Histological examination of the hearts of patients with IDCM shows patchy interstitial fibrosis, degenerated cardiomyocytes and dilatation of the cardiac chambers as the main pathological derangements of this disease.

IDCM is characterized by an increase in ventricular chamber size, reduced contractility, and clinical features of congestive heart failure. Mitral valve regurgitation and arrhythmias are also common. (55)

Genetic abnormalities in IDCM alterations in about 25 loci and genes have now been identified and most of these are cardiomyocyte-specific or myocyte specific genes, including those encoding sarcomeric, structural and nuclear membrane proteins, or components of calcium metabolism. (56) The association between myocyte integrity and a severe reduction in myocardial blood flow, which predicts progressive heart failure and poor prognosis of cardiomyopathies, has been well established. The impaired vasodilator capacity is an independent predictor of subsequent cardiac events and is associated with an increased relative risk of death and further progression of heart failure. The restoration of adequate myocardial blood supply might be a promising therapeutic target in these patients. (57)

Many larger clinical trials provide evidence for the involvement of vascular disorders in IDCM include: differences in myocardial perfusion and perfusion reserve between IDCM patients and healthy individuals; direct association between myocardial perfusion and poor prognosis in IDCM; and defective vascularization associated with altered angiogenic and vasculogenic mechanisms in these patients. These data, however, do not indicate an irrefutable causal relationship between vascular dysfunction and the origin of the disease. These reported deficiencies could have an important role

in disease progression and might affect the prognosis. (58)

7.3.- Coronary microvascular disease in Infiltrative Cardiomyopathies

Infiltrative cardiomyopathies are characterized by the deposition of abnormal substances within the heart tissue, causing the ventricular walls to develop either diastolic dysfunction or, less commonly, as a late presentation, systolic dysfunction. (59) They show also a significant coronary microvascular remodeling (60) This broad term describes a family of both inherited and acquired forms of the disease. Amyloidosis and Anderson-Fabry disease are the two conditions most frequently associated with CMD. (61)

7.3.1.- Coronary microvascular disease in Amyloidosis

There are more than 30 recognized proteins that can deposit as amyloid and amyloidosis. There are four major subtypes of amyloidosis: AL (or primary), ATTR AA, Aß2M. AL (or primary) and ATTR types are the most common forms of cardiac amyloidosis, representing together the 98%. Amyloid vascular deposits are often observed in the AL-type in parallel with a marked interstitial deposition of circulating free light chains. (62) AL amyloid fibrils are cardiotoxic and increase the thickness of the ventricular wall, attributing the replacement of dead myocytes and the expansion of extracellular volume. The wall of the epicardial arteries, mainly the adventitia, may be infiltrated, although significant luminal obstruction rarely occurs. In type AL, the intramural microvasculature is altered in up to 90% of patients. (63) Amyloid deposition first occurs in the tunica media progressing towards the adventitia and the intima until total obstruction occurs. Severe microvascular obstruction leads to focal ischemia and replacement fibrosis aggravating LV dysfunction. (64) This mechanism increases oxidative stress. Altogether, the pathogenic mechanisms of CMD in amyloidosis include structural changes of microvasculature, functional abnormalities and extravascular factors. Dorbala et al. quantified Myocardial Blood Flow (MBF), CFR, and minimal coronary vascular resistance in a cohort of symptomatic patients with amyloidosis and without obstructive atherosclerosis, and reported significantly reduced MBF both at rest and during hyperemia with a lower CFR, paralleled by an increase of minimal coronary resistance irrespective of the LV mass or amyloidosis subtype. (41)

7.3.2.- Coronary microvascular disease in Anderson-Fabry disease

Anderson-Fabry disease is caused by an X-linked inherited deficiency of lysosomal a-galactosidase A. The glycosphingolipid deposition determines multiorgan damage with renal, cardiac and cerebrovascular involvement. (65) Globotriaosylceramide deposits are present in myocytes, conduction tissue, vascular endothelium, smooth muscle cells and valve tissue (66) The myocardium shows a series of changes, above all myocyte hypertrophy. Progressive myocardial scarring and deterioration of LV function occur in a significant percentage of patients. (67) The proliferation of smooth muscle and endothelial cells narrowing intramural arteries all contribute to raising coronary vascular resistance and increase myocardial oxygen demand, generating ischemia. (68)

7.4.- Coronary microvascular disease in Sarcoidosis Cardiomyopathy

The most common site of infiltration of sarcoid granulomas is the LV free wall followed by the septum, right ventricle, and atria. The granulomatous inflammation damages the myocytes and patchy replacement fibrosis appears as soon as the myocyte integrity is affected, whilst epicardial arteries does not show structural changes. (69) Systemic inflammation leads to impairment of microvascular function and can be attributed to replacement fibrosis. There are recent studies quantifying MBF and CFR point at a functional CMD attributable to the adverse effects of inflammatory cytokines, TNF-a, and oxidative species in endothelium-mediated CMD. (70) The impairment of vasodilatory capacity can be a warning of the lethal progression of the cardiac involvement and seems to purport a prognostic value. (71)

8.- Conclusion

CMD represents a fusion of functional and structural abnormalities in the coronary microcirculation, with implications in the prognosis of patients, so evaluation should be considered in patients with symptoms of angina and without obstructive coronary artery disease. Likewise, CMD plays a leading role in cardiomyopathy, contributing to its progression and prognosis. DCM constitutes a challenge and, in the future, it could constitute a new therapeutic target, although more studies in this field will be necessary.

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