Current perspectives

Coronary microvascular dysfunction and ischemia in hypertrophic cardiomyopathy. Mechanisms and clinical consequences

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Symptoms and signs of myocardial ischemia are often found in patients with hypertrophic cardiomyopathy (HCM) despite angiographically normal coronary arteries. Myocardial ischemia is deemed responsible for some of the lethal complications of HCM including ventricular arrhythmias, sudden death, progressive left ventricular remodeling, and systolic dysfunction. In the past decade, a number of studies using positron emission tomography have demonstrated severe impairment of the vasodilator response to dipyridamole in the majority of HCM patients, not only in the hypertrophied septum but also in the non-hypertrophied left ventricular free wall. In the absence of coronary stenoses, this finding is indicative of diffuse microvascular dysfunction, in line with the autoptic evidence of widespread abnormalities of the intramural coronary arterioles. In turn, microvascular dysfunction represents a very likely substrate for recurrent ischemia. This may account for the fact that microvascular dysfunction has recently been shown to represent an early and powerful predictor of an unfavorable outcome in HCM. The aim of this article is to provide a concise overview of the available evidence of microvascular dysfunction and ischemia in HCM, and to speculate on the potential implications for management.

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Hypertrophic cardiomyopathy (HCM) is a genetically determined disease with a wide range of clinical manifestations and pathophysiological substrates[1-13]. HCM is associated with significant mortality due to sudden and unexpected cardiac death[1-4,8,11]. Moreover, in about one third of patients the clinical course is progressive and disabling, leading to chronic limiting symptoms and complications such as atrial fibrillation and stroke and ultimately causing heart failure-related death[1,6,7,10,11].

Symptoms and signs of myocardial ischemia are often found in patients with HCM despite angiographically normal coronary arteries. Myocardial ischemia is responsible for some of the lethal complications of HCM including ventricular arrhythmias, sudden death, progressive left ventricular (LV) remodeling and systolic dysfunction[14-22]. In the past decade, a number of studies in HCM patients have demonstrated marked impairment of the vasodilator response to dipyridamole, and hence of the coronary vasodilator reserve (CVR), not only in the hypertrophied septum, but also in the non-hypertrophied LV free wall. In the absence of coronary stenoses, this finding is indicative of diffuse microvascular dysfunction, in line with the autoptic evidence of widespread remodeling and narrowing of the intramural coronary arterioles[16,17].

Under normal circumstances, the small coronary arterioles < 450 μm in diameter are the principal determinants of coronary vascular resistance[23-25]. According to Chilian et al.[26] a 50% drop in the perfusion pressure, relative to the aortic, may be observed in vessels between 70 and 440 μm in diameter, which is consistent with 40-50% of the total coronary vascular resistance being located in pre-arterioles > 100 μm. These vessels receive autonomic innervation and their diameter may be altered by stimulation of these nerves[27]. Nearly all of the remaining resistance lies in vessels < 100 μm in diameter which are also those responsible for the autoregulation of myocardial blood flow (MBF)[25]. In addition to intravascular resistances, myocardial perfusion is also influenced by extravascular

forces, particularly due to the intramyocardial pressure which is generated throughout the contractile cycle[28]. The intramyocardial pressure is maximal during systole and in the subendocardial layers where it exceeds the aortic pressure[29].

Although direct visualization of the coronary microcirculation has been achieved in experimental animal preparations using intravital microscopy and stroboscopic epi-illumination of the heart[30,31], there is no technique which enables the direct visualization of the human coronary microcirculation *in vivo*. The resistive vessels in the coronary circulation are not generally visible on angiography and are too small to be amenable to selective catheterization. Therefore, the study of the human coronary microcirculation is indirect and relies on the assessment of parameters which reflect its functional status, such as the coronary blood flow. This is principally regulated by the coronary microcirculation and thus its measurement provides an index of microvascular function[32].

With the development of quantitative MBF measurement using positron emission tomography (PET), it has been possible to challenge the function of the coronary microvasculature by measuring CVR, calculated as the ratio of the near maximal flow during pharmacologically-induced coronary vasodilation to baseline flow. PET studies in healthy human volunteers have established that CVR in response to intravenous dipyridamole or adenosine is 3.5 to 4.0. The measurement of CVR is useful for the assessment of the functional significance of coronary stenoses in patients with coronary artery disease. In addition, PET is particularly helpful in those circumstances where CVR is diffusely (and not regionally) blunted, e.g. HCM or hypertensive heart disease, due to a widespread abnormality of the coronary microcirculation[33].

Following the recent demonstration of its prognostic role in HCM[34,35], clinical interest in microvascular dysfunction has been renewed. The aim of this article is to provide a concise overview of the available evidence of microvascular dysfunction and ischemia in HCM, and to speculate on the potential implications for management.

An early report of myocardial ischemia due to small vessel disease

In 1976, Bartoloni Saint Omer et al.[36] described the sudden death of an 8-year-old child with HCM, previously asymptomatic, who collapsed whilst at rest. *Post-mortem* examination of the heart revealed massive asymmetrical hypertrophy of the interventricular septum (up to 30 mm in thickness); within the septum there was evidence of a recent, large myocardial infarction, in the absence of epicardial coronary artery disease. At the microscopic level, the authors described profound disarray of the myocardial fibers, fibrosis, and marked structural abnormalities of the intramural coronary arteries. The latter were characterized by intimal thickening, prevalently due to an abundance of disorganized elastic fibers, causing deformation and irregular narrowing of the vessel lumen (Fig. 1). The authors concluded that the abnormalities of the intramural vessels justified a critical, chronic impairment of myocardial perfusion in the interventricular septum, potentially exposing the patient to repetitive myocardial ischemia. A recent re-examination of the case suggests that myocardial bridging and compression of the left anterior descending coronary artery may also have been instrumental in precipitating diffuse myocardial ischemia of the interventricular septum[37].

The report by Bartoloni Saint Omer et al.[36] represents the earliest report describing myocardial infarction in the context of small vessel disease in HCM, and has subsequently been confirmed and expanded by numerous studies[14-17,20]. At present, small vessel disease is considered an established feature of HCM, although its pathogenesis remains unclear[1,14-22].

Clinical manifestations of myocardial ischemia in hypertrophic cardiomyopathy

Myocardial ischemia may be clinically silent in many patients with HCM[38]. Conversely, chest pain is a frequent complaint, but is not a reliable marker of ischemia[18,21,39]. Typical angina related to effort or meals is relatively rare, and patients more often complain of prolonged episodes of atypical chest pain, usually occurring at rest, or of paroxysmal dyspnea[18,21,39,40]. In the seminal study published by Braunwald et al.[2] in 1964, 39% of HCM patients complained of chest pain. In more recent reports from tertiary referral centers and

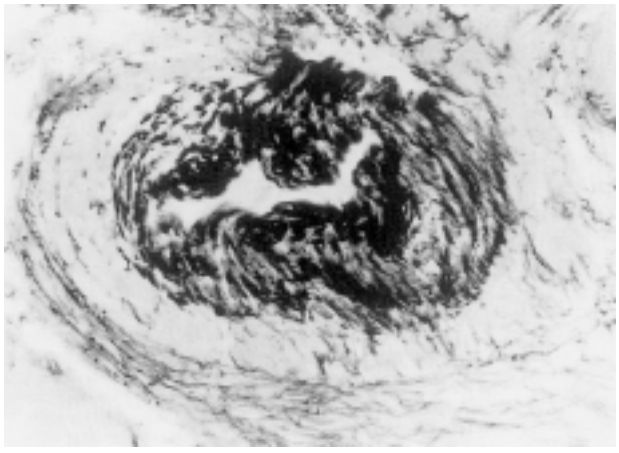

Figure 1. *Post-mortem examination of an 8-year-old child with hypertrophic cardiomyopathy who died suddenly due to myocardial infarction (Weigert stain, ×320). Microscopic examination of the interventricular septum showed marked intimal thickening of the intramural coronary arteries, largely due to an abundance of disorganized elastic fibers. Reproduced from Bartoloni Saint Omer et al.[36], with permission.*

community-based institutions, the prevalence of chest pain was found to be similar or higher[3,6,7,18,21].

Angina in HCM patients is generally believed to be due to impairment of the coronary microcirculation, since epicardial arteries have a normal appearance at angiography[16-19]. When present, however, epicardial coronary artery disease is associated with a greater risk in HCM patients as compared with the general population[41]. Thus, the possibility of superimposed atherosclerotic coronary artery disease should always be considered in adult patients with HCM.

Finally, as for the young patient described previously, ventricular arrhythmias and sudden death may represent the first clinical manifestation of ischemia[36]. A direct causal link between acute myocardial ischemia and life-threatening arrhythmias has occasionally been demonstrated[42], but is very difficult to establish in most patients who present with sudden death[16].

Instrumental evidence of ischemia

Over the years, a number of techniques have been employed to assess the occurrence of myocardial ischemia in patients with HCM. Typical ST-T changes on the ECG have been documented during Holter ECG, exercise testing, rapid atrial pacing, and following the onset of atrial fibrillation with a rapid ventricular response rate[15,18-21,42]. ECG signs of myocardial ischemia have also been observed in HCM patients undergoing stress echocardiography with dipyridamole[43]. Unfortunately, the ECG changes are neither a sensitive nor a specific marker of ischemia, due to marked basal ST-T alterations secondary to LV hypertrophy in most patients[39]. Likewise, LV wall motion abnormalities elicited by dobutamine infusion during stress echocardiography are suggestive but not specific for myocardial ischemia, and may be accounted for by other pathophysiological mechanisms[44].

Elegant catheterization studies have provided direct evidence of myocardial ischemia in HCM patients by documenting lactate production in the coronary sinus during atrial pacing[15,19,20]. In a classic work by Cannon et al.[19], 14 out of 20 patients with HCM and normal coronary arteries developed angina associated with lactate production and a decreased great cardiac vein flow during incremental pacing up to 150 b/min. This vessel is the satellite vein of the left anterior descending coronary artery, and drains blood from the antero-septal wall – usually the most hypertrophied myocardial region in HCM. Therefore, the authors concluded that, as in secondary hypertrophy, ischemia was probably a direct consequence of microvascular dysfunction within the hypertrophied myocardium due to increased intraventricular pressures and abnormal myocellular-capillary relationships[19]. Subsequent studies have shown that the degree of flow impairment is indeed related to the magnitude of hypertrophy[45,46]; however, microvascular dysfunction is not confined to the hypertrophied regions of the myocardium, but is rather a widespread feature of HCM hearts, pointing to a primary involvement of the small vessels in the disease process[47].

Conventional scintigraphic techniques have been repeatedly employed in HCM patients[15,38,39,48-54]. Defects during single-photon emission computed tomography (SPECT) thallium-201 myocardial perfusion imaging are a common finding[15,38,49,50]. Fixed defects are associated with increased LV cavity dimensions, reduced systolic function and lower peak oxygen consumption, and are usually interpreted as areas of primary fibrosis or scarring[38,39]. Reversible defects induced by exercise are more often observed in patients with a preserved systolic function[38,39,54], and are interpreted as markers of myocardial ischemia because of a high concordance with metabolic evidence of ischemia induced by pacing or by infusion of sympathomimetic drugs[38].

Unfortunately, reversible thallium-201 defects in HCM patients correlate poorly with symptoms such as angina or dyspnea. This discrepancy is due to intrinsic limitations of the technique[39]. For example, because thallium-201 scintigraphy does not allow absolute quantification of flow, diffuse blunting of flow may be missed even in patients with severely impaired perfusion[53]. As a consequence, SPECT is not routinely employed in the assessment of HCM patients.

Evidence of coronary microvascular dysfunction by positron emission tomography

PET allows non-invasive assessment of MBF in basal conditions and in conditions of near-maximal vasodilation following dipyridamole infusion, by injection of tracers such as ^{13}N-labeled ammonia or ^{15}O-labeled water[47,54-59]. Besides having a spatial resolution superior to that of SPECT, PET allows the quantification of the regional MBF and CVR. Thus, PET allows the detection of a homogeneously reduced CVR when a SPECT scan may be completely normal[39]. Moreover, with a spatial resolution of ~4-5 mm (full width at half maximum), PET allows the assessment of the transmural distribution of flow and the calculation of the subendocardial to subepicardial flow ratio[55-58].

An inadequate increase in MBF following the intravenous administration of dipyridamole has been documented in the majority of HCM patients studied with PET (Figs. 2 and 3)[47,54-59]. On average, while resting MBF is not dissimilar from that of normal controls, the increase in MBF after dipyridamole infusion is significantly blunted, and may even be reduced below resting values, suggesting absolute hypoperfusion[47]. Of note, the dipyridamole flow is markedly impaired not only in the hypertrophied septum, but also in the non-hypertrophied LV free wall[47]. In the absence of epicardial coro-

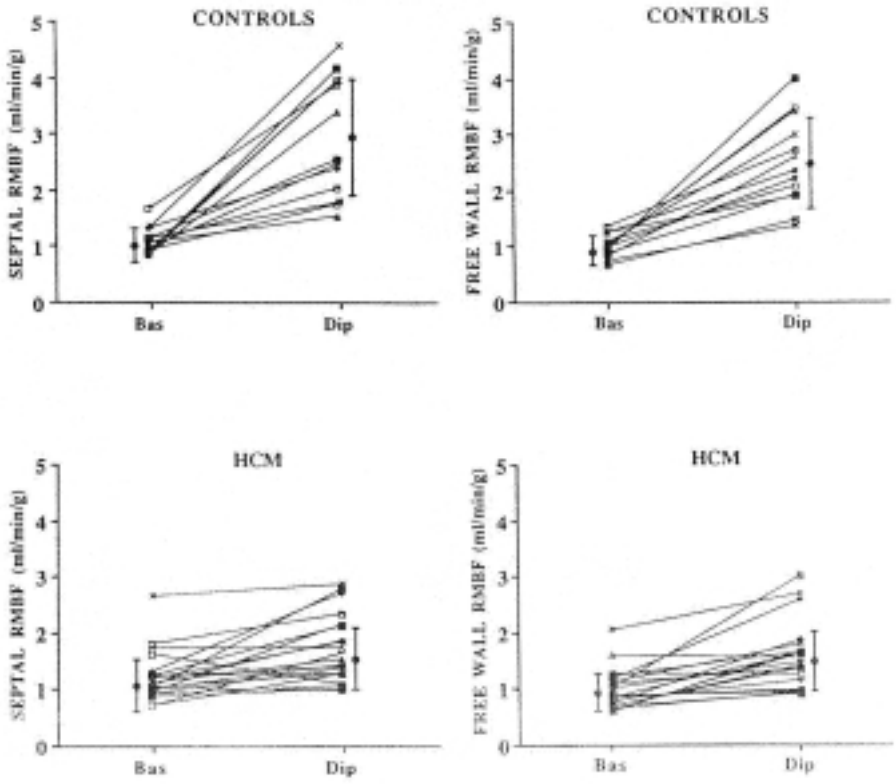

Figure 2. *Individual values of septal and free wall myocardial blood flow (RMBF) at baseline (Bas) and after dipyridamole (Dip) infusion in control subjects* (top panels) *and in patients with hypertrophic cardiomyopathy (HCM)* (bottom panels). *After Dip, RMBF in patients with HCM increases significantly less than in control subjects, both in the hypertrophied septum and in the non-hypertrophied left ventricular free wall. Reproduced from Camici et al.[47], with permission.*

nary artery disease, these findings suggest a primary and diffuse impairment of the coronary microcirculation in HCM: indeed, the abnormalities of the intramural coronary arteries described *post-mortem* are also diffuse, and not limited to the most hypertrophied regions of the left ventricle[16,17]. Finally, PET was able to show that the greatest extent of microvascular impairment tends to occur at the subendocardial level. Indeed, HCM patients with marked LV hypertrophy (> 25 mm) showed selective subendocardial hypoperfusion following dipyridamole infusion, defined as a subendocardial to subepicardial MBF ratio < 0.8[55-58].

Relevance of microvascular dysfunction to myocardial ischemia

In the early reports, the pathophysiological explanation of ischemia in HCM patients rested on the inadequate perfusion of markedly hypertrophic regions of the myocardium and on the elevated intraventricular pressures due to outflow obstruction, as in aortic stenosis[19]. However, it is now well established that even individuals with mild hypertrophy and no obstruction may suffer from chest pain and develop evidence of myocardial ischemia, pointing to a wider range of pathogenetic mechanisms[15,39]. Although the genesis of ischemia in HCM is still poorly understood, several pathophysiological features have been identified which may account for chronic myocardial hypoperfusion (Fig. 4). Among these, microvascular dysfunction caused by structural and functional intramural vessel abnormalities is the most probable cause of diffuse blunting of CVR[16,17], whereas other contributing factors, such as reduced capillary density and increased extravascular compressive forces, are probably confined to the most hypertrophied regions of the myocardium[45,46]. Moreover, in patients with outflow obstruction or severe diastolic dysfunction, pathological increases in the intracavitary pressures and wall stress probably play a pivotal role in the genesis subendocardial hypoperfusion[19].

Long-term, microvascular dysfunction and a blunted CVR are thought to set the stage for myocardial ischemia and necrosis by reducing the likelihood of adequate perfusion in the face of increasing demands[34,47]. By intervening upon such an unfavorable substrate, several triggers, such as exercise, arrhythmias and intraventricular gradients, may precipitate ischemia by augmenting oxygen requirements (Fig. 4). For example, myocardial ischemia probably explains the ominous effects of atrial fibrillation with a rapid ventricu-

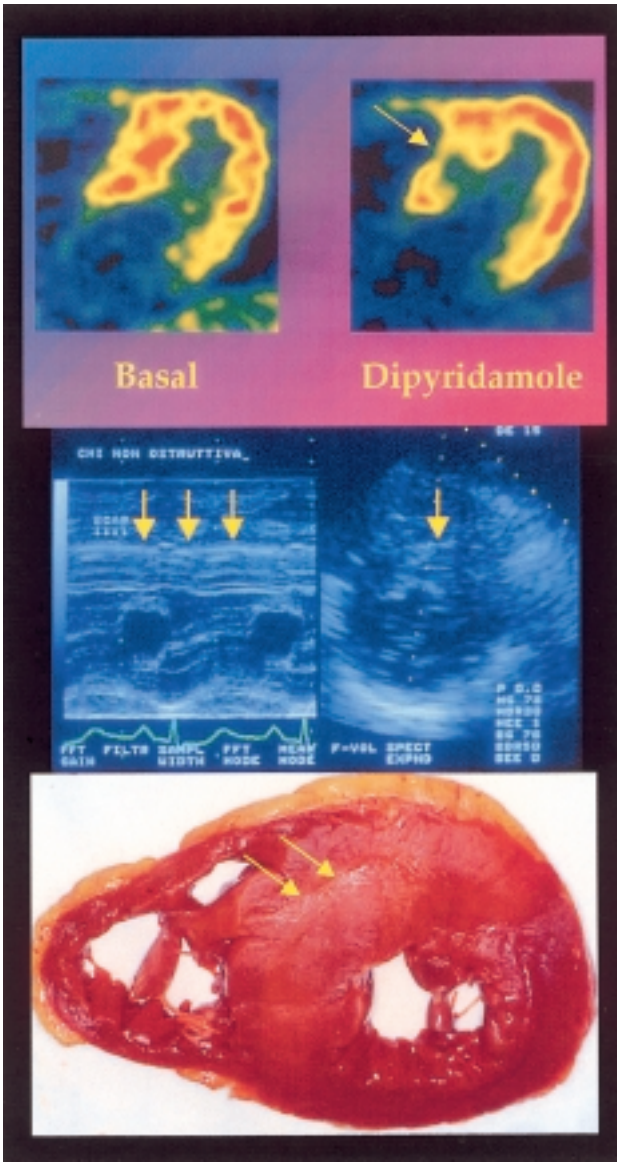

Figure 3. *Septal hypoperfusion and scarring in a male patient with non-obstructive hypertrophic cardiomyopathy.* Top panel: *positron emission tomography scan (at age 43) showing myocardial perfusion at basal conditions and following dipyridamole infusion. After dipyridamole, a well-defined area of hypoperfusion is evident in the interventricular septum* (arrow). Middle panel: *echocardiographic parasternal short-axis view (at age 43), showing a hypertrophic, structurally irregular interventricular septum; the hyperechogeneic area within the septal wall was suggestive of intramyocardial fibrosis and interpreted as scarring* (arrows). Bottom panel: *following the death of the patient at 46 years of age due to progressive heart failure, autoptic examination of the heart documented the presence of a translucent area of replacement fibrosis secondary to myocardial ischemia within the hypertrophied anterior septum* (arrows).

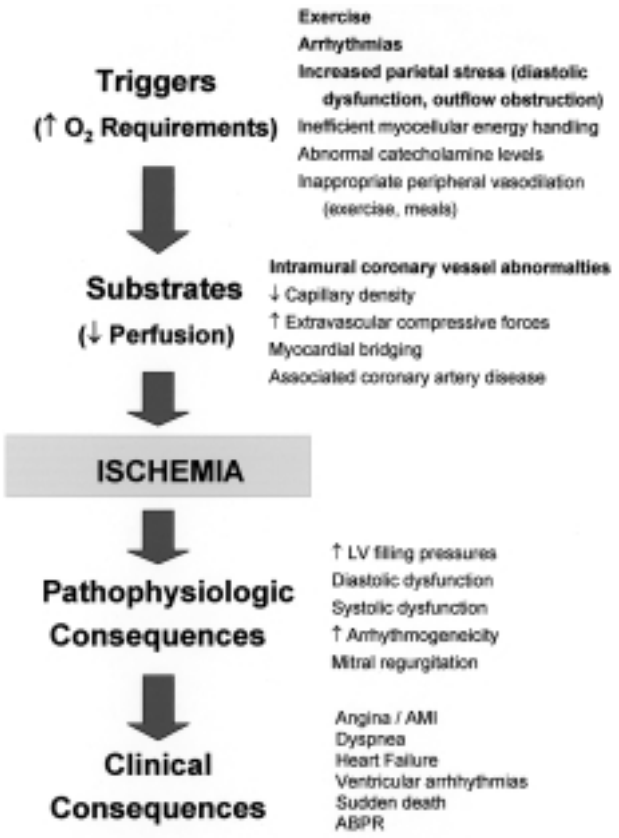

Figure 4. *Pathophysiological pathways leading to the clinical manifestations of ischemia in patients with hypertrophic cardiomyopathy. ABPR = abnormal blood pressure response; AMI = acute myocardial infarction; LV = left ventricular.*

lar response[12,42], as well as the occurrence and adverse prognostic implications of an abnormal blood pressure response to exercise in patients with HCM[60-63].

Microvascular dysfunction and outcome

Despite a wealth of studies dedicated to the characterization of microvascular function and ischemia in HCM over the last two decades, the impact of microvascular dysfunction on prognosis has only very recently been described, by our group[34]. We reported on the long-term outcome of 51 HCM patients, all in NYHA functional class I or II, prospectively followed after the initial measurement of resting and dipyridamole MBF by means of PET. In agreement with previous studies, dipyridamole MBF was severely blunted in HCM patients, as compared to normal controls (1.50 ± 0.69 vs 2.71 ± 0.94 ml/g/min, $p < 0.001$), with comparable degree of impairment in the interventricular septum and the LV free wall.

During an average follow-up > 8 years, 31% of the patients died or presented with severe clinical deterioration (a combined endpoint including cardiac death, progression to NYHA functional class III-IV, or life-threatening ventricular arrhythmias requiring an implantable defibrillator): each of these endpoints was significantly related to the degree of dipyridamole MBF impairment (Fig. 5). At age-adjusted multivariate analysis, a low dipyridamole MBF was the most powerful independent predictor of outcome in our cohort, with a 9.6 times increased risk of cardiovascular mortality for patients in the lowest tertile (i.e. with a dipyridamole flow ≤ 1.1 ml/g/min). Specifically, all the 4 heart failure-related deaths and 3 of 5 sudden deaths oc-

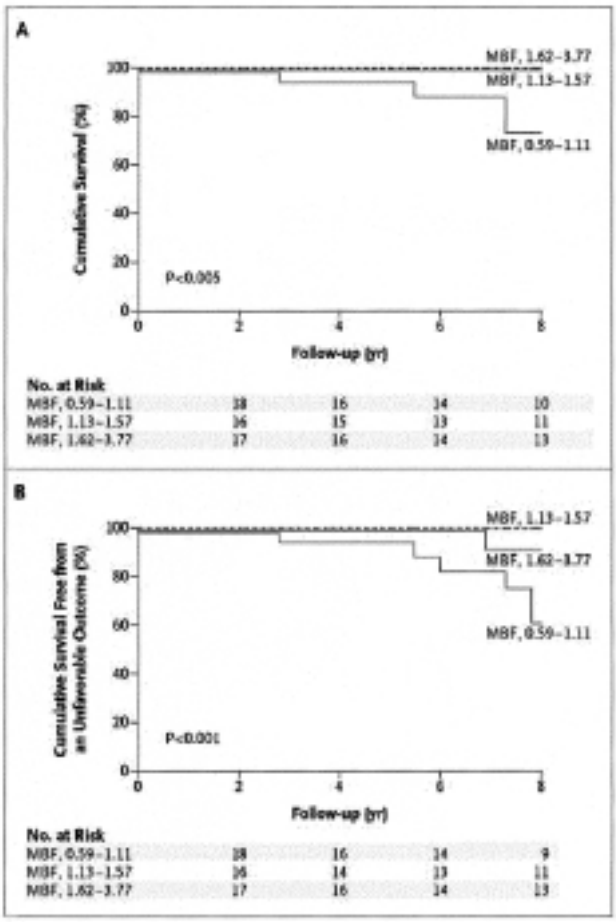

Figure 5. *Myocardial blood flow (MBF) values after dipyridamole infusion and long-term prognosis. Patients were divided into three equal groups according to their MBF after dipyridamole infusion.* Panel A *shows the overall cumulative survival, and* panel B *the cumulative survival free from an unfavorable outcome (a combined endpoint including cardiac death, progression to NYHA functional class III-IV, or life-threatening ventricular arrhythmias requiring an implantable defibrillator). Reproduced from Cecchi et al.[34], with permission.*

curred among the 18 patients in the lowest tertile of dipyridamole flow[34].

It is noteworthy that at the time of the PET scan none of the patients had severe symptoms, and only a few would have been considered at high risk on the basis of the established indicators of outcome[1,8]. Nevertheless, substantial microvascular dysfunction could already be demonstrated in most of those patients who subsequently deteriorated or died, several years before their clinical progression[34]. These findings have intriguing implications, in that PET evaluation of myocardial flow may significantly improve risk stratification and allow the implementation of preventive measures in clinically stable patients with HCM.

Implications for other diseases

Diffuse coronary microvascular dysfunction causing impairment of the CVR has been documented in a variety of cardiac conditions other than HCM[64-69]. Patients with hypertension, aortic stenosis and dilated cardiomyopathy may all exhibit, in addition to a reduced CVR, an impaired vasodilator response to dipyridamole or adenosine[64-68]. Impaired microvascular function may be demonstrated in hypertensive patients even before the development of myocardial hypertrophy[66], and in patients with dilated cardiomyopathy before any clinical evidence of heart failure[68]. Thus, microvascular dysfunction appears to intervene early in the course of these diseases, often before they are clinically overt.

Whether and to what extent microvascular dysfunction is relevant to outcome in cardiac conditions other than HCM remains to be seen. However, an impaired dipyridamole MBF has recently been shown to predict a poor prognosis in patients with idiopathic dilated cardiomyopathy[68]. Thus, the hypothesis that microvascular dysfunction may represent a common substrate of progression for several diseases appears plausible, and may have implications for the treatment of different cardiomyopathies[69].

Implications for the management of hypertrophic cardiomyopathy

At present, no specific treatment has shown long-term benefit in HCM patients with microvascular dysfunction. Treatment with verapamil, despite failure to increase the vasodilator response to dipyridamole, may produce a more physiological redistribution of the transmural MBF and increase subendocardial perfusion[58]. Recent studies on the no-reflow phenomenon following myocardial infarction have confirmed a clinically relevant vasodilator capacity of verapamil on the coronary microcirculation[23]. Moreover, verapamil has been shown to improve myocardial perfusion, possibly by ameliorating the coronary microvascular function in hypertensive patients[70]. In clinical practice, both verapamil and beta-blockers are known to improve silent ischemia, chest pain, and breathlessness in HCM[71-74], and although this may be largely due to a reduction in heart rate and oxygen consumption, a beneficial effect on the microcirculatory function is also possible. ACE-inhibitors have been shown to improve transmural myocardial perfusion and restore impaired subendocardial flow in a canine model of dilated cardiomyopathy, by virtue of a nitric oxide-dependent mechanism[75]. In a small pilot study, ACE-inhibitors reversed small vessel changes, improved endothelial function and reduced periarteriolar fibrosis in hypertensive patients[76]. On the basis of these preliminary but promising studies, the possibility that pharmacological treatment may positively modify the coronary microvascular function in patients with HCM merits further investigation in the near future.

A final consideration regards the role of outflow obstruction. Recently, in a large multicenter population

from Italy and the United States, patients with obstructive HCM have been shown to have a significantly worse outcome than non-obstructive patients[9]. Although related to a number of pathophysiological factors, the clinical impact of obstruction is probably also mediated by ischemia, particularly at the subendocardial level[77]. Conversely, the well-known clinical benefits of surgical or percutaneous relief of the obstruction may be partly mediated by a reduction in the intraventricular wall stress and subendocardial ischemia[77]. Thus, interventions aimed at relieving outflow obstruction may represent an important option for the amelioration of microvascular function in HCM, and should be considered early in obstructive patients with evidence of myocardial ischemia. To this regard, a large multicenter registry has recently demonstrated for the first time that surgical LV myotomy-myectomy has a strikingly protective effect on the long-term survival of patients with obstructive HCM, as compared to conservative management[78].

Conclusions

Coronary microvascular dysfunction is a common feature in HCM, representing the most likely substrate of myocardial ischemia and a strong predictor of long-term outcome. Recent evidence suggests that microvascular dysfunction might be favorably modulated by pharmacological treatment, with important and far-reaching clinical implications involving conditions such as hypertensive heart disease and dilated cardiomyopathy.

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