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Review article

## The coronary circulation and blood flow in left ventricular hypertrophy

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## ABSTRACT

Two distinct types of left ventricular hypertrophy (LVH) have been described: the so called “physiologic” hypertrophy, which is normally found in professional athletes, and “pathologic” LVH which is found in patients with inherited heart muscle disease such as hypertrophic cardiomyopathy (HCM) or patients with cardiac and systemic diseases characterized by pressure or volume overload. Patients with pathologic LVH have often symptoms and signs suggestive of myocardial ischemia despite normal coronary angiograms. Under these circumstances ischemia is due to coronary microvascular dysfunction (CMD). The abnormalities of the coronary microcirculation may be unrelated to the degree of LVH and cause a reduction in maximum myocardial blood flow which, in the absence of epicardial stenoses, is suggestive of CMD. There is no technique that enables direct visualization of coronary microcirculation in vivo in humans. Therefore, its assessment relies on the measurement of parameters which reflect its functional status, such as myocardial blood flow and coronary flow reserve which is an integrated measure of flow through both the large epicardial coronary arteries and the microcirculation. In this review article we discuss the pathophysiological mechanisms responsible for CMD in patients with primary and secondary LVH and how the recognition of this phenomenon is providing new important information on patient stratification and prognosis. Finally, we discuss how assessment of CMD may be used as a valuable surrogate marker to test the efficacy of old and new drugs. This article is part of a Special Issue entitled ‘Coronary Blood Flow SI’.

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## 1. Introduction

The following definition of left ventricular hypertrophy (LVH) can be found on Wikipedia: LVH is the thickening of the myocardium (muscle) of the left ventricle of the heart. The etymology (from Greek πέρ “excess” + τροφή “nourishment”) derives from the observation that generally hypertrophy is a reaction to aerobic exercise and

strength training, albeit LVH is most frequently referred to as a pathological reaction to cardiovascular disease.

In fact, two distinct types of LVH have been described: the so called “physiologic” hypertrophy, which is normally found in professional athletes, and “pathologic” LVH which is found in patients with genetic cardiomyopathies such as hypertrophic cardiomyopathy (HCM) or patients with cardiac and systemic diseases characterized by pressure or volume overload. In both cases demonstration of myocardial thickening has been considered the hallmark of LVH and regression of wall thickness is the main goal of treatment. Left ventricular mass in athletes is comparable to LVH seen in patients

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with essential hypertension of mild to marked severity [1]. In athletes, however, the growth of muscular and non-muscular compartments of the heart is proportionate to each other and tissue homogeneity is preserved. On the contrary, in patients with pathologic LVH, tissue homogeneity gives way to heterogeneity, as a disproportionate involvement of non-cardiomyocyte cells accounts for pathologic remodeling of tissue structure [2].

The normal myocardium is composed of a variety of cells: cardiomyocyte and non-cardiomyocyte, which include endothelial and vascular smooth muscle cells and fibroblasts. Cardiomyocyte hypertrophy is but one of many structural alterations in LVH. Fibroblasts undergo hyperplasia and conversion to myofibroblasts, along with hypertrophy of vascular smooth muscle cells. Non-cellular elements are central to myocardial remodeling in LVH and include expansion of interstitial and perivascular collagen that makes up the extracellular matrix [3]. Changes in relative intramyocardial capillary density and arteriolar thickening are also characteristic of the hypertrophied heart [4].

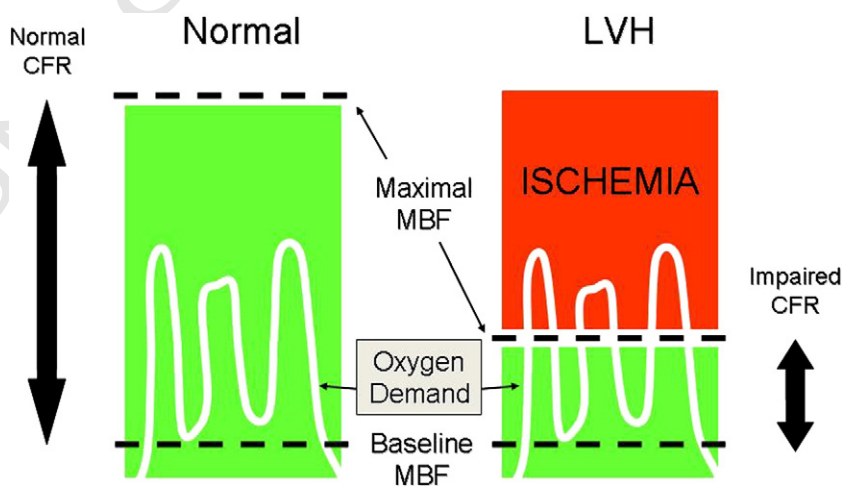
Patients with pathologic LVH have often symptoms and signs suggestive of myocardial ischemia despite normal coronary angiograms [5]. Under these circumstances ischemia is due to coronary microvascular dysfunction (CMD). The abnormalities of the coronary microcirculation may be unrelated to the degree of LVH and cause a reduction in maximum myocardial blood flow which, in the absence of epicardial stenoses, is suggestive of CMD [6]. HCM is also characterized by CMD which is unrelated to the extent of regional LVH and is an independent predictor of prognosis [7,8]. Coronary resistance is distributed in series along the vascular bed and more than 90% of total resistance resides in vessels less than 300  $\mu\text{m}$  diameter, autoregulatory adjustments are mainly mediated by arterioles less than 150  $\mu\text{m}$  diameter [9]. Total resistance is determined by two phenomena: 1 – the caliber of the resistance vessels (vascular resistance); 2 – the deformation of these vessels by the mechanical motion of the beating heart (extravascular resistance) [9,10]. CMD has been demonstrated in patients with HCM and those with LVH secondary to systemic hypertension. In these two patient groups CMD is primarily sustained by an increase in the vascular component of resistance due to anatomical changes in the intramural coronary arterioles (Fig. 1). In both cases there is massive medial hypertrophy with a resultant increase in the wall/lumen ratio. These changes, however, have not been observed in the intramural coronary vessels of patients with LVH due to aortic stenosis, implicating extravascular mechanisms as primarily responsible for CMD in these patients [5]. Other important factors that contribute to myocardial ischemia in LVH and

increase the vulnerability of the hypertrophied heart, include increased oxygen demand, contractile inefficiency that can compromise the energetics of the myocyte and contribute to diastolic dysfunction further impairing coronary blood flow which normally occurs almost entirely ( $\geq 90\%$ ) in this phase of the cardiac cycle.

## 2. Myocardial blood flow and coronary microvascular dysfunction

There is no technique that enables direct visualization of coronary microcirculation in vivo in humans. Therefore, its assessment relies on the measurement of parameters which reflect its functional status, such as myocardial blood flow (MBF) and coronary flow reserve (CFR). CFR is an integrated measure of flow through both the large epicardial coronary arteries and the microcirculation [11]. In the absence of obstructive stenoses on the epicardial arteries, a reduced CFR is a marker of CMD. Although a single cutoff value of CFR (e.g.  $\leq 2.0$ ) below which microvascular function is deemed abnormal would be useful clinically, it must be noted that, in normal humans, CFR varies according to age and gender [12]. Therefore, it is essential to compare CFR data in patients with those obtained in age- and sex-matched normal subjects. Adenosine is the vasodilator most widely used to assess hyperemic blood flow because of its safety profile. However, some limitations must be taken into consideration. When administered systemically hypotension and reflex tachycardia alter the coronary blood flow response and coronary vasomotor tone mediated by  $\alpha$ -receptors is not fully eliminated resulting in a “near” maximal vasodilation [13]. Resting myocardial blood flow is linearly related to cardiac work. Therefore, when comparing different patients in the clinical setting it is important to correct resting myocardial blood flow for the main determinants of external cardiac workload, i.e. as blood pressure and heart rate (rate-pressure product; RPP). A corrected CFR can then be calculated by dividing hyperemic flow by RPP-corrected resting MBF [14]. More complex is the assessment of CMD in territories subtended by stenotic coronary arteries where the evaluation of microvascular function depends on the clinical context and  $\alpha$ -adrenergic vasoconstriction is enhanced by atherosclerosis [15].

As proposed by Camici and Crea [5], CMD can be classified in the following four groups: 1) CMD occurring in the absence of obstructive epicardial coronary artery disease and myocardial diseases (type A); 2) CMD occurring in the context of cardiomyopathies (type B); 3) CMD occurring in the presence of obstructive epicardial coronary



**Fig. 1.** In normal individuals, the coronary flow reserve (CFR, i.e. the ability of the coronary microvasculature to increase myocardial blood flow – MBF) guarantees adequate blood supply to meet varying demands of the myocardium in different physiologic situations. In patients with LVH, coronary flow reserve is impaired due to different mechanisms, and exposes the myocardium to recurrent microvascular ischemia when increased oxygen demand cannot be adequately met, such as during exercise or sustained arrhythmias.

t1.1 **Table 1**  
 Pathogenetic mechanisms of coronary microvascular dysfunction.  
 t1.2 Modified from ref [5].

t1.3	<i>Structural alterations</i>	
t1.4	Luminal obstruction	Microembolization
t1.5	Vascular wall infiltration	Infiltrative heart disease
t1.6	Vascular remodeling	HCM, systemic hypertension
t1.7	Dilutional vascular rarefaction	Aortic stenosis and systemic hypertension
t1.8	Perivascular fibrosis	Aortic stenosis and systemic hypertension
t1.9	<i>Functional alterations</i>	
t1.10	Endothelial dysfunction	CV risk factors smoking, hyperlipidemia, diabetes etc.
t1.12	Smooth muscle cell dysfunction	HCM, systemic hypertension
t1.13	Autonomic nervous system dysfunction	following coronary re-canalization
t1.14	<i>Extravascular alterations</i>	
t1.16	Extramural compression	Aortic stenosis, HCM, systemic hypertension
t1.17	Reduction in diastolic perfusion time	Aortic stenosis

153 artery disease (type C); 4) iatrogenic CMD (type D). Pathogenetic  
 154 classification of microvascular dysfunction is illustrated in Table 1 [5].

### 155 3. Myocardial blood flow measured by positron emission tomography

156 Positron emission tomography (PET) has been shown to allow  
 157 non-invasive and accurate quantification of regional MBF if suitable  
 158 tracers are used and appropriate mathematical models applied.  
 159 These PET measurements of MBF, for which the symbol  $F/W$  is also  
 160 used, have units of volume per time per unit weight of myocardium  
 161 (i.e. ml/min/g) [11,16].

162 Different tracers can be used for measuring MBF using PET, includ-  
 163 ing oxygen-15 labeled water ( $H_2^{15}O$ ) [17–21],  $^{13}NH_3$  [22–25] and the  
 164 cationic potassium analog rubidium-82 ( $^{82}Rb$ ) [26,27].  $^{13}NH_3$  and  
 165  $^{82}Rb$  are given intravenously as boluses. In the case of  $H_2^{15}O$  the tracer  
 166 can be administered as an intravenous bolus injection [17,19,28,29],  
 167 an intravenous slow infusion [29,30], or by inhalation of oxygen-15  
 168 labeled carbon dioxide ( $C^{15}O_2$ ) which is then converted to  $H_2^{15}O$  by  
 169 carbonic anhydrase in the lungs [18]. Generator-produced  $^{82}Rb$  is a  
 170 very appealing MBF tracer because it does not require a cyclotron  
 171 on site and has a very short  $t_{1/2}$  (78 s) [27].

172 Because of its ability to provide non-invasive regional absolute  
 173 quantification of MBF, PET has been widely used to assess CFR in  
 174 healthy volunteers. Chareonthaitawee et al. [12] have investigated  
 175 the range of resting and hyperemic MBF in a large population  
 176 ( $n = 160$ ) of healthy males and females over a broad range of ages  
 177 (21 to 86 years). They found that baseline and hyperemic MBF are  
 178 heterogeneous both within and between individuals. Baseline and  
 179 hyperemic MBF exhibit a similar degree of spatial heterogeneity,  
 180 which appears to be temporally stable. Resting myocardial perfusion  
 181 ranged from 0.59 to 2.05 ml/min/g (average  $0.98 \pm 0.23$  ml/min/g)  
 182 and adenosine-induced hyperemic perfusion ranged from 1.85 to  
 183 5.99 ml/min/g (average  $3.77 \pm 0.85$  ml/min/g). Significant differences  
 184 within subjects were found comparing different segments with each  
 185 other, except for anterior versus lateral regions. MBF was significantly  
 186 higher in females than in males. There was a significant linear associ-  
 187 ation between age and baseline MBF, partly related to changes in ex-  
 188 ternal cardiac workload with age. Hyperemic MBF declines over  
 189 65 years of age.

190 Different studies have tested the short term reproducibility of MBF  
 191 measurements using PET with  $^{13}NH_3$  and  $H_2^{15}O$ . [20,31]. Repeated  
 192 measurements of resting and hyperemic MBF using intravenous  
 193 dipyridamole and adenosine during the same study session were  
 194 not significantly different, demonstrating the validity of the techni-  
 195 que. The variability of hyperemic flow was larger, as indicated by  
 196 the larger repeatability coefficient, and was paralleled by a greater

variability of the rate pressure product. This could mean that the  
 greater variability of MBF during stress is more likely due to a variable  
 response to vasodilators rather than to a larger measurement error. In  
 a subsequent study from the same group, the authors tested the fea-  
 sibility and reproducibility of MBF measurement during supine bicy-  
 cle exercise. The study results demonstrated the feasibility of this  
 protocol which was found at least as repeatable as using adenosine  
 stress. [21] More recently, Jagathesan et al. [32] have tested the long  
 term reproducibility of MBF measurement at rest and following dobu-  
 tamine stress in patients with stable coronary artery disease using  
 PET with  $H_2^{15}O$ . Dobutamine induced reproducible changes in both  
 global and regional MBF and flow reserve over a time interval of  
 24 weeks. The reproducibility of MBF and CFR with dobutamine was  
 comparable with the short-term repeatability reported for adenosine  
 and physical exercise in healthy subjects.

### 4. Primary hypertrophy

Genetic cardiomyopathies comprise a wide spectrum of familial  
 diseases characterized by considerable clinical heterogeneity [33–  
 36]. The current ESC classification identifies four major groups  
 based on phenotype: HCM, dilated cardiomyopathy, arrhythmogenic  
 right ventricular cardiomyopathy and restrictive cardiomyopathy; a  
 fifth group includes unclassified conditions such as isolated left ven-  
 tricular non-compaction [37]. Despite substantial differences among  
 these entities, there is significant overlap in genetic etiology, pheno-  
 typic aspects and clinical manifestations, often overriding strict classi-  
 fications. All cardiomyopathies share common elements such as the  
 modality of transmission, generally autosomal dominant and incom-  
 pletely penetrant, an increased risk of arrhythmias and sudden cardiac  
 death, as well as a variable tendency to progress towards heart  
 failure and its complications [35,37]. In addition, virtually all cardio-  
 myopathies seem to share some degree of CMD, which can be  
 detected even at early stages and is related with disease progression  
 and long-term outcome [5,38–40]. Multiple mechanisms underlie  
 CMD in the various types of familial cardiomyopathies, which are  
 likely different in the various conditions, and in many cases remain  
 to be elucidated. One notable exception is represented by HCM, a con-  
 dition in which the causes, clinical correlates and prognostic implica-  
 tions of CMD have been thoroughly investigated over the last two  
 decades, providing important elements for risk stratification and  
 promising treatment options for this condition [5,7,8,41].

HCM is the most common genetic heart disease, with a 1:500  
 prevalence in the general population, and is generally associated  
 with mutations in one of eight genes coding for sarcomere proteins,  
 including myosin binding protein C (MYBPC3), thick filament pro-  
 teins (beta-myosin heavy chain [MYH7] and the regulatory and es-  
 sential light chains [MYL2 and MYL3]), and thin filament proteins  
 (troponin-T [TNNT2], troponin-I [TNNI3] alpha-tropomyosin [TPM1],  
 and alpha-actin [ACTC]) [33,35,42]. To date, however, over 20 genes  
 have been described as HCM-causing, and include those coding for  
 Z-disk proteins such as titin, muscle LIM protein, telethonin, myoze-  
 nin 2 and vinculin, as well as rare variants causing rare storage syn-  
 dromes which result in HCM phenocopies, such as the  $\gamma 2$  subunit of  
 AMP-dependent protein kinase (PRKAG2) and the liposomal-associ-  
 ated membrane protein 2 (LAMP2) [35].

The hallmark of HCM is represented by primary LVH, which is gen-  
 erally asymmetric and develops in the absence of cardiac or systemic  
 triggers [33,35]. Besides LVH, however, the HCM phenotype involves  
 a complex interplay of myocardial disarray, interstitial fibrosis, mitral  
 valve and sub-valvular abnormalities, and coronary microvascular  
 remodeling [43]. At the arteriolar level, HCM patients exhibit marked  
 wall thickening of intramural coronary arterioles, largely due to me-  
 dial hypertrophy and intimal hyperplasia, which cause severe reduc-  
 tion in luminal area [5,44,45]. These structural abnormalities are  
 considered the most relevant substrate of CMD which, in the presence

of increased oxygen demand, such as may occur with exercise or sustained arrhythmias, ultimately exposes the myocardium to recurrent ischemia and its consequences [5,8,46]. Additional features such as myocyte disarray, interstitial fibrosis, reduced capillary density and increase in subendocardial LV wall stress due to obstruction may all contribute to impairment of flow and CMD [5,45,47]. Compelling evidence for the occurrence of myocardial ischemia in HCM patients, despite normal coronary angiograms, comes from in vivo studies demonstrating net lactate release in coronary venous blood during atrial pacing [48] as well as from post-mortem studies on patients who died suddenly, or at transplant, showing frequent and often extensive areas of myocardial damage (Fig. 2) [45,49,50] exhibiting all stages of ischemic injury; from an acute phase with coagulative necrosis and neutrophilic infiltrate, to a subacute phase with myocytolysis and granulation tissue healing, to a chronic phase characterized by post-necrotic replacement-type fibrosis [45]. Unfortunately, myocardial ischemia is often silent in HCM patients, and symptoms are not reliable in identifying patients with severe CMD. In addition, several techniques employed over the years to assess the occurrence myocardial hypoperfusion or ischemia, such as standard exercise testing, stress echocardiography and thallium-201 scintigraphy, have proven neither sensitive nor specific in this disease [5,48,51,52].

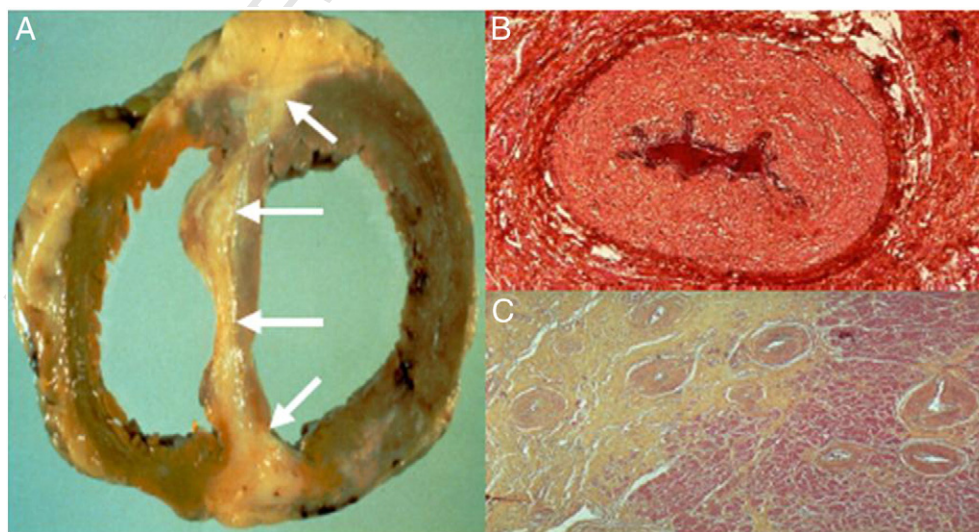
In the early nineties, a study from our group using PET first demonstrated the occurrence of severe CMD in HCM patients, not only in the hypertrophied septum, but also in the non-hypertrophied LV free wall [7]. Subsequent studies using PET and, more recently, cardiac magnetic resonance (CMR), have confirmed that CMD is a diffuse phenomenon in HCM hearts. Nevertheless, the absolute degree of microvascular impairment remains partly related to the extent of LVH, with most severe blunting generally occurring at the septal level, where maximum wall thickening is usually present [41]. In addition, the subendocardial layers of the LV were found to have more severe CMD compared to the subepicardium, likely due to the effects of extravascular compressive forces and elevated intraventricular pressures that are higher in the inner LV layers [5,53]. The latter account for improvement of subendocardial perfusion following invasive relief of obstruction with surgical myectomy or alcohol septal ablation [54,55].

In the last decade, important pathophysiological information regarding the long-term consequences of ischemia has been acquired in HCM patients following the introduction of CMR. Convincing

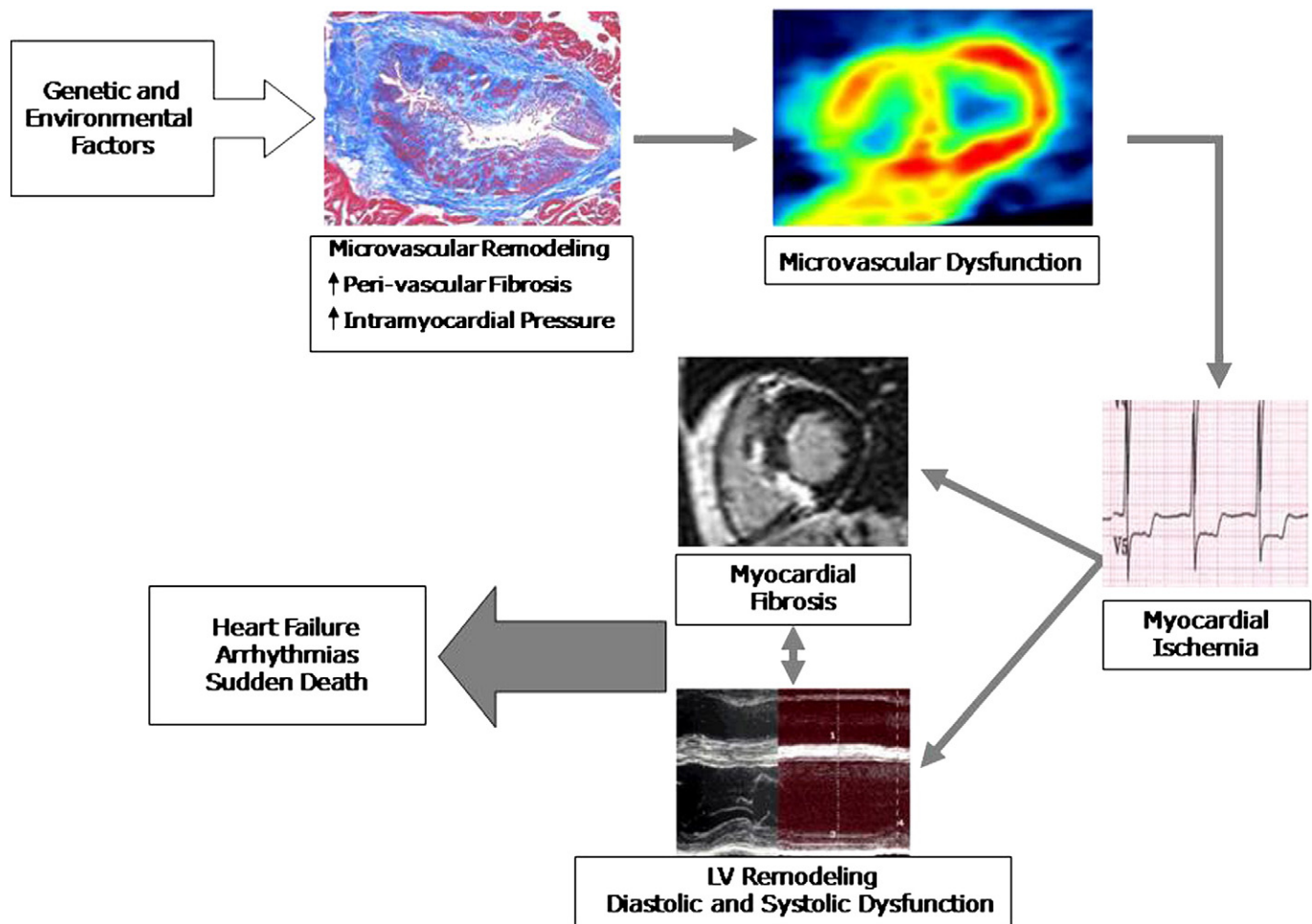
evidence has been accrued that late gadolinium enhancement (LGE), as visualized by CMR, is representative of myocardial fibrosis in HCM, based on several case reports which have compared in vivo CMR findings with explanted specimens [56]. In large HCM cohorts, approximately 50–80% of patients demonstrate areas of LGE, in variable patterns, occupying on average 10% of the overall LV myocardial volume [57,58]. The extent of LGE is inversely related to segmental wall thickening and LV ejection fraction, suggesting a direct relationship between extent of myocardial fibrosis and degree of LV function impairment [58]. Furthermore, substantial CMD has been described in LV segments with LGE, but also in those that are contiguous, as compared to remote, to LGE [59,60]. These findings suggest that CMD over time may lead to recurrent ischemia and myocyte death, thus acting as a localizer of replacement fibrosis [51].

Noticeably, severe impairment of microvascular function and myocardial fibrosis are significantly more prevalent among HCM patients harboring sarcomere gene mutations, compared to those that are genotype-negative [61], accounting for the increased long-term prevalence of ventricular dysfunction and heart failure reported in the genotype-positive subgroup [42]. Thus, the specific genetic defect causing HCM may represent a major determinant of microvascular remodeling, following molecular pathways that are largely independent of hypertrophy itself and potentially date back to the early phases of cardiac development [36].

The chain of events leading from microvascular remodeling to CMD, ischemia and replacement fibrosis, has important clinical implications for long-term outcome in HCM patients (Fig. 3) [5,51]. In about one-third of HCM 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 [33,43]. In this subgroup, consistent evidence points to CMD as a critical determinant of clinical progression and adverse outcome [51]. We previously reported on the long-term outcome of 51 HCM patients prospectively followed after the initial measurement of dipyridamole-MBF by PET [8]. During an average follow-up of more than 8 years, 31% of the patients died or experienced severe clinical deterioration. At multivariate analysis, a hyperemic flow value  $\leq 1.1$  ml/min/g, reflecting severe CMD, was the most powerful independent predictor of outcome in our cohort, with a 9.6 independent increase in risk of cardiovascular mortality [8]. In addition, patients with the most severe degrees of CMD showed higher risk of progressive LV remodeling and systolic



**Fig. 2.** Small-vessel disease and the morphologic basis for myocardial ischemia in HCM. (A) Native heart of a patient with end-stage HCM who underwent transplantation. Large areas of gross macroscopic scarring are evident throughout the LV myocardium (white arrows). (B) Intramural coronary artery in cross-section showing thickened intimal and medial layers of the vessel wall associated with small luminal area. (C) Area of myocardium with numerous abnormal intramural coronary arteries within a region of scarring, adjacent to an area of normal myocardium. Original magnification 55x. Reprinted, with permission, from Maron et al. [44].



**Fig. 3.** Proposed chain of pathophysiologic events linking microvascular remodeling and dysfunction to myocardial ischemia and LV remodeling and their consequences on patient outcome.

Modified from Maron et al., [51].

dysfunction, including the so-called end-stage phase [62]. It is noteworthy that at the time of PET scan, none of the patients had severe symptoms, and only a few would have been considered at high risk based on the established indicators of outcome [34, 8]. Altogether these findings have stimulating implications, in that assessment of myocardial flow and fibrosis may significantly improve risk stratification and allow the implementation of preventive measures in patients with HCM [5,49,51,63].

Finally, among male genotype-negative patients with HCM, a subset of 2–4% is likely to be affected by the cardiac variant of Anderson Fabry disease (AFD), an X-linked disease caused by mutations in the gene encoding alpha-galactosidase A, which results in accumulation of a glycosphingolipid, globotriaosylceramide, within lysosomes [64]. This accumulation leads to cellular dysfunction, particularly in the endothelium, resulting in tissue hypoperfusion. Classic AFD is a multi-organ disease with associated cardiac manifestations including arrhythmias, valvular abnormalities and cardiomyopathy [64]. However, the cardiac variant of the disease often exhibits little extracardiac involvement, making the diagnosis difficult, and presents with a cardiomyopathy characterized by mild to moderate degrees of LVH generally seen in male patients over the age of 40 years [40,65]. Despite being labeled as a myocardial storage disease, glycosphingolipid deposition accounts for less than 3% of the total increase in cardiac mass, the rest being expression of true, and as yet unexplained cardiomyocyte hypertrophy [65]. Patients with AFD may have angina, progressively deteriorating LV systolic function and myocardial scarring despite angiographically normal coronary arteries. These abnormalities are secondary to severe CMD, comparable to

that observed in HCM, although due to different mechanisms, in that endothelial globotriaosylceramide deposition and myocardial fibrosis, rather than microvascular remodeling, are believed to play a major role [5,64,65]. Unfortunately, in the only pilot trial with enzyme replacement therapy in AFD patients, no improvement in coronary microvascular function could be observed, despite a significant reduction in plasma concentrations of globotriaosylceramide [40].

### 5. Secondary hypertrophy

Exercised-induced cardiac adaptations are thought to be benign, and include increased cardiac mass, enhanced aerobic capacity, and diastolic enlargement, resulting in increased ventricular stroke volume and cardiac output [66]. These changes are largely the consequences of endurance exercise training, such as long distance running or swimming, and are associated with eccentric remodeling. On the other hand physical conditioning based on strenuous strength training, such as weight lifting and wrestling, causes concentric cardiac hypertrophy with a modest increase in cardiac output but without chamber dilatation and an increase in peripheral resistance, the intermittent pressure-overload and concentric hypertrophy may not have the same benefits as endurance training. There is evidence that prolonged exercise conditioning including a strength component [67] and endurance training such as marathon running in subjects over 50 years [68,69] cannot be distinguished from pathological hypertrophy and can potentially lead to myocardial disease. LVH induced by intense physical training in elite athletes is accompanied by an increase in coronary flow capacity [70]. It seems unlikely, though,

that the increase of hyperemic MBF could be related to an increase in capillary or arteriolar density. In swine undergoing treadmill training, capillary growth occurring in the early phases may outgrow the increase in LV mass. However, with prolonged training, capillary growth does not exceed but rather matches the increase in left ventricular mass [71]. The supernormal coronary capacity is more likely to be ascribed to shifts of the neuro-humoral and metabolic regulation.

Thyroid hormone action markedly stimulates the cardiac protein synthesis and leads to concentric cardiac hypertrophy and neo-angiogenesis [72]. When hyperthyroidism is of a limited duration, a “physiological” hypertrophic phenotype prevails characterized by increased SERCa2 levels, increased MHC alpha levels, and decreased MHC beta levels. Angiogenesis stimulated by thyroid hormone is initiated at the integrin receptor ( $\alpha v\beta 3$ ) for the hormone on endothelial and vascular smooth muscle cells [73].

Functional and structural alterations of the coronary circulation have been well documented in all forms of pathologic LVH [74]. In children ventricular hypertrophy induced by pressure overload, e.g. aortic coarctation, is paralleled by angiogenesis, hence the capillary density is similar to normal hearts. Conversely, in adults with acquired aortic stenosis capillary density can be decreased [75]. If capillary density is estimated as capillary number per unit area the density is decreased proportionally to the increase of the volume of the myocytes [76]. When vascular growth does not match myocyte growth there is relative rarefaction rather than absolute decrease in the number of capillaries. As a consequence minimal coronary resistance per gram of tissue is increased. This picture is worsened when medial hypertrophy of the vessels ensues and results in luminal narrowing. Besides myocyte hypertrophy coronary arterioles undergo structural and functional alterations in patients with systemic hypertension [77]. On the one hand vessel and lumen areas in hypertensive patients with LVH are significantly enlarged compared with those in hypertensive patients without LVH [78]. On the other hand intramyocardial arterioles  $<80\ \mu\text{m}$  show a thickening of the wall with a twofold increase of the wall/lumen ratio. In parallel there is increased perivascular fibrosis. Larger intramyocardial arterioles do not show a significant wall thickening [79]. As a consequence CFR is reduced [6,80–82] and minimal coronary resistance is increased significantly [78]. The reduction of CFR in hypertrophied hypertensive hearts is caused both by a concomitant increase of resting MBF [78], due to higher workload and oxygen consumption, and a reduction of hyperemic response [83] to endothelial dependent [78,84] and independent [78] stressors. The impairment of endothelial function seems to be a consequence rather than cause of the reduction of hyperemic flow [84,85] and it can be reversed by appropriate treatment [82,86–88]. Interestingly, spontaneously hypertensive rats treated for 8 weeks with perindopril alone or in combination with indapamide had evidence of reverse remodeling of the coronary microvasculature, paralleled by an increased coronary flow. The authors found a significant inverse relationship between hyperemic coronary flow and arteriolar medial area. Indapamide alone led to a similar reduction in medial area, but had no effect on coronary flow supporting the hypothesis that perindopril may increase MBF not only by promoting reverse remodeling of the coronary microvessels, but also by improving endothelial function [76,82].

Increased myocardial and extravascular compressive forces contribute mechanically to flow impediment in LVH [89]. The subendocardium is underperfused during systole and it must compensate by means of a reverse gradient flow in diastole [90]. Elevated end diastolic pressure in the long term can restrain subendocardial perfusion particularly during physical or pharmacological stress causing signs and symptoms of ischemia [91] in the absence of significant epicardial lesions [92]. Moreover, the risk of ischemia is higher in dilated hearts which have exhausted the coronary reserve already under resting conditions [93].

In aortic stenosis the structure of the arterioles is preserved, the external matrix and fibroblasts and myofibroblasts [79] are increased

together with biomarkers of matrix turnover [94]. The current guidelines indicate surgery for aortic stenosis (AS) when the left ventricular (LV) ejection fraction is  $<50\%$  or when symptoms (class I for ESC, class IIb for AHA:ACC) are unmasked during an exercise test [95]. The incidence of angina pectoris is between 30% and 40% of patients with aortic stenosis in the absence of coronary artery disease; however, no relationship has been demonstrated between angina pectoris and impairment of flow reserve in these patients. Moreover, in asymptomatic AS, the LV ejection fraction may remain in the normal range for years despite the occurrence of profound LV remodeling [96,97] multidirectional impairment of myocardial strain [98] and concomitant decrease of the vasodilatory capacity of the microcirculation [90,99].

Rajappan and colleagues measuring MBF with positron emission tomography in patients with AS found that total MBF to the heart at rest increased proportionally with LV mass, suggesting that the demand of the hypertrophied myocardium is met by an increase in baseline MBF [90]. This latter can be envisaged as a compensating mechanism of adaptation within the coronary microcirculation for the increased hemodynamic and intramural forces that the LV are subjected to. CFR is reduced both in the subepicardium and in the subendocardium, although at greater haemodynamic workloads, the subendocardial microcirculation appears to be affected to a greater extent than the subepicardium. This would suggest, as it is often clinically apparent, that as the severity of the aortic stenosis increases, the compensation afforded by hypertrophy of the myocardium is eventually offset by the hemodynamic effects exerted upon it. CFR is strongly related to the hemodynamic severity of valve stenosis, i.e. valve orifice area [100], and reduction in hyperemic diastolic perfusion time whereas there is only a weak correlation with LV mass [90]. A subsequent study by Rajappan et al. [101] lent further support to this notion demonstrating that in spite of a significant and prompt regression of LV mass after aortic valve repair and a reduction in total left ventricular blood flow, coronary microcirculatory function improved only slightly and remained blunted 1 year after aortic valve repair. The slight improvement in CFR was more closely related to changes in hemodynamic variables such as aortic valve area and diastolic perfusion time [102]. The Canadian TOPAS study analyzed patients with low-flow, low-gradient AS; this is a heterogeneous population consisting of patients with “true” severe AS, in whom an afterload mismatch results from a severely stenotic valve; and “pseudo-severe” AS, in whom the valve is only mildly or moderately stenotic, but appears severe due to difficulties in determining disease severity under low-flow conditions. Patients with true severe AS showed a strong trend towards a higher resting MBF and greater impairment of CFR compared with patients with “pseudo-severe” AS, consistent with a greater haemodynamic burden on the left ventricle [103]. The results were in apparent discrepancy with the findings of Rajappan et al.: on the one hand there was a strong relationship of CFR with indexes of stenosis severity on the other hand Burwash and colleagues observed that resting MBF and not hyperaemic MBF, was directly related to stenosis severity in patients with low-flow, low-gradient AS. In this latter condition end diastolic LV pressure and wall stresses were likely to be more elevated during near-maximal vasodilation. Thus, similarly to what has been observed in conscious dogs the pre-load [104] more than the afterload can be held responsible for the impairment in hyperemic blood flow. Moreover, in the TOPAS substudy [103] there was a higher incidence of coronary artery disease whereas the population described by Rajappan et al. had angiographically normal coronary arteries [90].

## 6. Conclusions

The availability of techniques such as PET that enables the non-invasive measurement of myocardial blood flow in humans in vivo has contributed to highlight the role of coronary microvascular remodeling and dysfunction in patients with primary and secondary LVH.

Undoubtedly, our understanding of the mechanisms leading to ischemia in patients with LVH has improved significantly and the in

525 vivo demonstration of CMD with PET is providing new important infor-  
526 mation on patient stratification and prognosis and may become also a  
527 valuable surrogate marker to test the efficacy of old and new drugs.

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