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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'.

Contents

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 μm diameter, autoregulatory adjustments are mainly mediated by arterioles less than 150 μm 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 (≥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. ≤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 α-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 α-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

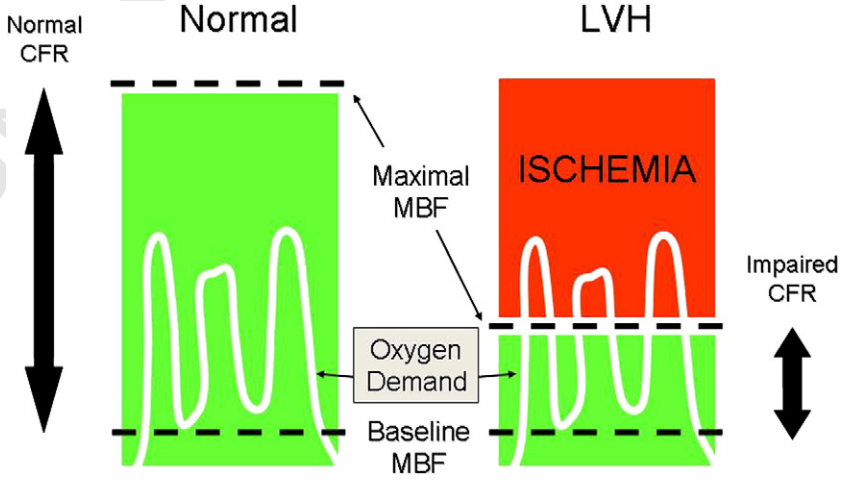

Fig. 1. In normal individuals, the coronary flow reserve (CFR, i.e. the ability of the coronary microvasculature to increase myocardial blood flow — MBF) guarantees adequate blood supply to meet varying demands of the myocardium in different physiologic situations. In patients with LVH, coronary flow 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.

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

Structural alterations	
Luminal obstruction	Microembolization
Vascular wall infiltration	Infiltrative heart disease
Vascular remodeling	HCM, systemic hypertension
Dilutional vascular rarefaction	Aortic stenosis and systemic hypertension
Perivascular fibrosis	Aortic stenosis and systemic hypertension
Functional alterations	
Endothelial dysfunction	CV risk factors smoking, hyperlipidemia, diabetes etc.
Smooth muscle cell dysfunction	HCM, systemic hypertension
Autonomic nervous system dysfunction	following coronary re-canalization
Extravascular alterations	
Extramural compression	Aortic stenosis, HCM, systemic hypertension
Reduction in diastolic perfusion time	Aortic stenosis

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

3. Myocardial blood flow measured by positron emission tomography

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

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

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

Different studies have tested the short term reproducibility of MBF measurements using PET with $^{13}NH_3$ and $H_2^{15}O$. [20,31]. Repeated measurements of resting and hyperemic MBF using intravenous dipyridamole and adenosine during the same study session were not significantly different, demonstrating the validity of the technique. The variability of hyperemic flow was larger, as indicated by 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 feasibility and reproducibility of MBF measurement during supine bicycle 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 dobutamine 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 ventricular non-compaction [37]. Despite substantial differences among these entities, there is significant overlap in genetic etiology, phenotypic aspects and clinical manifestations, often overriding strict classifications. All cardiomyopathies share common elements such as the modality of transmission, generally autosomal dominant and incompletely 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 cardiomyopathies 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 condition in which the causes, clinical correlates and prognostic implications 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 proteins (beta-myosin heavy chain [MYH7] and the regulatory and essential 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, myozenin 2 and vinculin, as well as rare variants causing rare storage syndromes which result in HCM phenocopies, such as the γ2 subunit of AMP-dependent protein kinase (PRKAG2) and the liposomal-associated membrane protein 2 (LAMP2) [35].

The hallmark of HCM is represented by primary LVH, which is generally 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 medial hypertrophy and intimal hyperplasia, which cause severe reduction in luminal area [5,44,45]. These structural abnormalities are considered the most relevant substrate of CMD which, in the presence

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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

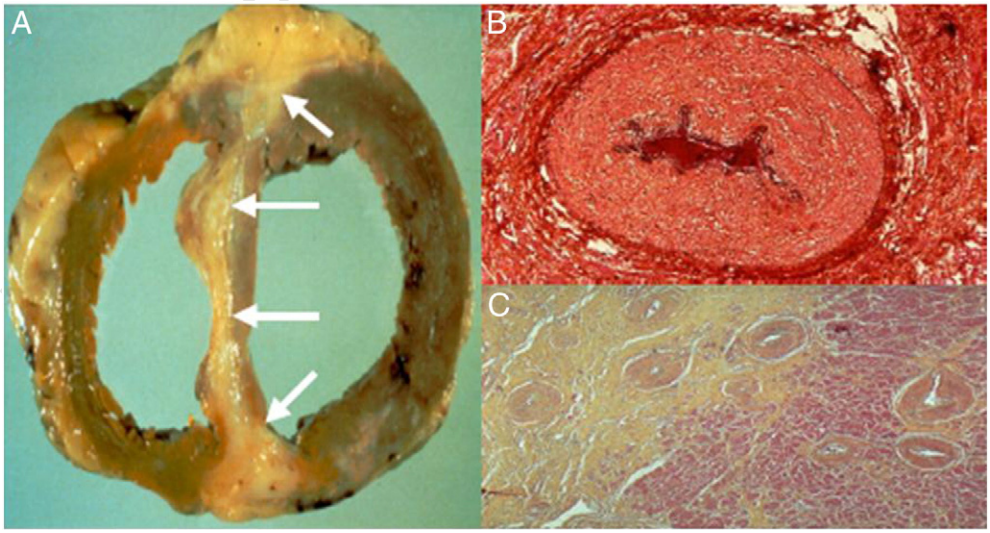

Fig. 2. Small-vessel disease and the morphologic basis for myocardial ischemia in HCM. (A) Native heart of a patient with end-stage HCM who underwent transplantation. Large areas of gross macroscopic scarring are evident throughout the LV myocardium (white arrows). (B) Intramural coronary artery in cross-section 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 55×.
Reprinted, with permission, from Maron et al. [44].

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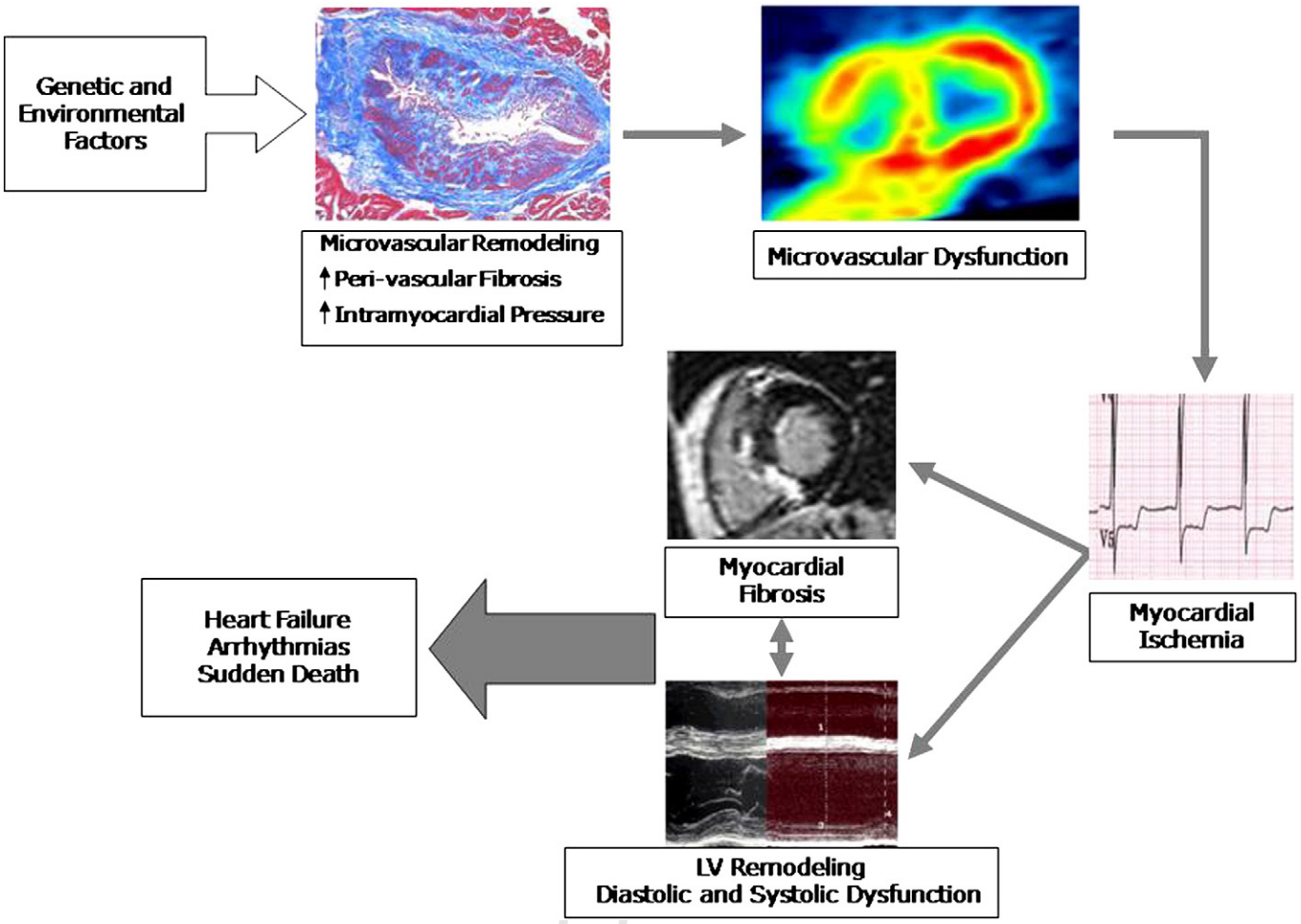

Fig. 3. Proposed chain of pathophysiologic events linking microvascular remodeling and dysfunction to myocardial ischemia and LV remodeling and their consequences on patient outcome.
Modified from Maron et al., [51].

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,

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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 μm 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, 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

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

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References

[1] Shapiro LM, McKenna WJ. Left ventricular hypertrophy. Relation of structure to diastolic function in hypertension. Br Heart J 1984;51:637–42.
[2] Weber KT. Fibrosis and hypertensive heart disease. Curr Opin Cardiol 2000;15:264–72.
[3] Dixon JA, Spinale FG. Myocardial remodeling: cellular and extracellular events and targets. Annu Rev Physiol 2011;73:47–68.
[4] Raman SV. The hypertensive heart. An integrated understanding informed by imaging. J Am Coll Cardiol 2010;55:91–6.
[5] Camici PG, Crea F. Coronary microvascular dysfunction. N Engl J Med 2007;356:830–40.
[6] Choudhury L, Rosen SD, Patel D, Nihoyannopoulos P, Camici PG. Coronary vasodilator reserve in primary and secondary left ventricular hypertrophy. A study with positron emission tomography. Eur Heart J 1997;18:108–16.
[7] Camici P, Chiriatti G, Lorenzoni R, Bellina RC, Gistri R, Italiani G, et al. Coronary vasodilation is impaired in both hypertrophied and nonhypertrophied myocardium of patients with hypertrophic cardiomyopathy: a study with nitrogen-13 ammonia and positron emission tomography. J Am Coll Cardiol 1991;17:879–86.
[8] Cecchi F, Olivotto I, Gistri R, Lorenzoni R, Chiriatti G, Camici PG. Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. N Engl J Med 2003;349:1027–35.
[9] Bassenge E, Heusch G. Endothelial and neuro-humoral control of coronary blood flow in health and disease. Rev Physiol Biochem Pharmacol 1990;116:77–165.
[10] Heusch G. Heart rate in the pathophysiology of coronary blood flow and myocardial ischaemia: benefit from selective bradycardic agents. Br J Pharmacol 2008;153:1589–601.
[11] Kaufmann PA, Camici PG. Myocardial blood flow measurement by PET: technical aspects and clinical applications. J Nucl Med 2005;46:75–88.
[12] Chareonthaitawee P, Kaufmann PA, Rimoldi O, Camici PG. Heterogeneity of resting and hyperemic myocardial blood flow in healthy humans. Cardiovasc Res 2001;50:151–61.
[13] Heusch G. Adenosine and maximum coronary vasodilation in humans: myth and misconceptions in the assessment of coronary reserve. Basic Res Cardiol 2010;105:1–5.
[14] Uren NG, Melin JA, De Bruyne B, Wijns W, Baudhuin T, Camici PG. Relation between myocardial blood flow and the severity of coronary-artery stenosis. N Engl J Med 1994;330:1782–8.
[15] Baumgart D, Haude M, Gorge G, Liu F, Ge J, Grosse-Eggebrecht C, et al. Augmented alpha-adrenergic constriction of atherosclerotic human coronary arteries. Circulation 1999;99:2090–7.
[16] Camici PG, Rimoldi OE. The clinical value of myocardial blood flow measurement. J Nucl Med 2009;50:1076–87.
[17] Bergmann SR, Herrero P, Markham J, Weinheimer CJ, Walsh MN. Noninvasive quantitation of myocardial blood flow in human subjects with oxygen-15-labeled water and positron emission tomography. J Am Coll Cardiol 1989;14:639–52.
[18] Araujo LI, Lammertsma AA, Rhodes CG, McFalls EO, Iida H, Rechavia E, et al. Noninvasive quantification of regional myocardial blood flow in coronary artery disease with oxygen-15-labeled carbon dioxide inhalation and positron emission tomography. Circulation 1991;83:875–85.
[19] Iida H, Kanno I, Takahashi A, Miura S, Murakami M, Takahashi K, et al. Measurement of absolute myocardial blood flow with $H_2^{15}O$ and dynamic positron-emission tomography. Strategy for quantification in relation to the partial-volume effect. Circulation 1988;78:104–15.
[20] Kaufmann PA, Gnecchi-Ruscone T, Yap JT, Rimoldi O, Camici PG. Assessment of the reproducibility of baseline and hyperemic myocardial blood flow measurements with 15O-labeled water and PET. J Nucl Med 1999;40:1848–56.
[21] Wyss CA, Koepfli P, Mikolajczyk K, Burger C, von Schulthess GK, Kaufmann PA. Bicycle exercise stress in PET for assessment of coronary flow reserve: repeatability and comparison with adenosine stress. J Nucl Med 2003;44:146–54.
[22] Schelbert HR, Phelps ME, Hoffman EJ, Huang SC, Selin CE, Kuhl DE. Regional myocardial perfusion assessed with N-13 labeled ammonia and positron emission computerized axial tomography. Am J Cardiol 1979;43:209–18.
[23] Hutchins GD, Schwaiger M, Rosenspire KC, Krivokapich J, Schelbert H, Kuhl DE. Noninvasive quantification of regional blood flow in the human heart using N-13 ammonia and dynamic positron emission tomographic imaging. J Am Coll Cardiol 1990;15:1032–42.
[24] Krivokapich J, Smith GT, Huang SC, Hoffman EJ, Ratib O, Phelps ME, et al. ^{13}N ammonia myocardial imaging at rest and with exercise in normal volunteers. Quantification of absolute myocardial perfusion with dynamic positron emission tomography. Circulation 1989;80:1328–37.
[25] Muzik O, Beanlands RS, Hutchins GD, Mangner TJ, Nguyen N, Schwaiger M. Validation of nitrogen-13-ammonia tracer kinetic model for quantification of myocardial blood flow using PET. J Nucl Med 1993;34:83–91.
[26] Herrero P, Markham J, Shelton ME, Weinheimer CJ, Bergmann SR. Noninvasive quantification of regional myocardial perfusion with rubidium-82 and positron emission tomography. Exploration of a mathematical model. Circulation 1990;82:1377–86.
[27] El Fakhri G, Kardan A, Sitek A, Dorbala S, Abi-Hatem N, Lahoud Y, et al. Reproducibility and accuracy of quantitative myocardial blood flow assessment with (82) Rb PET: comparison with (13)N-ammonia PET. J Nucl Med 2009;50:1062–71.
[28] Bergmann SR, Weinheimer CJ, Brown MA, Perez JE. Enhancement of regional myocardial efficiency and persistence of perfusion, oxidative, and functional reserve with paired pacing of stunned myocardium. Circulation 1994;89:2290–6.
[29] Hermansen F, Rosen SD, Fath-Ordoubadi F, Kooner JS, Clark JC, Camici PG, et al. Measurement of myocardial blood flow with oxygen-15 labelled water: comparison of different administration protocols. Eur J Nucl Med 1998;25:751–9.
[30] Huang SC, Schwaiger M, Carson RE, Carson J, Hansen H, Selin C, et al. Quantitative measurement of myocardial blood flow with oxygen-15 water and positron computed tomography: an assessment of potential and problems. J Nucl Med 1985;26:616–25.
[31] Nagamachi S, Czernin J, Kim AS. Reproducibility of measurement of regional resting and hyperemic myocardial blood flow assessed with PET. J Nucl Med 1996;37:1626–31.
[32] Jagathesan R, Kaufmann PA, Rosen SD, Rimoldi OE, Turkeimer F, Foale R, et al. Assessment of the long-term reproducibility of baseline and dobutamine-induced myocardial blood flow in patients with stable coronary artery disease. J Nucl Med 2005;46:212–9.
[33] Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA 2002;287:1308–20.
[34] Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol 2003;42:1687–713.
[35] Watkins H, Ashrafian H, Redwood C. Inherited cardiomyopathies. N Engl J Med 2011;364:1643–56.
[36] Olivotto I, Cecchi F, Poggesi C, Yacoub MH. Developmental origins of hypertrophic cardiomyopathy phenotypes: a unifying hypothesis. Nat Rev Cardiol 2009;6:317–21.
[37] Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008;29:270–6.
[38] Jenni R, Wyss CA, Oechslin EN, Kaufmann PA. Isolated ventricular noncompaction is associated with coronary microcirculatory dysfunction. J Am Coll Cardiol 2002;39:450–4.
[39] Neglia D, L'Abbate A. Coronary microvascular dysfunction and idiopathic dilated cardiomyopathy. Pharmacol Rep 2005;57(Suppl):151–5.
[40] Elliott PM, Kindler H, Shah JS, Sachdev B, Rimoldi OE, Thaman R, et al. Coronary microvascular dysfunction in male patients with Anderson–Fabry disease and the effect of treatment with alpha galactosidase A. Heart 2006;92:357–60.
[41] Petersen SE, Jerosch-Herold M, Hudsmith LE, Robson MD, Francis JM, Doll HA, et al. Evidence for microvascular dysfunction in hypertrophic cardiomyopathy: new insights from multiparametric magnetic resonance imaging. Circulation 2007;115:2418–25.
[42] Olivotto I, Girolami F, Ackerman MJ, Nistri S, Bos JM, Zachara E, et al. Myofilament protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy. Mayo Clin Proc 2008;83:630–8.
[43] Olivotto I, Girolami F, Nistri S, Rossi A, Rega L, Garbini F, et al. The many faces of hypertrophic cardiomyopathy: from developmental biology to clinical practice. J Cardiovasc Transl Res 2009;2:349–67.
[44] Maron BJ, Wolfson JK, Epstein SE, Roberts WC. Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy. J Am Coll Cardiol 1986;8:545–57.
[45] Basso C, Thiene G, Corrado D, Buja G, Melacini P, Nava A. Hypertrophic cardiomyopathy and sudden death in the young: pathologic evidence of myocardial ischemia. Hum Pathol 2000;31:988–98.
[46] Krams R, Kofflard MJ, Duncker DJ, Von Birgelen C, Carlier S, Kliffen M, et al. Decreased coronary flow reserve in hypertrophic cardiomyopathy is related to remodeling of the coronary microcirculation. Circulation 1998;97:230–3.
[47] Schwartzkopff B, Mundhenke M, Strauer BE. Alterations of the architecture of subendocardial arterioles in patients with hypertrophic cardiomyopathy and impaired coronary vasodilator reserve: a possible cause for myocardial ischemia. J Am Coll Cardiol 1998;31:1089–96.
[48] Cannon III RO, Dilsizian V, O'Gara PT, Udelson JE, Schenke WH, Quyyumi A, et al. Myocardial metabolic, hemodynamic, and electrocardiographic significance of reversible thallium-201 abnormalities in hypertrophic cardiomyopathy. Circulation 1991;83:1660–7.
[49] Moon JC, McKenna WJ, McCrohon JA, Elliott PM, Smith GC, Pennell DJ. Toward clinical risk assessment in hypertrophic cardiomyopathy with gadolinium cardiovascular magnetic resonance. J Am Coll Cardiol 2003;41:1561–7.
[50] Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR, et al. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. Circulation 2006;114:216–25.

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[51] Maron MS, Olivotto I, Maron BJ, Prasad SK, Cecchi F, Udelson JE, et al. The case for myocardial ischemia in hypertrophic cardiomyopathy. J Am Coll Cardiol 2009;54:866–75.

[52] Cannon III RO, Schenke WH, Maron BJ, Tracy CM, Leon MB, Brush Jr JE, et al. Differences in coronary flow and myocardial metabolism at rest and during pacing between patients with obstructive and patients with nonobstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 1987;10:53–62.

[53] Gistri R, Cecchi F, Choudhury L, Montereggi A, Sorace O, Salvadori PA, et al. Effect of verapamil on absolute myocardial blood flow in hypertrophic cardiomyopathy. Am J Cardiol 1994;74:363–8.

[54] Soliman OI, Geleijnse ML, Michels M, Dijkmans PA, Nemes A, van Dalen BM, et al. Effect of successful alcohol septal ablation on microvascular function in patients with obstructive hypertrophic cardiomyopathy. Am J Cardiol 2008;101:1321–7.

[55] Jorg-Ciopor M, Namdar M, Turina J, Jenni R, Schwitter J, Turina M, et al. Regional myocardial ischemia in hypertrophic cardiomyopathy: impact of myectomy. J Thorac Cardiovasc Surg 2004;128:163–9.

[56] Moon JC, Reed E, Sheppard MN, Elkington AG, Ho SY, Burke M, et al. The histologic basis of late gadolinium enhancement cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Am Coll Cardiol 2004;43:2260–4.

[57] Choudhury L, Mahrholdt H, Wagner A, Choi KM, Elliott MD, Klocke FJ, et al. Myocardial scarring in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 2002;40:2156–64.

[58] Maron MS, Appelbaum E, Harrigan CJ, Buros J, Gibson CM, Hanna C, et al. Clinical profile and significance of delayed enhancement in hypertrophic cardiomyopathy. Circ Heart Fail 2008;1:184–91.

[59] Sotgia B, Sciagra R, Olivotto I, Casolo G, Rega L, Betti I, et al. Spatial relationship between coronary microvascular dysfunction and delayed contrast enhancement in patients with hypertrophic cardiomyopathy. J Nucl Med 2008;49:1090–6.

[60] Knaapen P, van Dockum WG, Gotte MJ, Broeze KA, Kuijer JP, Zwanenburg JJ, et al. Regional heterogeneity of resting perfusion in hypertrophic cardiomyopathy is related to delayed contrast enhancement but not to systolic function: a PET and MRI study. J Nucl Cardiol 2006;13:660–7.

[61] Olivotto I, Girolami F, Sciagrà R, Ackerman MJ, Sotgia B, Bos JM, et al. Microvascular function is selectively impaired in hypertrophic cardiomyopathy patients with sarcomere myofilament gene mutations. J Am Coll Cardiol. in press.

[62] Olivotto I, Cecchi F, Gistri R, Lorenzoni R, Chiriatti G, Girolami F, et al. Relevance of coronary microvascular flow impairment to long-term remodeling and systolic dysfunction in hypertrophic cardiomyopathy. J Am Coll Cardiol 2006;47:1043–8.

[63] O'Hanlon R, Grasso A, Roughton M, Moon JC, Clark S, Wage R, et al. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. J Am Coll Cardiol 2010;56:867–74.

[64] Clarke JT. Narrative review: Fabry disease. Ann Intern Med 2007;146:425–33.

[65] Morrissey RP, Philip KJ, Schwarz ER. Cardiac abnormalities in Anderson–Fabry disease and Fabry's cardiomyopathy. Cardiovasc J Afr 2011;22:38–44.

[66] Pelliccia A, Culasso F, Di Paolo FM, Maron BJ. Physiologic left ventricular cavity dilatation in elite athletes. Ann Intern Med 1999;130:23–31.

[67] Pelliccia A, Maron BJ, De Luca R, Di Paolo FM, Spataro A, Culasso F. Remodeling of left ventricular hypertrophy in elite athletes after long-term deconditioning. Circulation 2002;105:944–9.

[68] Breuckmann F, Mohlenkamp S, Nassenstein K, Lehmann N, Ladd S, Schmermund A, et al. Myocardial late gadolinium enhancement: prevalence, pattern, and prognostic relevance in marathon runners. Radiology 2009;251:50–7.

[69] Nassenstein K, Breuckmann F, Lehmann N, Schmermund A, Hunold P, Broecker-Preuss M, et al. Left ventricular volumes and mass in marathon runners and their association with cardiovascular risk factors. Int J Cardiovasc Imaging 2009;25:71–9.

[70] Radvan J, Choudhury L, Sheridan DJ, Camici PG. Comparison of coronary vasodilator reserve in elite rowing athletes versus hypertrophic cardiomyopathy. Am J Cardiol 1997;80:1621–3.

[71] White FC, Bloor CM, McKirnan MD, Carroll SM. Exercise training in swine promotes growth of arteriolar bed and capillary angiogenesis in heart. J Appl Physiol 1998;85:1160–8.

[72] Dillmann W. Cardiac hypertrophy and thyroid hormone signaling. Heart Fail Rev 2010;15:125–32.

[73] Luidens MK, Mousa SA, Davis FB, Lin H-Y, Davis PJ. Thyroid hormone and angiogenesis. Vascular Pharmacology. 52:142–5.

[74] Tanaka M, Fujiwara H, Onodera T, Wu DJ, Matsuda M, Hamashima Y, et al. Quantitative analysis of narrowings of intramyocardial small arteries in normal hearts, hypertensive hearts, and hearts with hypertrophic cardiomyopathy. Circulation 1987;75:1130–9.

[75] Rakusan K, Flanagan MF, Geva T, Southern J, Van Praagh R. Morphometry of human coronary capillaries during normal growth and the effect of age in left ventricular pressure-overload hypertrophy. Circulation 1992;86:38–46.

[76] Levy BI, Duriez M, Samuel JL. Coronary microvasculature alteration in hypertensive rats. Effect of treatment with a diuretic and an ACE inhibitor. Am J Hypertens 2001;14:7–13.

[77] Tomanek RJ. Response of the coronary vasculature to myocardial hypertrophy. J Am Coll Cardiol 1990;15:528–33.

[78] Hamasaki S, Al Suwaidi J, Higano ST, Miyauchi K, Holmes Jr DR, Lerman A. Attenuated coronary flow reserve and vascular remodeling in patients with hypertension and left ventricular hypertrophy. J Am Coll Cardiol 2000;35:1654–60.

[79] Schwartzkopff B, Frenzel H, Dieckerhoff J, Betz P, Flasshove M, Schulte HD, et al. Morphometric investigation of human myocardium in arterial hypertension and valvular aortic stenosis. Eur Heart J 1992;13(Suppl D):17–23.

[80] Schwartzkopff B, Mundhenke M, Strauer BE. Remodelling of intramyocardial arterioles and extracellular matrix in patients with arterial hypertension and impaired coronary reserve. Eur Heart J 1995;16(Suppl I):82–6.

[81] Akinboboye OO, Idris O, Goldsmith R, Berekashvili K, Chou RL, Bergman SR. Positron emission tomography, echo-doppler, and exercise studies of functional capacity in hypertensive heart disease. Am J Hypertens 2002;15:907–10.

[82] Neglia D, Fommei E, Varela-Carver A, Mancini M, Ghione S, Lombardi M, et al. Perindopril and indapamide reverse coronary microvascular remodelling and improve flow in arterial hypertension. J Hypertens 2010;29:364–72.

[83] Olsen MH, Wachtell K, Meyer C, Hove JD, Palmieri V, Dige-Petersen H, et al. Association between vascular dysfunction and reduced myocardial flow reserve in patients with hypertension: a LIFE substudy. J Hum Hypertens 2004;18:445–52.

[84] Schindler TH, Nitzsche EU, Olschewski M, Brink I, Mix M, Prior J, et al. PET-measured responses of MBF to cold pressor testing correlate with indices of coronary vasomotion on quantitative coronary angiography. J Nucl Med 2004;45:419–28.

[85] Nitenberg A, Antony I, Aptecar E, Arnoult F, Lerebours G. Impairment of flow-dependent coronary dilation in hypertensive patients. Demonstration by cold pressor test induced flow velocity increase. Am J Hypertens 1995;8:13S–8S.

[86] Naya M, Tsukamoto T, Morita K, Katoh C, Furumoto T, Fujii S, et al. Olmesartan, but not amlodipine, improves endothelium-dependent coronary dilation in hypertensive patients. J Am Coll Cardiol 2007;50:1144–9.

[87] Buus NH, Bottcher M, Jorgensen CG, Christensen KL, Thygesen K, Nielsen TT, et al. Myocardial perfusion during long-term angiotensin-converting enzyme inhibition or {beta}-blockade in patients with essential hypertension. Hypertension 2004;44:465–70.

[88] Schwartzkopff B, Brehm M, Mundhenke M, Strauer BE. Repair of coronary arterioles after treatment with perindopril in hypertensive heart disease. Hypertension 2000;36:220–5.

[89] Downey JM. Extravascular coronary resistance. In: Sperelakis N, editor. Physiology and pathophysiology of the heart. Kluwer Academic; 1995. p. 1109–23.

[90] Rajappan K, Rimoldi OE, Dutka DP, Ariff B, Pennell DJ, Sheridan DJ, et al. Mechanisms of coronary microcirculatory dysfunction in patients with aortic stenosis and angiographically normal coronary arteries. Circulation 2002;105:470–6.

[91] Frohlich ED. Fibrosis and ischemia: the real risks in hypertensive heart disease. Am J Hypertens 2001;14:194S–9S.

[92] Brush Jr JE, Cannon III RO, Schenke WH, Bonow RO, Leon MB, Maron BJ, et al. Angina due to coronary microvascular disease in hypertensive patients without left ventricular hypertrophy. N Engl J Med 1988;319:1302–7.

[93] Neglia D, Michelassi C, Trivieri MG, Sambuceti G, Giorgetti A, Pratali L, et al. Prognostic role of myocardial blood flow impairment in idiopathic left ventricular dysfunction. Circulation 2002;105:186–93.

[94] Zile MR, Desantis SM, Baicu CF, Stroud RE, Thompson SB, McClure CD, et al. Plasma biomarkers that reflect determinants of matrix composition identify the presence of left ventricular hypertrophy and diastolic heart failure. Circ Heart Fail 2011;4:246–56.

[95] Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, et al. Guidelines on the management of valvular heart disease: the task force on the management of valvular heart disease of the European society of cardiology. Eur Heart J 2007;28:230–68.

[96] Rosenhek R, Zilberszac R, Schemper M, Czerny M, Mundigler G, Graf S, et al. Natural history of very severe aortic stenosis. Circulation 2010;121:151–6.

[97] Galiuto L, Lotrionte M, Crea F, Anselmi A, Biondi-Zoccai GG, De Giorgio F, et al. Impaired coronary and myocardial flow in severe aortic stenosis is associated with increased apoptosis: a transthoracic Doppler and myocardial contrast echocardiography study. Heart 2006;92:208–12.

[98] Ng AC, Delgado V, Bertini M, Antoni ML, van Bommel RJ, van Rijnsoever EP, et al. Alterations in multidirectional myocardial functions in patients with aortic stenosis and preserved ejection fraction: a two-dimensional speckle tracking analysis. Eur Heart J 2011.

[99] Carabello BA. Clinical practice. Aortic stenosis. N Engl J Med 2002;346:677–82.

[100] Garcia D, Camici PG, Durand LG, Rajappan K, Gaillard E, Rimoldi OE, et al. Impairment of coronary flow reserve in aortic stenosis. J Appl Physiol 2009;106:113–21.

[101] Rajappan K, Rimoldi OE, Camici PG, Bellenger NG, Pennell DJ, Sheridan DJ. Functional changes in coronary microcirculation after valve replacement in patients with aortic stenosis. Circulation 2003;107:3170–5.

[102] Biederman RWW, Doyle M, Yamrozik J, Williams RB, Rathi VK, Vido D, et al. Physiologic compensation is supranormal in compensated aortic stenosis: does it return to normal after aortic valve replacement or is it blunted by coexistent coronary artery disease?: an intramyocardial magnetic resonance imaging study. Circulation 2005;112:I-429–36.

[103] Burwash IG, Lortie M, Pibarot P, de Kemp RA, Graf S, Mundigler G, et al. Myocardial blood flow in patients with low-flow, low-gradient aortic stenosis: differences between true and pseudo-severe aortic stenosis. Results from the multicentre TOPAS (Truly or Pseudo-Severe Aortic Stenosis) study. Heart 2008;94:1627–33.

[104] Hittinger L, Mirsky I, Shen YT, Patrick TA, Bishop SP, Vatner SF. Hemodynamic mechanisms responsible for reduced subendocardial coronary reserve in dogs with severe left ventricular hypertrophy. Circulation 1995;92:978–86.

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