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Review article

The coronary circulation and blood flow in left ventricular hypertrophy

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A B S T R A C T

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 πέρα “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...
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 vascular resistance resides in vessels less than 300 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 disease (type C).
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 (\( O_2^{15}C \)) 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 t1/2 (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 diprydiamole 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 bicycling 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 \( ^{15}O \) the tracer and the 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 t1/2 (78 s) [27].

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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
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 neutrophil infiltrate, to a subacute phase with myocyteysis 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 extracellular 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].

Notably, 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 dysfunction [34,35].
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 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 in-
crease 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 as-
cribed to shifts of the neuro-humoral and metabolic regulation.

Thyroid hormone action markedly stimulates the cardiac protein syn-
thesis and leads to concentric cardiac hypertrophy and neo-angiogenesis
[72]. When hyperthyroidism is of a limited duration, a “physiological”
angiogenic phenotype prevails characterized by increased SERCA2
levels, increased MHC alpha levels, and decreased MHC beta levels. An-
giogenesis stimulated by thyroid hormone is initiated at the integrin re-
ceptor (αvβ3) 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 chil-
dren 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 es-
timated as capillary number per unit area the density is decreased pro-
portionally to the increase of the volume of the myocytes [76]. When
vascular growth does not match myocyte growth there is relative rare-
fraction rather than absolute decrease in the number of capillaries. As a
consequence minimal coronary resistance per gram of tissue is in-
creased. This picture is worsened when medial hypertrophy of the ves-
sels ensues and results in luminal narrowing. Besides myocyte
hypertrophy coronary arterioles undergo structural and functional al-
terations in patients with systemic hypertension [77]. On the one
hand vessel and lumen areas in hypertensive patients with LVH are sig-
nificantly enlarged compared with those in hypertensive patients with-
out 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 intra-
myocardial arterioles do not show a significant wall thickening [79].
As a consequence CFR is reduced [60–82] and minimal coronary resis-
tance is increased significantly [78]. The reduction of CFR in hypertro-
phied 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 treat-
ment [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 micro-
vasculature, 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 re-
duction in medial area, but had no effect on coronary flow supporting
the hypothesis that perindopril may increase MBF not only by promot-
ing reverse remodeling of the coronary microvessels, but also by im-
proving endothelial function [76,82].

Increased myocardial and extravascular compressive forces con-
tribute mechanistically to flow impediment in LVH [89]. The subendo-
cardial is underperfused during systole and it must compensate by
means of a reverse gradient flow in diastole [90]. Elevated end dia-
stolic 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 guide-
lines indicate surgery for aortic stenosis (AS) when the left ventricu-
lar (LV) ejection fraction is <50% or when symptoms (class I for ESC,
IIIb for AHA/ACC) are unmasked during an exercise test [95]. The inci-
dence of angina pectoris is between 30% and 40% of patients with aor-
tic stenosis in the absence of coronary artery disease; however, no
relationship has been demonstrated between angina pectoris and im-
pairment of flow reserve in these patients. Moreover, in asymptom-
atic AS, the LV ejection fraction may remain in the normal range for
years despite the occurrence of profound LV remodeling [96,97] mul-
tidirectional impairment of myocardial strain [98] and concomitant
decline of the vasodilatory capacity of the microcirculation [90,99].

Rajappan and colleagues measuring MBF with positron emission to-
mography in patients with AS found that total MBF to the heart at rest in-
creased 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 haemo-
dynamic 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 demon-
strating 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 se-
verity 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 great-
er 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 se-
vurity 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 dia-
stolic LV pressure and wall stresses were likely to be more elevated dur-
ing 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 angio-
graphically 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 is-
chemia 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


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