Left ventricular hypertrophy (LVH) is growth in left ventricular mass caused by increased cardiomyocyte size. LVH can be a physiological adaptation to strenuous physical exercise, as in athletes, or it can be a pathological condition, which is either genetic or secondary to LV overload. Physiological LVH is usually benign and regresses upon reduction/cessation of physical activity. Pathological LVH is a compensatory phenomenon, which eventually may become maladaptive and evolve towards progressive LV dysfunction and heart failure (HF). Both interstitial and replacement fibrosis play a major role in the progressive decompensation of the hypertrophied LV. Coronary microvascular dysfunction (CMD) and myocardial ischemia, which have been demonstrated in most forms of pathological LVH, have an important pathogenetic role in the formation of replacement fibrosis and both contribute to the evolution towards LV dysfunction and HF. Noninvasive imaging allows detection of myocardial fibrosis and CMD, thus providing unique information for the stratification of patients with LVH. (Circ J 2016; 80: 555–564)

Key Words: Coronary microvascular dysfunction; Heart failure; Left ventricular hypertrophy; Myocardial fibrosis; Myocardial ischemia

Pathological LVH

LV geometry can be classified using 2 simple parameters: relative wall thickness (RWT), calculated as posterior wall thickness/2/LV internal diameter at end-diastole, and the LVM index (LWMi, normalized for body surface area or height). This classification permits categorization of LV geometry into 4 types: normal (RWT ≤ 0.42 and normal LWMi), concentric remodeling (normal LWMi with RWT >0.42), concentric (increased LWMi and RWT >0.42) or eccentric hypertrophy (increased LWMi and RWT ≤0.42) (Figure 1).
DCM is generally caused by viral/bacterial myocarditis, exposure to cardiotoxic substances or is a manifestation of a systemic disease. Before cell death and fibrotic repair occur, multiple factors contribute to contractile dysfunction, including abnormalities in sarcolemmal integrity, energy production, calcium handling and force transmission. Both systolic and diastolic dysfunction worsen with time and EF is progressively reduced, with symptoms and signs of HF.

Secondary LVH
Cardiomyocyte hypertrophy is the primary mechanism by which the heart counteracts a protracted increase in stress (or load) on the ventricular wall. According to Laplace’s law, wall stress is directly related to LV cavity size and intracavitary pressure and inversely related to wall thickness. Thus, wall thickening will counteract, at least in part, the increased stress and oxygen demand caused by pressure or volume overload, although, in the long run, this compensatory mechanism may become maladaptive. On the other hand, several other nonhemodynamic factors, including activation of the adrenergic and renin-angiotensin-aldosterone (RAAS) systems, release of growth factors and cytokines, contribute to the development of LVH.

Pressure Overload
In most cases, pressure overload manifests as arterial hypertension (AH) or aortic stenosis (AS). The most common condition associated with an increase in cardiac afterload and wall stress is AH. Approximately 20–60% of patients with uncomplicated AH have evidence of increased LVM on echocardiography. LVM can increase from wall thickening, chamber dilatation or both. Wall thickening occurs more commonly in response to pressure overload whereas chamber dilatation occurs more commonly in response to volume overload. Although LV wall thickness is more closely related to systemic diastolic blood pressure (concentric hypertrophy), reflecting pure pressure load caused by increased systemic vascular resistance, LVM

Primary LVH
Variable degrees of LVH are present in most forms of primary myocardial diseases, including hypertrophic (HCM) and dilated (DCM) cardiomyopathy.

HCM
Given its Mendelian inheritance, HCM was the first cardiomyopathy to be associated with a genetic origin, and specific mutations in genes encoding sarcomeric proteins can be identified in over 50% of patients. The mechanisms responsible for LVH development in HCM remain incompletely understood. Impaired myofibrillar contractile function, mainly caused by abnormal cardiomyocyte calcium cycling and sensitivity, is thought to be the key mechanism triggering compensatory hypertrophy, although other factors may play a role, including disturbed biomechanical stress sensing and altered energy homeostasis. Hypertrophy is generally asymmetrical (with wall thickness >15 mm) and affects predominantly the interventricular septum, although it may also be symmetrical or localized to the apex or posterior wall. LV volumes are normal or reduced, systolic function is preserved and there is often evidence of hypercontractility with EF higher than normal and near obliteration of the cavity in systole. HCM is characterized by variable degrees of diastolic dysfunction that may be severe enough to cause symptoms of HF despite a normal EF. In a minority of patients, the disease evolves towards severe remodeling of the LV with cavity enlargement, wall thinning and progressive impairment of systolic function, a condition known as endstage HCM.

DCM
Progressive LV cavity enlargement, wall thinning and hypertrophy caused by an in-series disposition of sarcomeres with slippage of the fibers characterize DCM. The LV tends to become spherical and hypertrophy is eccentric. Gene mutations can be detected in 20–30% of patients with the DCM phenotype and involve proteins of the membrane-scaffolding apparatus, sarcomeric proteins, nuclear envelope proteins, calcium-handling proteins and transcription cofactors of the cell energy-generating machinery. In all other cases, DCM is generally caused by viral/bacterial myocarditis, exposure to cardiotoxic substances or is a manifestation of a systemic disease. Before cell death and fibrotic repair occur, multiple factors contribute to contractile dysfunction, including abnormalities in sarcolemmal integrity, energy production, calcium handling and force transmission. Both systolic and diastolic dysfunction worsen with time and EF is progressively reduced, with symptoms and signs of HF.
is more closely related to systolic blood pressure, suggesting an influence of both pressure and volume load (eccentric hypertrophy). 17,18

In most patients with mild to moderate AH and LVH, systolic performance at rest is normal or mildly increased and a varying degree of diastolic dysfunction can be present. LVH may evolve to overt systolic or diastolic dysfunction (or both) with the corresponding clinical presentation of HF with preserved (HFpEF) or reduced EF (HFrEF). 23

**AS** Valvular AS is the second-most prevalent adult valve disease, occurring in 4% of patients older than 75 years. 19 Severe LVH is found in 17% of symptomatic patients with mild to moderate AS20 and in 67% of those with asymptomatic severe AS. 21 The increased LV afterload produced by AS results in a structural hypertrophic adaptation that is generally concentric, characterized by wall thickening with normal LV cavity dimensions. 22 Systolic performance at rest is normal or mildly increased and diastolic dysfunction is present. 22 The natural history of AS is characterized, in most cases, by progressive LV dysfunction and HF, although it may be favorably changed by valve replacement, particularly in those patients with preserved EF before surgery. 23

**Volume Overload** In most cases of volume overload, the enlarged intracavitary volume contributes to the increased LV systolic pressure and afterload, leading to a combined pressure and volume overload and an eccentric pattern of hypertrophy.

**Mitral Regurgitation (MR)** Isolated MR is the only heart disease that generates a pure volume overload because the extra volume is ejected into a low-pressure chamber (left atrium). 24 Pure volume overload induces an increase in diastolic stress, leading to an in-series disposition of the sarcomeres and thus increasing myocyte length. This in turn produces an increase in LV chamber volume, allowing the LV to augment stroke volume to accommodate the extra volume lost in regurgitation. This high-volume/low-pressure state produces an enlarged, thin-walled chamber that represents the classical geometry of eccentric hypertrophy. This eccentric remodeling has a temporary favorable influence on diastolic function, which is usually supra normal in patients with compensated disease. 25,26 Clinical HF occurs lately, with the development of a progressive reduction in systolic and diastolic function.

**Aortic Regurgitation (AR)** Volume overload in AR is caused by the back flow of blood into the LV during diastole. As in MR, the LV cavity is enlarged and the stroke volume increased. Moreover, the interaction of the large stroke volume with the elasticity of the aorta increases systolic blood pressure. In fact, although many AR patients are normotensive, systolic pressure in AR is approximately 50 mmHg higher than in MR. 27 This unique combined pressure and volume overload leads to hypertrophic remodeling that is both eccentric and concentric, 28 producing the heaviest LV in valvular heart disease, 29 which eventually results in both diastolic and systolic dysfunction and overt HF. 30,31
Abnormalities in the function and structure of the coronary microcirculation impair the control of myocardial blood flow (MBF) and can contribute to the pathogenesis of myocardial ischemia.

According to Camici and Crea, patients with LVH have type 2 CMD (ie, occurring in the absence of demonstrable coronary artery disease (CAD), but with evidence of myocardial disease). CMD determines significant blunting of hyperemic MBF and reduction of coronary flow reserve (CFR). This impairment of coronary physiology predicts development of LV dysfunction in patients with LVH.

Radvan et al measured MBF and CFR with positron emission tomography in a group of elite rowers (all with LVMi >131 g/m$^2$) and a group of age- and sex-matched sedentary controls. They found that both resting and hyperemic (dipyridamole) MBF and CFR in the athletes and normal controls were comparable. Similar results were obtained in subsequent studies comparing MBF and CFR in elite athletes and control subjects, suggesting that MBF and CFR are preserved in athletes with physiological LVH.

CMD in Primary LVH

In HCM, both severe structural remodeling of intramural coronary arterioles and increased perivascular fibrosis has been described. These structural changes, in addition to the increased extravascular compression, cause severe CMD that can be demonstrated by a severely blunted maximal MBF and reduced CFR. The anatomical basis of CMD is supported by the

### Table. Myocardial Perfusion and Coronary Flow Reserve in Normal Controls, and Primary and Secondary LVH Patients

<table>
<thead>
<tr>
<th>Method</th>
<th>n</th>
<th>MBFR (ml/g/min)</th>
<th>MBFH (ml/g/min)</th>
<th>CFR</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET</td>
<td>3.484</td>
<td>0.82±0.06</td>
<td>2.86±1.29</td>
<td>3.55±1.36</td>
<td>Gould et al$^{38}$</td>
</tr>
<tr>
<td>PET</td>
<td>10</td>
<td>0.74±0.17</td>
<td>2.69±1.15</td>
<td>3.58±1.02</td>
<td>Radvan et al$^{41}$</td>
</tr>
<tr>
<td>PET</td>
<td>14</td>
<td>0.8±0.2</td>
<td>NA</td>
<td>6.1±1.9</td>
<td>Toraa et al$^{42}$</td>
</tr>
<tr>
<td>Doppler</td>
<td>52</td>
<td>10.6±3.1 (ml/min)</td>
<td>61.9±17.8 (ml/min)</td>
<td>5.9±1.0</td>
<td>Hilick-Smith et al$^{43}$</td>
</tr>
<tr>
<td>HCM</td>
<td>PET</td>
<td>345</td>
<td>0.9±0.10</td>
<td>1.57±0.33</td>
<td>1.84±0.36</td>
</tr>
<tr>
<td>PET</td>
<td>23</td>
<td>1.02±0.39</td>
<td>1.55±0.58</td>
<td>1.51±0.48</td>
<td>Camici et al$^{44}$</td>
</tr>
<tr>
<td>PET</td>
<td>51</td>
<td>0.84±0.31</td>
<td>1.50±0.69</td>
<td>1.80±0.70</td>
<td>Cecchi et al$^{48}$</td>
</tr>
<tr>
<td>PET</td>
<td>61</td>
<td>–</td>
<td>1.90±0.90</td>
<td>–</td>
<td>Olivotto et al$^{46}$</td>
</tr>
<tr>
<td>DCM</td>
<td>PET</td>
<td>22</td>
<td>0.80±0.25</td>
<td>1.91±0.76</td>
<td>2.38±0.5</td>
</tr>
<tr>
<td>PET</td>
<td>67</td>
<td>0.69±0.23</td>
<td>1.53±0.79</td>
<td>2.22±0.89</td>
<td>Neglia et al$^{50}$</td>
</tr>
<tr>
<td>Hypertensive heart</td>
<td>PET</td>
<td>20</td>
<td>0.69±0.13</td>
<td>1.42±0.32</td>
<td>NA</td>
</tr>
<tr>
<td>PET</td>
<td>30</td>
<td>0.89±0.18</td>
<td>1.9±0.62</td>
<td>2.18±0.74</td>
<td>Rimoldi et al$^{51}$</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>PET</td>
<td>20</td>
<td>1.05±0.26</td>
<td>1.99±0.78</td>
<td>1.9±0.6</td>
</tr>
<tr>
<td>Doppler</td>
<td>24</td>
<td>23.3±10.1 (cm/s)</td>
<td>37.8±11.3 (cm/s)</td>
<td>1.76±0.5</td>
<td>Hilick-Smith et al$^{45}$</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>Doppler</td>
<td>31</td>
<td>42±8 (cm/s)</td>
<td>56±14 (cm/s)</td>
<td>2.1±0.5</td>
</tr>
</tbody>
</table>

CFR, coronary flow reserve; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; MBFH, myocardial blood flow during hyperemia; MBFR, myocardial blood flow at rest; NA, not available; PET, positron emission tomography.

**LV Geometry and Prognosis**

Khouri et al have proposed a new classification of LVH into 4 subgroups: eccentric non-dilated (or indeterminate hypertrophy), eccentric dilated, concentric non-dilated LVH and concentric dilated LVH (Figure 2). According to this classification, patients with eccentric hypertrophy can be subclassified into a low-risk (indeterminate hypertrophy or eccentric non-dilated LVH) and a high-risk group (dilated hypertrophy). Similarly, concentric hypertrophy can be subdivided into 2 risk groups: thick hypertrophy and both thick and dilated hypertrophy where the latter is the phenotype carrying the highest risk. Bang et al proved the prognostic validity of this classification in 939 hypertensive patients of the LIFE study (mean follow-up of 4 years), identifying a low-risk subset with eccentric non-dilated LVH and 3 subsets of LVH at high risk of developing LV dysfunction and HF. Garg et al validated this classification using cardic magnetic resonance in 2,458 subjects, demonstrating that the risk of HF and cardiovascular death was greater in those subject with either dilated hypertrophy or both thick and dilated hypertrophy. In patients with concentric dilated LVH, diastolic LV dysfunction is a frequent finding and is the functional determinant predisposing to HFpEF.

**CMD in LVH**

In the past 2 decades, CMD has emerged as an additional mechanism of myocardial ischemia. Abnormalities in the function and structure of the coronary microcirculation impair the control of myocardial blood flow (MBF) and can contribute to the pathogenesis of myocardial ischemia. According to Camici and Crea, patients with LVH have type 2 CMD (ie, occurring in the absence of demonstrable coronary artery disease (CAD), but with evidence of myocardial disease). CMD determines significant blunting of hyperemic MBF and reduction of coronary flow reserve (CFR). This impairment of coronary physiology predicts development of LV dysfunction in patients with LVH.
study of Basso et al.\textsuperscript{46} who found evidence of ischemic damage at autopsy in 19 patients with HCM who died suddenly. Within the septal myocardium, the small intramural coronary arteries showed varying degrees of medial hypertrophy-dysplasia and intimal hyperplasia and were closely related to fibrotic scars (Figure 4). The damage was either acute/subacute necrosis or fibrotic scarring, lending support to the clinical picture of ischemia occurring in the natural history of HCM. The patchy distribution of fibrosis may also contribute to life-threatening electrical instability.\textsuperscript{46} The degree of hyperemic MBF impairment is a powerful long-term predictor of adverse LV remodelling and systolic dysfunction,\textsuperscript{47} as well as an independent predictor of death and unfavorable outcome in HCM.\textsuperscript{48}

In DCM, different studies have shown not only that MBF abnormalities occur even in the early stages of the disease and in the absence of epicardial stenosis, but also that myocardial ischemia attributable to CMD may have an independent role in the progression of the disease.\textsuperscript{49} Furthermore, it has been demonstrated that the severity of the hyperemic MBF impairment is a predictor of poor prognosis independent of the degree of LV functional impairment and of the presence of overt HF.\textsuperscript{50}

**CMD in Secondary LVH**

Patients with AH often have symptoms and signs suggestive of myocardial ischemia despite normal coronary angiograms. The abnormalities of the coronary microcirculation may be
unrelated to the degree of LVH and cause a reduction in maximum MBF and CFR. In the hypertensive heart there is remodeling of intramural coronary arterioles, because of hypertrophy of smooth muscle cells, and increased collagen deposition in the tunica media, with varying degrees of intimal thickening and perivascular fibrosis. Although the anatomic changes affecting the microcirculation are similar in hypertension and HCM, they are usually more severe in the latter condition. The remodeled, hypertrophied vascular wall leads to an increase in medial wall area, with a relative reduction of the vessel’s lumen. These changes are induced, at least in part, by excessive activation of the RAAS. In fact, treatment with angiotensin-converting enzyme inhibitors may revert microvascular remodeling and improve MBF in experimental and clinical AH. In patients with stage 1 or 2 AH and LVH, CFR is transmurally blunted and inversely related to systolic blood pressure. Detection of CMD is crucial to identify patients with AH at higher risk of developing LV dysfunction and HF. In a study investigating the prognostic role of CMD in 2,783 consecutive patients with suspected or known CAD (80% of patients had AH), it was found that CFR was a powerful, independent predictor of cardiac mortality and provided meaningful incremental risk stratification over other known risk factors. In particular, patients in the highest tertile of CFR, indicating preserved vasodilator function, had an extremely low rate of cardiac mortality (<0.5%/year). Conversely, intermediate and severely reduced CFR were associated with an adjusted hazard ratio for cardiac mortality of 3.4 and 5.6, respectively. In that study, the addition of CFR to clinical variables, such as rest LVEF, LVEF reserve and the extent of myocardial scarring, resulted in the correct reclassification of approximately one-third of all intermediate risk patients.

In patients with severe AS, CFR impairment is directly proportional to the reduction of aortic valve area and diastolic perfusion time, but there is no significant correlation with LVM. Moreover, CFR increases after aortic valve replacement and this increase occurs in parallel with regression of LV hypertrophy.

Reduced CFR can be demonstrated not only in patients with pressure overload but also in those with volume overload, such as MR, where CFR is reduced mainly because of elevation of the baseline resting flow velocity. This reduction of CFR correlates with the increase in LV preload, mass and volume overload and CFR improves after mitral valve surgery. A reduced CFR was demonstrated only in an animal model of AR.

**Myocardial Ischemia, Tissue Fibrosis and Progression From LVH to LV Dysfunction and HF**

Myocardial fibrosis is an important determinant in the pathogenesis of HF, regardless of etiology. It may be regional, such as the replacement fibrosis observed following myocardial infarction, or a more diffusely distributed interstitial fibrosis as observed in the most advanced cardiomyopathies. Histopathological studies have shown that the myocardial fibrosis in HCM, AH and AS is associated with increased risk of cardiac sudden death and congestive HF. Cardiovascular magnetic resonance (CMR) offers a unique opportunity to noninvasively quantify LVM and myocardial fibrosis with high accuracy and reproducibility, by means of late gadolinium enhancement (LGE). Replacement myocardial fibrosis following experimental myocardial infarction in animals coincides with areas of LGE in which transmural extension is also used to assess myocardial viability.

Midwall LGE is present in nonischemic DCM, where it has been associated with adverse cardiac remodeling and increased risk of malignant arrhythmia. Even in the absence of replacement fibrosis, increased extracellular collagen (interstitial fibrosis) is found in many cardiac conditions. Diffuse myocardial fibrosis and remodeling of the myocardial extracellular space can be measured through changes in native (non-contrast) myocardial T1 relaxation times, post-contrast T1 times, and derived estimates of extracellular volume (ECV), using both native and post-contrast T1 values. These techniques can help to discriminate the different etiologies of LVH and detect progression of disease.

**Myocardial Fibrosis in Primary LVH**

In HCM, replacement fibrosis can be the consequence of chronic, repeated episodes of microvascular ischemia, leading to myocyte death and replacement of the space with myofibroblasts, leading to progressive systolic impairment. Approximately 70% of HCM patients have evidence of LGE on CMR. Olivotto et al found substantial amounts of LGE in a subset of patients with HCM and low-normal EF values (50–65%) in comparison with patients with higher EF, but little or no association was found between EF and several standard clinical and demographic parameters, such as age, sex, LV cavity dimensions, wall thickness or LVM. Myocardial fibrosis was an independent predictor of adverse outcome in the study by O’Hanlon et al, which assessed the presence, amount and prognostic role of LGE in 217 patients with HCM followed for 3.1±1.7 years. LGE is also associated with an increased prevalence of ventricular tachyarrhythmia and sudden death. A word of caution is necessary, though; indeed Ismail et al confirmed that the amount of myocardial fibrosis was a strong predictor of sudden cardiac death, but this effect was offset after adjusting for LVEF. Thus, despite being a valuable marker, LGE does not provide the incremental independent prognostic information to LVEF and further work is required to clarify the reciprocal role of myocardial fibrosis and other markers of risk in HCM.

In DCM, diffuse interstitial fibrosis can be frequently observed in histological specimens and can lead in the long term to irreversible replacement fibrosis. The occurrence of replacement fibrosis in patients with DCM is approximately 35%. Myocardial fibrosis in DCM patients has been identified as an independent predictor of adverse clinical outcomes. The presence of midwall fibrosis is an independent predictor of all-cause mortality and cardiovascular hospitalization, independent of ventricular remodeling and EF. In addition, midwall fibrosis predicts sudden cardiac death and ventricular tachyarrhythmia, especially if the conduction system is involved, suggesting a potential role for CMR in the risk stratification of patients with DCM who may need device therapy.

**Myocardial Fibrosis in Secondary LVH**

In 83 patients with AS, AH, or HCM, LGE was present with a high prevalence in all forms of LVH (AS 62%, AH 50%, HCM 72%) without significant differences between primary and secondary LVH, and correlated with the LVM. The results of that study suggest that LGE is a common finding in adaptive LVH caused by pressure overload and the patchy pattern is most likely caused by focal ischemic necrosis. In a study of AH, patients with nocturnal non-dipper blood pressure patterns had larger LVM and scar volume than those with dipper patterns. In moderate and severe AS, both ischemic subendocardial
Conclusions

Pathological LVH develops in response to different genetic, physical and biochemical stimuli and represents the first step in ventricular remodeling. Although LVH can be initially compensatory, eventually it may become maladaptive and evolve towards progressive LV dysfunction and HF.

Both interstitial and replacement fibrosis play a major role in the progressive decompensation of the hypertrophied LV. CMD and myocardial ischemia, which have been demonstrated in most forms of pathological LVH, have an important pathogenetic role in the formation of replacement fibrosis and contribute to the evolution towards LV dysfunction and HF (Figure 5). Noninvasive imaging allows detection of myocardial fibrosis and CMD, thus providing unique information for the stratification of patients with LVH.

Disclosures

P.G.C. acts as a consultant for Servier.

References


