Biomarkers of pathophysiology in hypertrophic cardiomyopathy: implications for clinical management and prognosis

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The study of biomarkers and their signalling pathways has allowed the development of new therapeutic strategies in a range of disorders. The aim of the present systematic review is to provide an overview of different biomarkers in patients with hypertrophic cardiomyopathy that could give some insight into the pathophysiological mechanism(s) underlying the typical clinical and histological manifestations of the disease. Several pathophysiological models are presented and discussed, including studies that have investigated these biomarkers for diagnostic and prognostic reasons, in relation to disease progression and/or mortality.

Keywords
Hypertrophic cardiomyopathy • Biomarkers • Pathophysiology

Introduction

Hypertrophic cardiomyopathy (HCM) has been defined morphologically by unexplained hypertrophy in the absence of haemodynamic stress, and at the histological level by myocyte disarray, fibrosis, and abnormalities of the intramyocardial small vessels. HCM is a monogenic cardiac disease with an autosomal dominant pattern of heritability and different penetrance, with a prevalence in the general population of 1/500. Mutations in 11 genes of contractile sarcomeric proteins have been shown to produce the disease, and more than 400 different mutations have been discovered so far, most of them of the missense type. In at least 25% of patients, asymmetrical septal hypertrophy leads to a significant pressure gradient between the apical left ventricular (LV) chamber and the left ventricular outflow tract (LVOT), resulting in the so-called ‘hypertrophic obstructive cardiomyopathy’ (obstructive HCM) presentation.

Majority of patients with obstructive HCM are asymptomatic but some can present with heart failure or arrhythmias. Thromboembolic events are frequent and potentially serious causes of mortality and morbidity amongst HCM patients. Indeed, the incidence of stroke is around 3% per patient-year, especially in patients with HCM an atrial fibrillation, or those with obstructive HCM. Arrhythmias and premature sudden cardiac deaths (SCDs) are also common in HCM. Ultimately, about 10% of obstructive HCM patients progress to an end-stage dilated phase with LV wall thinning, cavity enlargement, and systolic dysfunction that resembles a dilated cardiomyopathy.

Biomarkers are molecules that are objectively (and easily) measured by laboratory techniques, which can give us useful information about normal biological processes, abnormal pathophysiology, and prognosis, as well as in assisting differential diagnosis. The most active fields in cardiovascular medicine in which biomarkers have shown to be useful are ischaemic heart disease and heart failure. Such biomarkers have also been used to predict the risk for coronary artery disease and its sequelae. For example, B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-pro-BNP) are useful in the diagnostic and prognostic pathway for patients with heart failure.

Could biomarkers help in understanding the pathophysiology of HCM? The clinical and pathological characteristics of HCM could involve a number of diverse mechanisms that include inflammation, endothelial dysfunction, fibrosis, and extracellular matrix degradation, as well as coagulation and platelet activation. In each of...
these processes, different molecules involved in the different pathophysiological pathways can be detected in the blood, providing us with information on subgroups of patients may be at increased risk for subsequent cardiovascular events. The detection of appropriate biomarkers could potentially provide tools to diagnose and stratify these patients.

The aim of the present systematic review is to provide an overview of different biomarkers in patients with HCM that could give some insights into the pathophysiological mechanism(s) underlying the typical clinical and histological manifestations of the disease.

Search strategy

We performed a comprehensive literature search by using electronic bibliographic databases (MEDLINE, EMBASE, The Cochrane Library, and DARE) and combinations of the following keywords: HCM, treatment, hypertrophy, cardiomyopathy, inflammation, cytokines, C-reactive protein, interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), s-Fas, s-FasL, apoptosis, endothelin, Von Willebrand factor (vWF), soluble thrombomodulin (sTM), tissue factor pathway inhibitor (TFPI), asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA), platelet function, CD40 ligand, soluble CD40 ligand, Beta thromboglobulin (β-TG), P-Selectin, coagulation markers, fibrinogen, platelet-derived growth factor (PDGF), fibrinopeptide A, thrombin-antithrombin III complex, fibrinolysis, thrombotic, prothrombic fragment 1 + 2 (F1+2), D-Dimer, plasmin-alpha2-plasmin inhibitor complex, aldosterone, fibrosis, apoptosis, matrix metalloproteinases (MMPs), tissue inhibitor of matrix metalloproteinases (TIMPs), brain natriuretic peptide (BNP), NT-pro-BNP, atrial natriuretic peptide (ANP), insulin growth factor-1 (IGF-1), transforming growth factor-β (TGF-β), angiotensin 2, and calcineurin.

Bibliographies of all selected articles and review articles were reviewed for other relevant articles. Where necessary, study authors were contacted to obtain further data.

Morphological and microscopic characteristics of hypertrophic cardiomyopathy

Macroscopically, HCM is characterized by unexplained left or right ventricular hypertrophy in the presence of an increased external load, which is usually asymmetric in affecting different portions of the ventricles.

Microscopic changes in obstructive HCM include myocyte hypertrophy and disarray, as well as increased interstitial fibrosis and small intramural coronary artery abnormalities. Myocyte disarray is a characteristic feature of HCM, seemingly preceding hypertrophy and fibrosis. The high degree of disarray observed in obstructive HCM is distinctive and involves substantial portions of LV wall.

Fibrosis is another important component of the pathophysiology of obstructive HCM. Histological examination demonstrates an increase of connective tissue between individual cells and deposition of large amounts of collagen and fibronectin. However, the distribution and severity of fibrosis can be quite variable.

For example, fibrosis is greater beneath the endocardium and is more prominent in the interventricular septum area compared to the free LV wall.

Abnormalities in small intramural coronary arteries and subendocardial arterioles have also been observed at autopsy in obstructive HCM subjects. The walls of these intramural vessels, especially in the ventricular septum, are thickened and the vessel lumen is frequently narrowed. There is hypertrophy of the intima and an abnormal ultrastructure of endothelial cells, providing a morphological substrate for functional impairment of the endothelium. These abnormal vessels are usually within the areas of fibrous tissue or in close proximity to these areas.

Pathophysiology of hypertrophic cardiomyopathy

While the aetiology of HCM has been extensively studied, its pathogenesis is not completely understood. All of the knowledge accumulated has largely been obtained from animal models. Indeed, the initial defects caused by the mutant proteins are diverse and a common mode of pathogenesis is believed to exist, ultimately converging into impaired cardiac myocyte function.

In vitro functional studies have shown that HCM mutants alter sarcomere function in two different ways: first, by decreasing the translocating filament activity and/or force leading to a reduction of power production. It can also increase in vitro motility rates of filament sliding and/or force. The molecular changes subjacent to these observations seem to vary, and include reduced crossbridge kinetics, reduced ATPase activity, altered calcium sensitivity, and impaired excitation–contraction coupling. Altogether these points to the diversity of the molecular and cellular mechanisms could be involved in the pathogenesis of the final HCM phenotypes seen clinically.

It is still unknown how a mutation of a sarcomeric protein, the functional defect observed, and the development of the microscopic characteristics of HCM are linked. Several hypotheses have been proposed. The most accepted one suggests that HCM mutations induce functional defects in myocyte contractility, thus producing diastolic and systolic dysfunction that induces increased wall stress, a reduction of stroke volume, and, consequently, an activation of stress responsive trophic and mitotic factors (such as ACE1, angiotensin II, IGF-1, TGF-β, TNF-α, IL-6, and endothelin). These molecules increase the entrance of calcium into the cells and the activation of transcriptional pathways that lead to the diverse histological and structural phenotypes of HCM including cardiac hypertrophy, interstitial fibrosis, and myocyte disarray.

The problem with this hypothesis is that not all the mutations produce hypocontractility, as HCM mutations in some thin filament regulatory proteins (e.g. troponin I and α-tropomyosin) actually increase the force of contraction. Therefore, decreased contractility per se cannot be the sole stimulus to hypertrophy. In an alternative model where there is an increase in the force of
contraction, the induced hypertrophy is directly as a consequence of hypercontractility.22

The final model that can explain the hyper- and hypocontractility observed in both previous models is the 'energy compromise' hypothesis.35 For example, myosin ATPase uses at least 70% of adenosine triphosphate (ATP) hydrolysis in the cardiac myocyte, and perturbation of either the motor itself or its regulation may alter the efficiency of ATP usage by the sarcomere.31 In HCM patients, there is a reduction of the phosphocreatine to ATP ratio, which is an indicator of the energetic state of cardiac muscle. Such inefficient utilization of ATP results in the need for more energy to produce the same amount of force. For example, in an α-MHC403/+ murine model of HCM, the demand of more ATP to produce myocyte contraction results in ATP depletion, thus affecting a highly ATP-dependent process, the sarcoplasmic reticulum calcium pump (SERCA), leading to accumulation of Ca++ in the citosol29 (Figure 1).

Support for this hypothesis comes from the study of other human diseases that limit myocardial energy production or cellular energy homeostasis, such as mitochondrial tRNA mutations,36 Friedreich's ataxia,37 defects in fatty acid uptake through CD36 deficiency,38 mitochondrial fatty acid oxidation through very-long chain acyl-CoA dehydrogenase deficiency,39 and mutations in the g2 regulatory subunit of AMP-activated protein kinase.40,41 Consequently, less ATP is available to maintain normal calcium reuptake, and thus, there is an increase in the citosolic calcium and activation of calcium-dependent transcriptional signals [the most important of which seems to be calcineurin, and the downstream transcription factors NFAT (nuclear factor of activated T cells) and MEF-2 (myocyte enhancer factor)] leading to hypertrophy and fibrosis.42–44

Of note, homeostasis of calcium in the sarcomere is of great importance in the pathogenesis of HCM. Evidence of this role comes from the study of mutations in calcium regulatory proteins showing the development of HCM phenotype.45 The accumulation of free Ca++ results in an increase in both the transcription and translation of proteins involved in calcium handling, such as SERCA, NCX, and RyR2, leading to an increase in the production of these proteins. This increase in protein production results in an increase in the amount of calcium available for contraction, leading to an increase in the force of contraction. Therefore, the increase in intracellular calcium can be due to two different mechanisms. On one hand, following the theory of energy depletion, the mutated sarcomeric proteins will use more adenosine triphosphate to produce the same force of contraction. Therefore, it will compromise calcium reuptake by the SERCA transporter into the endoplasmic reticulum and more calcium will be available inside the cells. On the other hand, activation of a number of different receptor classes lead to an increase in intracellular calcium; these include angiotensin II, endothelin-1, TNF-α, and IL-6 and their signalling pathways including the mitogen-activated protein kinase cascade (MAPK), protein kinase C (PKC), the phosphatidyl inositol kinase (PI(3)K)/Akt/glycogen synthase kinase 3β (GSK3β) pathway. This increase in intracellular calcium will modulate transcription via modification of nuclear factors of activated T cells (NFAT), myocyte enhancer factor-2 (MEF2) that will induce hypertrophy through the activation of foetal isoforms of proteins. The same molecules aforementioned plus aldosterone and TGF-β will activate pathways that will modulate the production of transcription factors such as nuclear factor kappa B (NF-κB), activating protein-1 (AP-1), small mothers against decapentaplegic (SMAD), signal transducer, and activator of transcription (STAT) that will be integrated and eventually will drive MMPs and TIMPs transcription remodelling the extracellular matrix. Sr, sarcoplasmic reticulum; SERCA, sarcoplasmic reticulum calcium pump; CaM, calmodulin; SHR, steroid hormone receptor, HRE, hormone response element.

Figure 1 Schematic demonstrating in summary some of the known hypertrophic and fibrosis signalling pathways. Calcium plays a central role in the pathogenesis of hypertrophic cardiomyopathy (HCM). The increase in intracellular calcium could be due to two different mechanisms. On one hand, following the theory of energy depletion, the mutated sarcomeric proteins will use more adenosine triphosphate to produce the same force of contraction. Therefore, it will compromise calcium reuptake by the SERCA transporter into the endoplasmic reticulum and more calcium will be available inside the cells. On the other hand, activation of a number of different receptor classes lead to an increase in intracellular calcium; these include angiotensin II, endothelin-1, TNF-α, and IL-6 and their signalling pathways including the mitogen-activated protein kinase cascade (MAPK), protein kinase C (PKC), the phosphatidyl inositol kinase (PI(3)K)/Akt/glycogen synthase kinase 3β (GSK3β) pathway. This increase in intracellular calcium will modulate transcription via modification of nuclear factors of activated T cells (NFAT), myocyte enhancer factor-2 (MEF2) that will induce hypertrophy through the activation of foetal isoforms of proteins. The same molecules aforementioned plus aldosterone and TGF-β will activate pathways that will modulate the production of transcription factors such as nuclear factor kappa B (NF-κB), activating protein-1 (AP-1), small mothers against decapentaplegic (SMAD), signal transducer, and activator of transcription (STAT) that will be integrated and eventually will drive MMPs and TIMPs transcription remodelling the extracellular matrix. Sr, sarcoplasmic reticulum; SERCA, sarcoplasmic reticulum calcium pump; CaM, calmodulin; SHR, steroid hormone receptor, HRE, hormone response element.
HCM patients are IL-6 and TNF-α protein. Inflammatory biomarkers that have been most studied in HCM and IL-6 drive production of reactant proteins, including C-reactive protein. Cytokines are pleiotropic proteins that regulate leukocyte activity. Inflammatory biomarkers

HCM with LGE by CMR

References | Biomarker | Patient population | Findings
---|---|---|---
Zen et al. (2005) | IL-6, TNF-α, ANP, BNP, s-Fas, s-FasL | 38 HNCM, 11 DHCM patients, and 10 normal subjects | In HNCM and DHCM, TNF-α and IL-6 were slightly higher compared with normal subjects and sFas increased significantly. IL-6 was significantly higher in DHCM compared with HNCM. Thus, IL-6 may play an important role in the status of HCM and its progression to DHCM
Hogre et al. (2004) | IL-6, TNF-α | 19 patients with HCM, 31 patients with DCM, and 20 healthy subjects | TNF-alpha was not elevated in HCM. The markedly elevated IL-6 levels did not correlate with the left ventricular function in HCM patients
Nagae et al. 2001 | TNF-α | 15 HOCM patients at baseline and after successful NSRT | Significant reduction of TNF-α alters non-surgical septal reduction therapy. TNF-α may play a pathogenetic role in the hypertrophy of pressure overload
Buzas et al. (2004) | IL-6, TNF-α, sFas, sIL-6R | 31 DCM patients, 19 HCM patients, and 20 healthy controls | HCM patients have higher IL-6 and sIL-6R levels when compared with healthy individuals. DCM patients exhibit elevated concentrations of TNF-alpha, sFas, IL-6, and sIL-6R. The data indicate the activation of the pro-apoptotic TNF and Fas pathways in DCM patients, and an anti-apoptotic shift in HCM patients
Penicka et al. (2001) | sTNFRI | 66 patients with HCM and 30 age-matched healthy subjects | sTNFRI levels were higher in severely symptomatic patients, and in patients with reduced LV systolic and diastolic reserve during dobutamine stress echocardiography
Dimitrow et al. (2007) | C-reactive protein | 42 HCM patients (16 with LVOT obstruction) and 29 controls | C-reactive protein levels are different between control and HCM patients but only due to the subgroup with LVOT obstruction
Payá et al. (2008) | C-reactive protein | 120 patients with HCM, 83 HCM with LGE by CMR | No relation between C-reactive protein values and fibrosis, severity of hypertrophy, clinical symptoms nor any of the clinical variables known to be associated to prognosis in HCM, including NT-pro-BNP

ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; DCM, dilated cardiomyopathy; DHCM, dilated hypertrophic cardiomyopathy; HCM, hypertrophic cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; HNCM, hypertrophic non-obstructive cardiomyopathy; IL-6, interleukin 6; LV, left ventricle; LVOT, left ventricular outflow tract; NSRT, non-surgical septal reduction therapy; sFas, soluble Fas; s-FasL, soluble Fas ligand; sIL-6R, soluble interleukin 6 receptor; sTNFRI, soluble tumour necrosis factor receptor 1; TNF-α, tumour necrosis factor α; LGE, late Gadolinium enhancement.

Biomarkers associated with hypertrophic cardiomyopathy

Inflammatory biomarkers

Cytokines are pleiotropic proteins that regulate leukocyte activity. In the acute-phase response, cytokines such as interleukin (IL)-1 and IL-6 drive production of reactant proteins, including C-reactive protein. Inflammatory biomarkers that have been most studied in HCM patients are IL-6 and TNF-α.67–51 (Table 1). Both can be expressed in the myocardium under various forms of stress and are capable of modulating cardiac function by a variety of mechanisms including the induction of LV hypertrophy, cardiomyopathy, and apoptosis in cardiac myocytes.50–56 Indeed, the progressive loss of cardiac myocytes due to apoptosis would contribute to the overall deterioration of myocardial function.56

IL-6 is a pro-inflammatory cytokine secreted by all the nucleated cells of the heart. IL-6 is also considered a ‘myokine’, which is a cytokine produced in the muscle that is elevated in response to muscle contraction. Indeed, skeletal muscle is a major source of this cytokine. Smooth muscle cells in the tunica media of many blood vessels also produce IL-6, as a pro-inflammatory cytokine.57 IL-6 may also induce the expression of MMPs and TNF-α.59 HCM patients have higher levels of IL-6 compared with healthy controls.47,50,51 However, IL-6 levels did not correlate with LV function,48 although the overexpression of IL-6 and IL-6 receptor in mice leads to the development of cardiac hypertrophy.53

TNF-α is a multifunctional cytokine with a broad range of concentration-dependent effects involved in systemic inflammation, the regulation of immune cells function, and stimulation of the acute phase reaction. TNF-α has been detected in several human cardiac-related conditions, including congestive heart failure, the hypertrophic growth response in cardiac myocytes, and septal cardiomyopathy.52,59 TNF-α can also participate in different pathways causing apoptosis50 and it is a cytokine capable of producing fibrosis through the activation of MMPs and TIMPs.51 Various studies in HCM have generally found an increase in TNF-α levels,47,49 with one exception.48 It is plausible that TNF-α may play a pathogenetic role in HCM. While pressure or volume overload contributes to the development of left
hypertrophy and cardiomyopathy,\textsuperscript{62} septal ablation of HCM patients leads to a reduction of TNF-\(\alpha\), myocyte size, and collagen content that is accompanied by an increase in LV volumes and a reduction in LV hypertrophy and chamber stiffness.\textsuperscript{49} Genetic studies show that an uncommon allele of the TNF-\(\alpha\)-308G/A polymorphism, which produces more TNF-\(\alpha\), is associated with greater LV mass index and clinical diagnosis at a younger age in patients with HCM.\textsuperscript{61} Finally, it has been shown that transgenic mice that overexpress TNF-\(\alpha\) develop LVH, dilated cardiomyopathy, and premature death.\textsuperscript{52} There are also significant differences in soluble TNF receptor 1 (sTNFR1) serum levels between patients with HCM and healthy subjects.\textsuperscript{64} The levels can be related to functional class, being higher in patients with NYHA III–IV and also with reduced LV systolic and diastolic reserve during dobutamine stress echocardiography.\textsuperscript{64} Importantly, TNF-\(\alpha\) may play an important role in the status of HCM and its progression to dilated HCM. Indeed, increases in TNF-\(\alpha\) are marked in those patients with the dilated phase of HCM indicating a strong pro-apoptotic activation effect.\textsuperscript{47} It is possible that the sustained long-term overexpression of TNF-\(\alpha\) may induce cardiac myocyte apoptosis.\textsuperscript{65}

An inflammatory marker, C-reactive protein has also been studied in HCM. For example, Dimitrow et al.\textsuperscript{66} showed that C-reactive protein was more elevated in HCM patients than in controls. In our laboratory, we failed to demonstrate a relation between C-reactive protein values with fibrosis as measured by MRI, the severity of hypertrophy, clinical symptoms nor any of the clinical variables known to be associated to prognosis in HCM, including NT-pro-BNP.\textsuperscript{67}

In summary, TNF-\(\alpha\) and IL-6 might be involved in the pathogenesis of HCM, but there is no clear activation mechanism. It is possible that an increase in mechanical overload could be the trigger that stimulates the production of these two cytokines (IL-6 and TNF-\(\alpha\)).\textsuperscript{58} IL-6 may induce the expression of MMPs and TNF-\(\alpha\) causing fibrosis.\textsuperscript{58} In mice, the overexpression of IL-6 and IL-6 receptor leads to the development of cardiac hypertrophy;\textsuperscript{53} it is possible that this will work in the same way in humans. Elevated TNF-\(\alpha\) levels may identify patients with a more severe cardiomyopathy, as well as early progression to a dilated cardiomyopathy who could benefit from more aggressive intervention.

**Apopotic biomarkers**

Fas is an apoptosis-signalling receptor molecule on the surface of a number of cell types including the mycardium. Fas antigen is expressed in various tissues, and its soluble form, sFas, lacks the transmembrane domain.\textsuperscript{69} Binding of sFas to Fas inhibits apoptosis (Table 1).\textsuperscript{70}

A related molecule, Fas ligand (Fas-L) is a type II transmembrane protein that belongs to the TNF family. The binding of Fas-L, sFas-L, or agonistic anti-Fas antibodies to Fas induces apoptosis in the targeted cell.\textsuperscript{71,72} Plasma sFas-L levels in patients from HCM group are significantly decreased compared to normals and this reduction was even more marked in patients with dilated HCM.\textsuperscript{47} sFas is also increased significantly in HCM compared to normal subjects, and dilated HCM patients with high sFas levels demonstrated deterioration of mitral E wave deceleration time, an index of LV diastolic function, as well as a high incidence of worsening heart failure.\textsuperscript{47} Thus, plasma sFas levels could potentially be a prognostic predictor in dilated HCM patients.

**Markers of endothelial function**

Microvascular dysfunction is a common finding in HCM patients and its extent is an important prognostic marker.\textsuperscript{73} Impairment of endothelium-dependent coronary vasodilatation has been shown in patients with HCM.\textsuperscript{74–77} These patients had an abnormal vasoconstrictor response of the coronary artery to acetylcholine,\textsuperscript{74} the cold pressor test,\textsuperscript{77} and pacing stimulation,\textsuperscript{76} which are various stressor tests that measure endothelium-dependent vasomotor reactivity. Extravascular compressive forces may play an important role in the microvascular dysfunction in HCM.\textsuperscript{78} In addition, hyperaemic myocardial blood flow as measured by PET scan is severely blunted, with particularly pronounced hypoperfusion at the subendocardial layer, indicative of microvascular dysfunction (Table 1).\textsuperscript{73,78}

Plasma vWF is an established marker of endothelial damage/dysfunction.\textsuperscript{79,80} Only two published articles have compared vWF levels between patients with HCM and age- and gender-matched controls. There were no statistically significant differences between both groups and vWF levels were not related to functional class.\textsuperscript{81,82}

Recently, Dimitrow et al.\textsuperscript{82} found that other markers of endothelial dysfunction, such as soluble thrombomodulin (sTM) and tissue factor pathway inhibitor (TFPI) were elevated in HCM compared to healthy individuals. Also, there was an elevation of markers related to the nitric oxide pathways, including asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA).\textsuperscript{82} The obstructive HCM subgroup displayed higher values of ADMA, SDMA, and sTM compared with the non-obstructive HCM subgroup.\textsuperscript{82} These findings suggest that endothelium in HCM could well be functionally abnormal.

Endothelin-1 (ET-1) is a potent vasoconstrictor produced by vascular endothelial cells and causes hypertrophy in cultured heart muscle cells,\textsuperscript{84} perhaps by activating the reexpression of cardiac-specific foetal genes.\textsuperscript{84} In HCM patients, ET-1 levels are significantly increased by more than two-fold compared with controls.\textsuperscript{85,86} ET-1 mRNA synthesis in the heart is also upregulated in hypertrophied hearts by pressure overload.\textsuperscript{87,88} It is uncertain whether the increase of ET is the cause of the hypertrophy or it contributes to the pathophysiology of HCM. However, there is a report showing that ET\(_A\) (receptor antagonist A) blockade can cause LV hypertrophy by pressure overload in vivo, suggesting a role of ET-1 in the development of cardiac hypertrophy.\textsuperscript{87}

HCM patients have well-documented evidence of endothelial dysfunction, which can be detected in peripheral blood as elevation of endothelial-related biomarkers, as well as impaired endothelium-dependent coronary vasodilatation. The precise mechanisms of endothelial dysfunction in HCM are unknown, but the impaired hyperaemic myocardial blood flow correlates independently with LV mass. It is possible that a thickened ventricle could generate extravascular compressive forces that play a role in the microvascular dysfunction seen in HCM. Another possibility is the induction of structurally abnormal and altered endothelial...
hypertrophy by platelet derived growth factor (PDGF), which is produced by disturbed platelets (see below).

**Platelets and platelet function**

Yarom et al.\(^9\) were the first to show morphometric and chemical differences in platelets in HCM patients that consisted in increased cell size, decreased phosphorus concentration, and increased permeability to cations, suggesting membrane and energy metabolism aberrations in such patients. Patients with HCM had high induced and spontaneous platelet aggregation which was positively correlated with LVH mass.\(^3\) Moreover, platelets were especially sensitive to the aggregation with a thromboxane A2 analogue \(^8\). The inhibition of PDGF signalling using receptors antagonists could open a new future field in the treatment of HCM, but many more studies are required.

**Prothrombotic markers**

Thromboembolic events in patients with HCM are very frequent. Alterations in the plasma levels of molecular markers of the prothrombotic and fibrinolytic status have been reported in patients with HCM (Table 2).

### Table 2: Endothelial, platelet function, and coagulation biomarkers in hypertrophic cardiomyopathy patients

<table>
<thead>
<tr>
<th>References</th>
<th>Biomarker</th>
<th>Patient population</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimitrow et al. 2007(^6)</td>
<td>TAT, F1+2, sCD40L, β-TG; P-selectin; IL-6; TNF-α</td>
<td>HCM patients (16 with LVOT obstruction and 29 controls)</td>
<td>LVOT obstruction is independently associated with enhanced thrombin generation and platelet activity in HCM</td>
</tr>
<tr>
<td>Varol et al. 2005(^5)</td>
<td>vWF</td>
<td>29 HCM and 29 control subjects</td>
<td>vWF levels are not increased in patients with hypertrophic cardiomyopathy and there is no relation to functional class</td>
</tr>
<tr>
<td>Dimitrow et al. 2007(^2)</td>
<td>sTM, vWF, TFPI, ADMA, SDMA</td>
<td>29 HCM patients including 11 with LVOT obstruction and 29 controls</td>
<td>sTM, TFPI, ADMA, and SDMA were elevated in HCM patients compared with controls. vWF levels were similar in both groups. In LVOT subgroup, higher values of ADMA, SDMA, and sTM were found compared with the HNCM. In conclusion, HCM patients show specific features of endothelial dysfunction</td>
</tr>
<tr>
<td>Hasegawa et al. 1996(^8)</td>
<td>Endothelin-1</td>
<td>26 HCM and 6 control subjects</td>
<td>Endothelin-1 was more than two-fold higher in hypertrophic cardiomyopathy patients than in control subject</td>
</tr>
<tr>
<td>Ogino et al. 2004(^9)</td>
<td>Endothelin-1</td>
<td>40 patients with HCM, 35 with hypertension, and 15 controls</td>
<td>Endothelin-1 concentrations were only slightly higher in HCM patients than in hypertensive and control patients</td>
</tr>
<tr>
<td>Yarom et al. 1982(^8)</td>
<td>Platelet</td>
<td>5 HCM patients</td>
<td>Increased cell size, decreased phosphorus concentrations, and increased permeability to cations in HCM patients</td>
</tr>
<tr>
<td>Riazanov et al. 2000(^9)</td>
<td>Platelet aggregation</td>
<td>45 HCM and 15 healthy controls</td>
<td>HCM patients have higher induced with thromboxane A2 analogue and spontaneous platelet aggregation. There is a positive correlation between platelet aggregation and the degree of LVH</td>
</tr>
<tr>
<td>Yamamoto et al. 1995(^9)</td>
<td>PF-4; β-TG, PLN-α2PI complex; fibrinopeptide A; TAT, D-dimer</td>
<td>13 patients with HCM, 17 DCM, and 20 normal subjects</td>
<td>Plasma levels of fibrinopeptide A and TAT in both patient groups were significantly higher than those in normal subjects. Plasma levels of D-dimer were higher in DCM patients</td>
</tr>
</tbody>
</table>

ADMA, asymmetric dimethylarginine; β-TG, beta-thromboglobulin; DCM, dilated cardiomyopathy; F1+2, prothrombin fragment 1+2; HCM, hypertrophic cardiomyopathy; HNCM, hypertrophic non-obstructive cardiomyopathy; IL-6, interleukin 6; LVOT, left ventricular outflow tract; PLN-α2PI complex, plasmin-alpha 2-plasmin inhibitor complex; PF4, platelet factor 4; P-selectin; sCD40-L, soluble CD40 ligand; SDMA, symmetric dimethylarginine; sTM, soluble thrombomodulin; TAT, thrombin-antithrombin III complex; TFPI, tissue factor pathway inhibitor; TNF-α, tumour necrosis factor α; vWF, von Willebrand factor.
Biomarkers of pathophysiology in HCM

Table 3 Fibrosis biomarkers and hormones in hypertrophic cardiomyopathy patients

<table>
<thead>
<tr>
<th>References</th>
<th>Biomarker</th>
<th>Patient population</th>
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<tbody>
<tr>
<td>Stroud et al. 2005</td>
<td>TIMP-4</td>
<td>18 normal and 16 HCM after alcohol-induced MI</td>
<td>Plasma TIMP-4 levels increased by 250% in the HCM patients when compared with normal controls</td>
</tr>
<tr>
<td>Fassbach and Schwartzkopff (2005)</td>
<td>PICP, ICTP, MMP-1, TIMP-1</td>
<td>26 HCM patients and 38 controls</td>
<td>TIMP-1 and PICP were elevated in HCM. Free MMP-1 was lower in HCM. Inhibition of collagenolysis by means of reduction of TIMP-1 and the increased production of PICP indicate collagen accumulation (fibrosis)</td>
</tr>
<tr>
<td>Lombardi et al. (2003)</td>
<td>PIINP, PICP, PINP, ICTP, MMP-1, MMP-2, MMP-9, TIMP-1</td>
<td>36 HCM patients and 14 controls</td>
<td>Patients had higher levels of PIINP, ICTP, MMP-2, MMP-9, and TIMP-1. Collagen turnover is enhanced in HCM patients</td>
</tr>
<tr>
<td>Noji et al. (2004)</td>
<td>MMP-2; MMP-3; MMP-9; TIMP-1</td>
<td>11 DHCM, 17 HCM, and 50 age-matched control subjects</td>
<td>MMP-2 and TIMP-2 were higher in DHCM. MMP-2 concentrations increased with NYHA functional class. TIMP-1 was higher in HCM patients than in control</td>
</tr>
<tr>
<td>Roldán et al. 2008</td>
<td>NT-pro-BNP, MMP-1; MMP-2 and MMP-9; TIMP-1</td>
<td>67 HCM patients</td>
<td>MMP-2 was associated with dyspnoea. MMP-9 was an independent factor associated with the presence of fibrosis in CMR. NT-pro-BNP was associated with fibrosis</td>
</tr>
<tr>
<td>Tsybaulev et al. (2004)</td>
<td>Aldosterone</td>
<td>11 HCM patients and 8 controls</td>
<td>Plasma aldosterone was similar between both groups. Myocardial aldosterone and aldosterone synthase mRNA levels were elevated by four- to six-fold in humans with HCM</td>
</tr>
<tr>
<td>Saeki et al. (2003)</td>
<td>IGF-1 and IGFBP-1</td>
<td>39 HOCM, 67 HNCM, and 18 DHCM</td>
<td>IGF-1 levels were higher in patients with HCM and lower in patients with DHCM. IGFBP-1 levels were significantly higher in patients with DHCM than in the other two groups</td>
</tr>
</tbody>
</table>

CMR, cardiac magnetic resonance; DHCM, dilated hypertrophic cardiomyopathy; HCM, hypertrophic cardiomyopathy; HNCM, hypertrophic non-obstructive cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; ICTP, type I collagen degradation product; IGF-1, insulin growth factor 1; IGFBP-1, insulin growth factor binding protein 1; MI, myocardial infarction; MMP, metalloproteinase; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; PICP, pro-collagen type I C-terminal peptide; PIIINP, N-terminal pro-peptide of collagen type III; PINP, procollagen type I N-terminal propeptide; TIMP, tissue inhibitors of metalloproteinases.

with LV diastolic volume. Dimitrow et al.66 found increased TAT and F1+2 levels in obstructive HCM, correlating positively with the LVOT gradient. Indeed, the turbulent flow in obstructive HCM might be involved in the prothrombotic state through an increase of shear stress.66

Matrix metalloproteinases

Matrix metalloproteinases (MMPs) are zinc-dependant endopeptidases with collagenase and/or gelatinase activity. Collectively they are capable of degrading various extracellular matrix proteins, but also can process a number of bioactive molecules. They play an important role in cardiac remodelling and fibrosis in other cardiovascular diseases, for example, myocardial infarction and development of dilated cardiomyopathy. MMPs are inhibited by specific endogenous tissue inhibitors of metalloproteinases (TIMPs) that comprises a family of four protease inhibitors (TIMP-1 through 4).95,96 The various molecules that influence the expression of MMPs and TIMPs in HCM patients are varied, including the renin angiotensin aldosterone system, oxidative stress, endothelin-1, TNF-α, sympathetic activation markers, and TGF-β1.97 The high grade of fibrosis seen in HCM could be due to an imbalance between MMPs and TIMPs with the accumulation of fibrous tissue (Table 3).

Impaired collagenolysis and an increased deposition of collagen have been seen in patients with HCM. In HCM, there is a reduction of MMP-1 to undetectable levels, with an increase of TIMP-1, TIMP-2, TIMP-4, MMP-2, and MMP-9.83,98–100 These changes result in enhanced collagen turnover, with an increase of collagen type I and a shift of collagen I to collagen III.99 This shift is not easy to explain because collagen I is apparently ‘stiffer’ than collagen III,101 but could well be a compensatory mechanism due to the increase in wall stiffness. MMP-2 correlates negatively with systolic function102 and levels significantly increase with higher NYHA functional class.100,102 TIMP-2 correlates positively with LV dimensions100 and diastolic dysfunction can be related to MMP-1 and MMP-2.99 In our group, we have shown that MMP-2 levels correlate with functional class and MMP-9 is an independent factor associated with late Gadolinium enhancement in cardiac magnetic resonance imaging,102 an established non-invasive method to assess the presence of fibrosis. This is important as an increase in cardiac collagen content has been associated with SCD in young patients with an 8-fold (14.1 ± 8.8 vs. 1.8 ± 1% of the tissue section; P < 0.0001) and three-fold (4.5 ± 1.3%; P < 0.001) increase compared with controls and systemic hypertensive patients, respectively.103 This raises the possibility of using treatments that could reduce the interstitial fibrosis and consequently reduce SCD. Interestingly, several authors have proposed the measurement of MMPs for the follow-up of HCM patients in order to analyse the beneficial effects of different therapies.104,105

Understanding how upstream molecules regulate MMP may provide clues to develop important therapeutic interventions. In animal models, several treatments have shown potential to reverse or attenuate interstitial fibrosis. Treatment with drugs that can block the activators of MMPs as losartan, spirinolactone, and N-acetylcysteine reduce the expression of collagen 1 alpha
(I) and TGF-β in a TnT mutant mouse, that in turn reduce interstitial fibrosis and improve diastolic dysfunction. In humans, the effects of atorvastatin on LV mass in patients with HCM have been investigated in a randomized placebo-controlled double-blind pilot study, but this did not demonstrate any effect of 9-month treatment with atorvastatin on LV mass reduction. Also in humans, the angiotensin blocker, losartan, has been shown to improve diastolic LV dysfunction in HCM, but no significant changes in LV wall and cavity measurements were observed. It is possible that some of the beneficial effects of ACE inhibitors in remodelling may be mediated through MMPs, at least in hypertensive patients. For now, the available data suggest a disturbed balance of collagen synthesis and degradation with a predominance of inhibition of collagenolysis and collagen accumulation (fibrosis), which could explain passive diastolic dysfunction in patients with HCM. MMPs are probably associated with mechanisms of remodelling in patients with HCM and the progression to systolic dysfunction and heart failure, increase of LV dimension and wall thinning.

Hormones

Aldosterone is a steroid hormone produced by the glomerulosa zone of adrenal cortex in response to several factors, the most important of which is angiotensin II. Aldosterone has been implicated in several functions including the regulation of sodium and potassium plasma concentrations as well as in cardiac hypertrophy, fibrosis, and heart failure (Table 3). 

Tsybouleva et al. showed that aldosterone is a major link between sarcomeric mutations and cardiac phenotype in HCM, although mean serum aldosterone levels were not significantly different between HCM and control subjects; however, myocardial aldosterone and cardiac aldosterone synthase (CYP11B2) mRNA levels were increased four- and seven-fold respectively, when compared with normal hearts. Aldosterone induced expression of cardiac hypertrophic markers in rat cardiomyocytes and has a profibrotic response in rat cardiac fibroblasts, inducing the expression of TGF-β1, a major profibrotic factor and in turn, the production of collagens. Blockade of mineral corticoid receptor with spironolactone in a cTnTQ92 mutant mouse model of HCM normalized myocardial collagen content, attenuated myocyte disarray, and improved diastolic function. Myocyte disarray, the pathological hallmark of HCM, seems to be due to the disruption of cadherin-mediated myocyte–myocyte adhesion at the adherens junction, which is reduced by spironolactone treatment.

Growth factors

IGF-1 has short-term insulin-like metabolic effects and long-term growth-factor-like effects on cell proliferation and differentiation of various cell types. IGF-1 is produced in different cell types and it acts locally in both autocrine and paracrine fashions. Several reports have shown that the expressions of the mRNA and protein levels for IGF-1 are increased in the myocardium of HCM. IGF-1 levels were significantly higher in patients with obstructive or non-obstructive HCM, and lower in patients with heart failure-HCM when compared with healthy control subjects. IGFBP-1 (insulin-like growth factor binding protein 1) levels are also significantly higher in HCM patients with heart failure compared to the other three groups (Table 3).

Myonecrosis markers: troponin

Troponins I and T are very sensitive and specific indicators of cardiac myocyte injury, and have been used in the diagnosis and prognosis of acute coronary syndromes. Sato et al. compared HCM patients with normal and altered troponin levels and correlated the differences with echocardiographic findings, and higher troponin levels were associated with a significantly lower fractional shortening and thicker interventricular septum. Of note, 4 of 12 patients with increased troponin T experienced end stage dilated HCM, suggesting that an increase in troponin T concentration in HCM may be an indicator of subclinical myocyte injury and/or progression to dilated HCM. In another paper, Pop et al. showed that increased troponin release may be present in patients with HCM secondary to exercise, which is reduced with β-blockade (Table 4).

The mechanism of myocyte injury in HCM is unknown. Abnormal troponin levels may be caused by relative myocardial ischaemia due to the imbalance between a hypertrophic heart and the insufficient coronary blood supply due to abnormal vessels. The other possibility is that myocyte abnormalities determined by gene mutation are causing myocyte injury. Troponins could be useful in determining the patients with higher risk to develop dilated phase of HCM and the effects of drug treatment on the evolution of HCM, but further studies are necessary.

Wall stress markers: natriuretic peptides (Table 4)

Atrial (ANP) and BNP are stable peptides that are synthesized predominantly in the atria and left ventricle, respectively, in response to elevated wall tension. Plasma levels of the peptides correlate positively with cardiac filling pressures, making them excellent markers for the presence of LV dysfunction and abnormal LV wall stress.

In various studies, plasma ANP and BNP levels were significantly increased in HCM compared with normal subjects. ANP does not correlate with symptoms or echocardiographically derived indices of LV structure or diastolic function. On the other hand, BNP levels correlate positively with symptoms of heart failure, hypertrophy severity, and Doppler echocardiographic signs of LV diastolic dysfunction. BNP has been used to predict clinical course (being worse with higher levels), peak oxygen consumption, and functional impairment. In HCM patients, both BNP and ANP are significantly higher in the subgroup that shows evidence of obstruction, and both correlate positively with left intraventricular pressure gradient. BNP in obstructive and non-obstructive HCM is 85-fold and 23-fold times elevated, respectively, compared with controls. Khan and Talwar have even proposed the measurement of BNP as an effective measure for screening of HCM, especially in children where the sensitivity of ECG and echocardiography alone is relatively low. As prognostic factors, plasma levels of NT-pro-BNP and ANP are independent predictors of cardiovascular events in patients with HCM. Elevated NT-pro-BNP levels are associated with incipient LV remodelling and fibrosis assessed by cardiac magnetic resonance, could be
used to diagnose insidious unfavourable LV remodelling and higher risk of sudden death in HCM. A recent paper proposes the clinical use of plasma BNP levels to identify non-obstructive HCM patients who are at risk of paroxysmal atrial fibrillation. As BNP is a marker of disease progression in non-obstructive HCM, serial assessment may provide non-invasive recognition of haemodynamic deterioration.

A proposed pathophysiological model linking biomarkers in hypertrophic cardiomyopathy

Trophic and mitotic factors as angiotensin II, IGF-1, TGF-β, endothelin 1, and IL-6 produced in the patients will activate the endothelium to mediate the expression of genes for growth factors, cytokines, and other proteins that drive cell proliferation, angiogenesis, and extracellular matrix remodelling.

Table 4 Wall stress and necrosis biomarkers

<table>
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<th>References</th>
<th>Biomarker</th>
<th>Patient population</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Payá et al. (2008)</td>
<td>NT-pro-BNP</td>
<td>120 patients with HCM: 83 HCM with LGE by CMR</td>
<td>HCM patients with LGE have higher levels of NT-pro-BNP</td>
</tr>
<tr>
<td>Ogino et al. 2004</td>
<td>ANP, BNP</td>
<td>40 patients with HCM, 35 with hypertension, and 15 controls</td>
<td>ANP and BNP were significantly higher in HCM than hypertensive and controls. BNP concentration significantly correlated with left intraventricular pressure gradient in HCM.</td>
</tr>
<tr>
<td>Sato et al. (2003)</td>
<td>Troponin T</td>
<td>30 HCM patients</td>
<td>Patients with positive troponin levels (&gt;0.02 ng/mL) had a FS significantly lower and interventricular septum significantly thicker. FS and VST decreased significantly between baseline and the end of a mean follow up in patients with positive troponin levels</td>
</tr>
<tr>
<td>Pop et al. (2006)</td>
<td>Troponin T</td>
<td>7 HCM patients</td>
<td>Elevated troponin levels after physical exercise that was diminished after the use of a β-blocker</td>
</tr>
<tr>
<td>Brito et al. (2004)</td>
<td>NT-pro-BNP</td>
<td>53 patients with HCM, 92 healthy relatives with no disease expression, 46 healthy volunteers</td>
<td>In HCM patients, NT-pro-BNP levels correlate directly with NYHA functional class, septal thickness, maximal wall thickness, left ventricular hypertrophy score, left atrial size, and mitral deceleration time and inversely with left atrial fractional shortening</td>
</tr>
<tr>
<td>Fahy et al. (1996)</td>
<td>ANP</td>
<td>14 HCM patients and 17 healthy controls</td>
<td>The concentration of ANP was significantly higher in patients with HCM than controls</td>
</tr>
<tr>
<td>Hasegawa et al. (1993)</td>
<td>BNP, ANP</td>
<td>39 HCM and 10 control subjects</td>
<td>Elevation of the BNP plasma level vs. control subjects, even higher in HCM. Elevation of the ANP plasma level vs. control subjects was mild</td>
</tr>
<tr>
<td>Yoshibayashi et al. (1993)</td>
<td>BNP, ANP</td>
<td>15 HNCM, 35 patients with LV hypertrophy, and 10 normal controls</td>
<td>Increased levels of BNP and ANP in HCM patients compared with controls and patients with left ventricular hypertrophy</td>
</tr>
<tr>
<td>Magga et al. (2008)</td>
<td>NT-pro-BNP</td>
<td>17 healthy controls and 24 patients HNCM</td>
<td>Elevated NT-pro-BNP levels in HCM patients compared to controls that are associated with incipient LV remodelling</td>
</tr>
<tr>
<td>Maron et al. (2004)</td>
<td>BNP</td>
<td>107 consecutive HCM patients</td>
<td>Plasma BNP is independently related to the presence and magnitude of heart failure symptoms in patients with HCM</td>
</tr>
<tr>
<td>Okawa et al. (2005)</td>
<td>BNP</td>
<td>45 HCM patients and 20 normal control subjects</td>
<td>The plasma BNP level correlated with Tei index in non-obstructive HCM</td>
</tr>
<tr>
<td>Arteaga et al. (2005)</td>
<td>NT-pro-BNP</td>
<td>71 HCM patients and 40 healthy subjects.</td>
<td>In HCM, plasma NT-pro-BNP levels are elevated and correlate positively with symptoms of heart failure, hypertrophy severity, and Doppler echocardiographic signs of left ventricular diastolic dysfunction</td>
</tr>
<tr>
<td>Mutlu et al. (2006)</td>
<td>NT-pro-BNP</td>
<td>80 HCM patients</td>
<td>NT-pro-BNP identifies patients at risk of cardiovascular death and hospitalization for worsening heart failure symptoms</td>
</tr>
<tr>
<td>Thaman et al. (2006)</td>
<td>NT-pro-BNP</td>
<td>171 HCM patients</td>
<td>NT-pro-BNP levels correlate with peak oxygen consumption in HCM</td>
</tr>
<tr>
<td>Nishgaki et al. (1996)</td>
<td>BNP and ANP</td>
<td>15 HOCM, 15 HNCM, 10 AS, 10 hypertensive, and 10 normal subjects</td>
<td>Plasma BNP levels were higher in the HOCM patients compared with HNCM, hypertensive heart disease, AS, and normal groups</td>
</tr>
<tr>
<td>Matsuura et al. (2008)</td>
<td>BNP</td>
<td>94 HNCM: 14 CAF, 18 PAF, and 65 NSR</td>
<td>PAF and CAF groups showed significantly higher plasma BNP levels than the NSR group. PAF is independently associated with high levels of BNP</td>
</tr>
<tr>
<td>Pieroni et al. (2007)</td>
<td>BNP</td>
<td>40 HCM patients</td>
<td>Progression to end-stage of HCM is characterized by further increase of myocardial and plasma BNP</td>
</tr>
</tbody>
</table>

ANP, atrial natriuretic peptide; AS, aortic stenosis; BNP, brain natriuretic peptide; CAF, chronic atrial fibrillation; CMR, cardiac resonance magnetic; FS, fractional shortening; HCM, hypertrophic cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; HNCM, hypertrophic non-obstructive cardiomyopathy; LGE, late Gadolinium enhancement; NSR, normal sinus rhythm; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; PAF, paroxysmal atrial fibrillation.
downstream signalling cascade that converge upon intracellular Ca++ and its downstream phosphatase Ca++ sensor protein calcineurin (Figure 1). This protein dephosphorylates a variety of cellular substrates, including nuclear factors of activated T cells (NFAT) and myocyte enhancer factor-2 (MEF2) that in turn will activate transcriptional processes inducing hypertrophy through the activation of foetal isoforms of proteins133 (Figure 1).

The study of promoter regions of MMPs and TIMPs has allowed us to identify transcription factors that control the expression of these two families of proteins.134 The same trophic and mitotic factors mentioned in the previous paragraph plus aldosterone and TNF-α, through parallel pathways (Figure 1), activate transcription factors (AP-1, STATs, NF-κB, β, and SMADs) that control the expression via activation/inhibition of MMPs and TIMPS.

The hypothesis of energy depletion with the consequent accumulation of Ca++ inside the cells by-pass all, therefore, mentioned signalling pathways and activate directly the calcium-dependent final common pathway. It is possible that all the trophic and mitotic molecules are induced and mediate further development of phenotypic characteristics, thus increasing the incidence of fibrosis and hypertrophy but without being the primary mechanism of the disease. Only small improvements in the phenotypic manifestations of the disease have been observed in animals treated with losartan,108 simvastatin,134 and spironolactone.105 It will be more important and effective to treat the calcium-dependent final common pathway.

Conclusions

The study of biomarkers in experimental models and clinical studies of HCM has given insight to possible disease mechanisms, but many more studies are clearly required. Moreover, the study of biomarkers in animal models and in patients with HCM-related mutations before and after all the phenotypic characteristics of the disease have appeared, will help identify molecules that could be active and trigger hypertrophy and/or fibrosis. Currently, biomarkers can be used as a diagnostic tool in HCM as well as to determine prognosis factors or progression of the disease. Finally, the study of biomarkers and their signalling pathways in HCM has enabled the investigation of new therapeutic strategies with the aim of altering phenotype rather than simply targeting the palliation of symptoms.

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References


