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## Aims and Scope

*Heart and Metabolism* is a quarterly journal focusing on the management of myocardial ischemia. Its aim is to inform cardiologists and other specialists about the newest findings of the role of metabolism in cardiac disease and to create awareness of its potential clinical implications. The management of patients with angina, as well as those with heart failure and hypertrophic or dilated cardiomyopathy, will also be discussed. Moreover, the effects of metabolic diseases such as diabetes mellitus on the heart will be highlighted. Each issue will include an editorial, followed by articles on a key topic. Experts in the field will explain the metabolic consequences of cardiac disease and the multiple potential targets for pharmacotherapy in ischemic and nonischemic heart disease.

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*The figure on the cover shows horizontal long axis images of positron emission tomography (PET; top) and single photon emission computed tomography (SPECT; bottom) studies in a patient who had asymmetrical septal hypertrophy. See page 18.*

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# Hypertrophic cardiomyopathies: role of genetic mutations in proteins involved in sarcomere function and energy metabolism in the pathogenesis of this disorder

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Hypertrophic cardiomyopathy (HCM) is usually associated with hypertrophy of the left ventricle in the absence of dilatation of the ventricular chamber. Diastolic dysfunction is a common feature of HCM, due both to impaired relaxation and reduced compliance. A greater susceptibility to arrhythmias and sudden death is also associated with HCM. The hypertrophy associated with HCM does not occur due to other causes of hypertrophy (such as hypertension or aortic stenosis), but rather due to genetically heterogeneous causes. Mutations in a number of different genes have been associated with HCM, many of these occurring in the cardiac sarcomeric proteins. The genetics of hypertrophic cardiomyopathy is nicely reviewed in this issue by Drs Kok and Baars, who describe the major sarcomeric protein mutations that result in hypertrophic cardiomyopathy. These authors also discuss the metabolic counseling that should be provided to patients with HCM.

The goal of therapy in symptomatic patients with HCM is to improve functional capacity and to improve the outflow tract gradient. Medical therapy with negative inotropic drugs such as  $\beta$ -blockers, verapamil, or disopyramide are a first-line approach to treating HCM. In this issue, Dr McKenna and colleagues outline the current clinical management of HCM. The need to treat arrhythmias that can

lead to sudden death is also stressed in these patients. However, patients with marked outflow tract obstruction may be unresponsive to medical therapy. This is important, since a significant proportion of patients with HCM have intraventricular pressure gradients due to left ventricular outflow tract obstruction. In this issue, Drs Seggerwits and Rigopoulos update the use of percutaneous transluminal septal myocardial ablation through alcohol-induced ablations of a septal branch as an approach to improve left ventricular outflow tract gradient.

Alterations in energy metabolism may also be an important contributor to contractile dysfunction in HCM patients. Impairment in oxidative metabolism is an early manifestation of HCM that may contribute to an energetic deficiency. The cardiac metabolic changes observed in HCM patients are nicely reviewed in this issue by Dr Tadamura. The concept that energetics is compromised in HCM is supported by a recent study by Javadpour et al [1], who show a decreased energetic driving force within the cardiomyocytes of mice containing a common sarcomeric mutation seen in HCM. This suggests that sarcomeric mutations in HCM can enhance the activation of myofibrillar ATPase activity, resulting in an excessive energy utilization by the contractile proteins. It also

raises the intriguing possibility that a mismatch in energy use by the heart may be one of the pathogenic mechanisms of familial HCM.

In addition to sarcomeric mutations resulting in an energetically deficient heart, evidence is also emerging that mutations in proteins involved in energy metabolism can contribute to HCM. Considerable interest has recently been generated in the possible involvement of mutations in AMP-activated protein kinase (AMPK), as a cause of hypertrophic cardiomyopathy [2,3,4]. AMPK is an important “fuel sensor” in the heart, that controls both fatty acid oxidation [5] and glucose uptake [6]. Mutations in the gamma subunit of AMPK are associated with HCM, glycogen accumulation in the heart, and electrophysiological abnormalities. In this issue, Dr Redwood discusses the potential involvement of AMPK mutations, as well as sarcomeric protein mutations, as contributing factors to energetic compromise in HCM. The key role that these mutations have in alterations in calcium homeostasis in HCM is also discussed.

Although the genetic mutations in HCM are diverse, understanding the cellular changes that occur in HCM should provide new and specific approaches to treating the clinical complications of HCM. While targeting the sarcomere is one potential approach, optimizing energy production in the heart

may be another novel therapeutic approach to treating HCM. ■

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# Cellular changes in hypertrophic cardiomyopathy

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## Abstract

The autosomal dominant disease, hypertrophic cardiomyopathy, is characterized by left ventricular hypertrophy and myocyte disarray. Molecular genetic work has shown that the disease is caused by mutations in at least nine sarcomeric protein genes, resulting in mutant proteins that are expressed and incorporated into the contractile apparatus, where they exert a dominant negative influence on cardiac contraction or relaxation, or both. This paper considers how the primary changes in contractile function may generate stimuli for myocyte hypertrophy, focusing on data that demonstrate calcium dysregulation and energetic compromise caused by the disease-causing mutations.

■ *Heart Metab.* 2003; 21:5–9.

**Keywords:** Cardiomyopathy, mutation, genetics, calcium, contractility, signal transduction

## Hypertrophic cardiomyopathy is caused by mutations in sarcomeric protein genes

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant inherited disorder affecting up to 1 in 500 of the population. It is characterized by unexplained asymmetric left ventricular hypertrophy and by myocyte disarray. A groundbreaking paper from the Seidman laboratory, published in 1990, was the first to report the identification of a specific mutant allele that causes HCM [1]. The affected gene was identified as *MYH7*, which encodes  $\beta$ -myosin heavy chain ( $\beta$ MyHC), the motor protein of the cardiac sarcomere, and the reported missense mutation resulted in an arginine to glutamine amino acid substitution at residue 403. Since this seminal report, at least 70 further HCM mutations in this gene have been reported, accounting for about one third of all affected individuals; in addition, by either linkage analysis or candidate gene screening, at least eight further disease genes that encode components of either the thick myosin filaments (most commonly cardiac myosin binding protein-C [MyBPC]) or the thin actin filaments (principally cardiac troponin T, a

component of the trimeric troponin complex, which is responsible for the calcium regulation of contractility) have been identified (see Refresher Corner in this issue). This has led to HCM being termed a disease of the sarcomere [2], in which the primary defect caused by the mutations is an alteration in the normal contraction or relaxation, or both, of cardiac muscle, giving rise to stimuli that promote cellular hypertrophy and ventricular remodeling.

Numerous biophysical, biochemical, and physiological studies have sought to determine the fundamental changes in contractility caused by HCM gene mutations [3]. Initial work focused on the  $\beta$ MyHC mutant proteins, which, in a number of studies using skinned muscle fibers and in-vitro sliding filament assays, were found to be less efficient motors than wild-type myosin, leading to lower sliding velocity and reduced force [4]. These findings led to the proposal that the hypertrophy produced by these mutations was compensatory, in response to the lower force generated by the mutant sarcomeres [5]. More recent work, however, has suggested that these  $\beta$ MyHC mutants are able to translocate actin filaments at faster (not slower) velocities, bringing some

of the earlier data into question [4]. Furthermore, functional analysis of mutant alleles of other hypertrophic cardiomyopathy genes has suggested that these are likely to act via a “hypercontractile” mechanism. For example, most HCM mutations in cardiac troponin T and other thin filament proteins appear to cause an increase in the calcium sensitivity of the regulation of contraction, thus causing increased force at any submaximal calcium concentration, and relaxation abnormalities [6].

### From contractile abnormality to stimulation of hypertrophy

Studies of models of acquired cardiac hypertrophy (for example via pressure overload) have suggested that a number of interrelated signaling pathways, including the mitogen-activated protein kinases, calmodulin-dependent protein kinase II (CaMKII), and calcineurin, are activated (*Figure 1*) [7–9]. Is one or more of these pathways triggered by the contractile changes brought about by the HCM mutant proteins?

As the cytoplasmic  $\text{Ca}^{2+}$  concentration,  $[\text{Ca}^{2+}]_i$ , is intimately linked to the regulation of contractility, it has been hypothesized that the HCM may cause  $\text{Ca}^{2+}$  dysregulation [10], possibly leading to increased  $[\text{Ca}^{2+}]_i$  and activation of the  $\text{Ca}^{2+}$ /calmodulin-sensitive phosphatase calcineurin, CaMKII, or  $\text{Ca}^{2+}$ -sensitive protein kinase C isoforms (*Figure 1*). There is some, albeit limited, experimental evidence for this in mouse models of HCM; for example, ventricular myocytes paced at physiological rates from Ile79Asn mutant troponin T hearts showed increased diastolic  $[\text{Ca}^{2+}]_i$  compared with those from nontransgenic animals. In most animal models, increases in diastolic  $[\text{Ca}^{2+}]_i$  have not been reported, although small but significant changes in the resting concentration are difficult to detect using the common spectroscopic indicators (eg, fura-2). Furthermore, the  $[\text{Ca}^{2+}]_i$  surrounding the contractile apparatus varies over a 10-fold range approximately once a second, as a result of the cardiac contraction-relaxation cycle, suggesting that sustained small increases in  $[\text{Ca}^{2+}]_i$  may be sensed in a distinct subcellular pool. The mechanism of CaMKII regulation, however, permits its sustained activation, as it undergoes autophosphorylation, which maintains the enzyme in its active form [11].

It has been suggested that increases in  $[\text{Ca}^{2+}]_i$  may be caused by “calcium trapping” by the mutant sarcomere [12], mediated by changes in the  $\text{Ca}^{2+}$  affinity of troponin C, widely believed to be the major  $\text{Ca}^{2+}$  buffer during the  $\text{Ca}^{2+}$  transient [13]. It is well established that the HCM mutants in troponin T, troponin I and  $\alpha$ -tropomyosin in general result in increased myofilament calcium sensitivity, which is likely to be mediated by an increase in the low-affinity, regulatory site of troponin C [14]. In addition, “hypercontractile”  $\beta$ MyHC or MyBPC mutants give an increase in strong myosin head binding, which in turn would increase  $\text{Ca}^{2+}$  binding by troponin C. A slower release of the “trapped” calcium at the end of the transient would reduce the efficiency of reuptake by the sarcoplasmic reticulum, resulting in both a heightened diastolic  $[\text{Ca}^{2+}]_i$  and a reduced sarcoplasmic reticular  $\text{Ca}^{2+}$  load. It is important to note, however, that increases in thin-filament  $\text{Ca}^{2+}$  sensitivity do not necessarily result in hypertrophy; for example, cardiomyocytes from mice expressing the slow skeletal isoform of troponin I show increased  $\text{Ca}^{2+}$  sensitivity, but the hearts appear to have normal morphology [15].

Another postulated mechanism resulting in calcium dysregulation involves energetic compromise [16]. The myosin ATPase accounts for at least 70% of 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; this is supported by data showing increased tension cost in mutant mouse fibers [17]. Chronic increase in the energy cost of maintaining normal power output will give rise to ATP depletion, which is predicted to affect other highly ATP-dependent processes in the cell, such as the sarcoplasmic reticulum calcium pump (SERCA), the ATPase with the greatest minimal energy requirement in muscle cells [18]. There is strong evidence that energy compromise occurs in the hearts of patients with HCM; a recent paper described similar (approximately 30%) reductions in phosphocreatine:ATP ratios in patients with mutations in  $\beta$ MyHC, MyBPC, or troponin T, in some cases before the development of hypertrophy [19]. In addition, in a mouse model of the original Arg403Gln myosin mutation, a comparable reduction in phosphocreatine:ATP ratio was measured, and it was suggested that the free energy change for

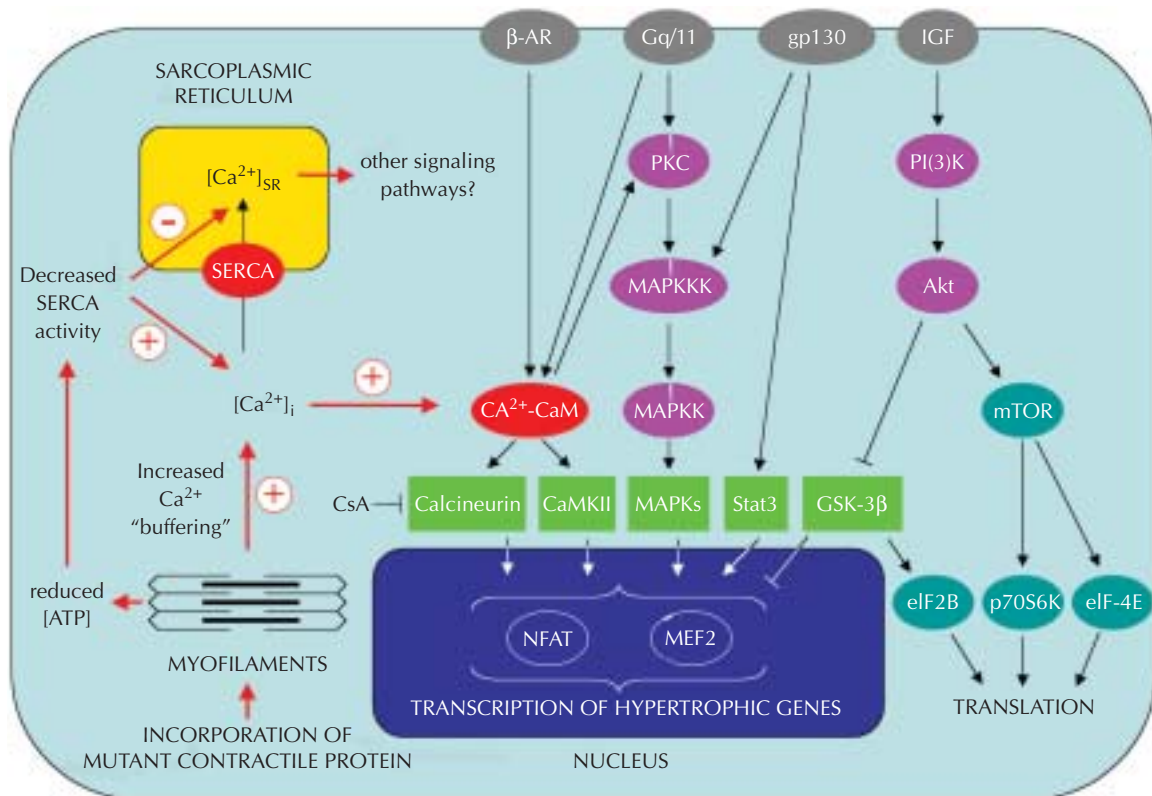


Figure 1. Some of the known hypertrophic signaling pathways and possible mechanisms by which hypertrophic cardiomyopathy mutations may increase diastolic calcium ion concentration ( $[Ca^{2+}]_i$ ). Activation of a number of different receptor classes leads to hypertrophic signaling; these include the angiotensin II, endothelin-1, and  $\alpha$ -adrenergic receptors (all of which act via the guanosine triphosphate [GTP]-binding proteins,  $G_q$  and  $G_{11}(G_{9/11})$ , along with  $\beta$ -adrenergic receptors ( $\beta$ -AR), glycoprotein 130 (gp130) tyrosine kinase, and the insulin-like growth factor-1 receptor (IGF). The signals are transduced by a variety of routes, including the mitogen-activated protein kinase cascade (MAPK/MAPKK/MAPKKK), protein kinase C (PKC), the phosphatidylinositol kinase (PI(3)K)/Akt/glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ) pathway, calmodulin-dependent protein kinase II (CaMKII) and the phosphatase, calcineurin. These pathways result in the modulation of transcription via modification of nuclear factors of activated T cells (NFAT), myocyte enhancer factor-2 (MEF2), and other intermediates. Effects on translation are mediated via mammalian target of rapamycin (mTOR) and GSK3 $\beta$ . The mechanisms by which hypertrophic cardiomyopathy mutant contractile proteins are postulated to increase diastolic  $[Ca^{2+}]_i$ , and hence activate  $Ca^{2+}$ -dependent pathways involving calcineurin, CaMKII, and  $Ca^{2+}$ -sensitive PKC isoforms are indicated with red arrows.  $[Ca^{2+}]_{SR}$ , sarcoplasmic reticulum calcium ion concentration; SERCA, sarcoplasmic reticulum calcium pump; CaM, calmodulin; CsA, cyclosporin A; Stat3, signal transducer and activator of transcription 3.

ATP hydrolysis was decreased to close to the minimal requirement for SERCA [20]. Further weight has been added to this hypothesis by the finding that HCM in combination with Wolff-Parkinson-White syndrome is caused by mutations in *PRKAG2*, which encodes the  $\gamma 2$  subunit of AMP-activated protein kinase (AMPK) [21]. This kinase, an  $\alpha\beta\gamma$  trimer of which  $\alpha$  is the catalytic subunit, is activated on ATP depletion, turning on energy-producing pathways (such as glycolysis) and inhibiting ATP-consuming

processes (such as fatty acid synthesis), and has been termed the fuel gauge of the cell [22]. Experimental evidence concerning the functional effects of the *PRKAG2* mutations is equivocal: analysis of the equivalent amino acid substitutions in the  $\gamma 1$  subunit [23] and in the yeast homologue, Snf1/Snf4 kinase [24], has suggested they may cause either increased kinase activity or constitutive activation, but cellular coexpression of  $\alpha$  and  $\beta$  AMPK subunits with either wild-type or mutant  $\gamma 2$  has shown that the mutations

result in reduced maximal activity or lower AMP dependence, or both [25]. Clearly, a reduction in the ability to sense low concentrations of ATP may lead to compromised SERCA activity, by the mechanism described above. Recent studies have also suggested that AMPK may directly interact with components of hypertrophic signaling pathways such as Akt and other downstream targets, and suppress translation [26–28], implying that reduction in AMPK activity may increase translation and act to promote hypertrophy.

Attempts to inhibit calcineurin using cyclosporin A (CsA) in the Arg403Gln myosin mouse model gave the somewhat confusing result of enhanced hypertrophy [12]. In addition, the increase in diastolic  $[Ca^{2+}]_i$  caused by CsA in wild-type animals was absent, clearly demonstrating  $Ca^{2+}$  dysregulation in the mutant mouse hearts. It is established that there is considerable crosstalk between calcineurin and other hypertrophic signaling pathways [29], and there are other instances of inhibition of a known hypertrophic mediator producing an unexpected result (eg, inhibition of p38 MAPK promoting hypertrophy [30]). In the sarcoplasmic reticulum of the Arg403Gln myosin mutant mouse heart, there is reduced  $Ca^{2+}$  load and concentrations of both calsequestrin and ryanidine receptor are diminished, leading to the suggestion that disruption of sarcoplasmic reticular  $Ca^{2+}$  homeostasis is a key mediator of the pathogenic process [31]. Interestingly, in this model the administration of the L-type  $Ca^{2+}$  channel inhibitor, diltiazem, restored to normal the concentrations of the sarcoplasmic reticulum proteins, and prevented the development of hypertrophy.

## Summary

Many of the effects on contractility produced by the sarcomeric protein gene mutations are understood, but the exact nature of the signaling pathways responsible for the generation of pathophysiological hypertrophy in HCM remains to be elucidated. It seems likely, however, that both disruption of  $Ca^{2+}$  homeostasis and energetic compromise are involved as triggers. It is hoped that future work will identify the exact changes involved, and that such findings may suggest the possibility of appropriately targeted pharmacological intervention. ■

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# Clinical management of hypertrophic cardiomyopathy

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## Abstract

Hypertrophic cardiomyopathy is a familial cardiac disorder with an estimated prevalence of 1 in 500. The majority of patients are asymptomatic although, with time, symptoms may occur and a minority of patients develop disease-related complications, which include supraventricular tachyarrhythmias, thromboembolic events, and heart failure. Sudden cardiac death is also an infrequent complication of the disease. This review examines current management strategies and the identification and treatment of individuals at risk from sudden cardiac death.

■ *Heart Metab.* 2003; 21:11–15

**Keywords:** Hypertrophic cardiomyopathy, sudden cardiac death

## Introduction

Hypertrophic cardiomyopathy (HCM), a familial cardiac disorder with an estimated prevalence of 1 in 500 [1], is defined by the presence of myocardial hypertrophy in the absence of a discernible cause such as systemic hypertension or aortic stenosis. To date, more than 100 mutations in ten genes encoding cardiac sarcomeric proteins that make up the basic contractile apparatus of the cardiac myocyte have been linked to HCM. The clinical manifestations of the condition are diverse, ranging from a benign asymptomatic course to severe heart failure, embolic stroke, and sudden cardiac death. The management of hypertrophic cardiomyopathy is aimed at relieving symptoms, preventing disease-related complications, identifying and treating individuals at increased risk of sudden cardiac death, and screening family members.

## Pathophysiology of hypertrophic cardiomyopathy

Hypertrophy usually develops during adolescence, but can occur at any time. Asymmetric septal hypertrophy – ie, hypertrophy affecting the interven-

tricular septum more than the free or posterior walls – is the most common pattern of hypertrophy seen, although concentric and apical hypertrophy, in addition to right ventricular involvement, are recognized. One third of patients have an intraventricular pressure gradient as a result of left ventricular outflow tract (LVOT) obstruction secondary to systolic anterior motion of the mitral valve [2]. Left ventricle systolic function is usually normal or hyperdynamic. Microscopically, hypertrophic cardiomyopathy is characterized by myocyte hypertrophy and disarray; other characteristic features include fibrosis and abnormal intramural coronary arteries with narrowed lumen [3, 4]. Diastolic dysfunction is present in the majority of patients and may be the result of myocardial hypertrophy, disarray, or ischemia, and a minority of patients may have features resembling restrictive cardiomyopathy.

## Presentation

The majority of patients do not experience disease-related symptoms; however, some patients complain of exertional and atypical chest pain, dyspnea or exercise limitation, palpitations, syncope, and presyncope. Syncope may be caused by paroxysmal

arrhythmia, LVOT obstruction, conduction system disease, or abnormal vascular responses during exercise. Clinical signs are generally limited to patients with LVOT obstruction and include a forceful left ventricular impulse, rapid upstroke to the arterial pulse, a palpable left atrial beat, a fourth heart sound, and a mid-late systolic murmur.

### Diagnosis

Hypertrophic cardiomyopathy may be initially suspected because of a heart murmur, family history, new symptoms, or abnormal electrocardiogram (ECG). Diagnosis of hypertrophic cardiomyopathy by identification of a known disease-causing mutation is rarely available, and at present the diagnosis usually rests on echocardiography when there is hypertrophy exceeding two standard deviations from the mean corrected for age, sex, and height [5–7]. The ECG is abnormal in the majority of patients with hypertrophic cardiomyopathy, although no specific changes are diagnostic. Left axis deviation, criteria for left ventricular hypertrophy with or without repolarization changes, left and or right atrial enlargement, and abnormal Q-waves are the most common features [8].

### Treatment

In patients with symptoms or significant exercise limitation, decisions regarding symptomatic treatment are generally guided by the presence or absence of LVOT obstruction.

#### *Treatment of patients with LVOT obstruction*

$\beta$ -Blockers are usually tried first. The beneficial effects of  $\beta$ -blockers appear to result from their negative inotropic actions, prolongation of diastole, reduction in myocardial oxygen demand, and reduction in LVOT obstruction. Verapamil is particularly effective in patients with chest pain and may also have beneficial effects on LVOT obstruction; however, in some patients the vasodilative effects may lead to serious hemodynamic compromise and verapamil should therefore be used cautiously in patients with LVOT obstruction.

If  $\beta$ -blockers or verapamil are ineffective, disopyramide can be tried. Disopyramide may reduce LVOT

obstruction and relieve symptoms through its negative inotropic properties; however, the initial hemodynamic benefits often decrease with time. Furthermore, patients are often unable to tolerate the high doses often required for symptomatic improvement (up to 600 mg/day), because of the anticholinergic side effects. Because disopyramide may shorten the atrioventricular nodal conduction time and thus increase the ventricular rate during paroxysmal atrial tachycardia, which occurs commonly in hypertrophic cardiomyopathy, supplementary treatment with  $\beta$ -blockers in low doses is advisable [9, 10].

For patients with significant LVOT obstruction ( $\geq 50$  mm Hg) in whom medication proves unsuccessful or side effects become intolerable, ventricular septal myotomy-myectomy (Morrow operation) guided by transesophageal echocardiography or alcohol septal ablation should be considered. The aim of myotomy-myectomy is to widen the outflow tract, reducing LVOT obstruction and systolic mitral leaflet septal contact. Success rates of more than 80% are reported, with perioperative mortality rates of 2% or less. Long-term relief of symptoms is maintained in up to 70% of patients [11–13]. Alcohol septal ablation involves the injection of alcohol into the perforators of the left anterior descending coronary artery, to cause a limited septal myocardial infarction. A decrease in outflow tract gradient is reported in 50–70% of patients and complication rates vary considerably, being closely related to the level of expertise at the center at which the procedure is performed [14–16]. The most common complication is high-grade atrioventricular block requiring a permanent pacemaker. For some patients in whom surgery or alcohol septal ablation is contraindicated, A.V. requested pacing using a short-programmed atrioventricular delay leading to delayed activation and less vigorous contraction of the interventricular septum may be an option; this results in gradient reduction in 30% to 50% of patients [17–19].

#### *Treatment of patients without LVOT obstruction*

Patients without LVOT obstruction constitute the majority of patients with hypertrophic cardiomyopathy. In these patients,  $\beta$ -blockers or calcium antagonists (verapamil or diltiazem) can be used to optimize heart rate, leading to inherent improvements

in myocyte relaxation and cardiac filling, and possibly a reduction in myocardial ischemia.

### Heart failure

In a minority of patients, symptoms of heart failure may accompany hypertrophic cardiomyopathy, associated with ventricular enlargement and wall thinning or restrictive physiology. Conventional heart failure management strategies should be used in these patients: eg, diuretics and angiotensin-converting enzyme inhibitors. However, because many of these patients have diastolic dysfunction and require relatively high filling pressures to achieve adequate ventricular filling, diuretics should be used cautiously. Some patients may eventually require heart transplantation.

### Supraventricular arrhythmias

Supraventricular arrhythmias – in particular atrial fibrillation and flutter – occur in 20% to 30% of patients with hypertrophic cardiomyopathy and often develop in association with progressive atrial enlargement, secondary to LVOT obstruction, diastolic dysfunction, mitral valve dysfunction, or combinations thereof. These arrhythmias can lead to profound hemodynamic compromise, although they are usually well tolerated if the ventricular rate can be controlled. New onset atrial fibrillation should be cardioverted. If that is unsuccessful,  $\beta$ -blockers and verapamil are usually efficacious in controlling the heart rate. Ablation of the atrioventricular node and implantation of a pacemaker is rarely required. Amiodarone is the most effective antiarrhythmic agent for the prevention of recurrent episodes of supraventricular tachyarrhythmia. Recurrent or even brief episodes of atrial fibrillation/flutter in hypertrophic cardiomyopathy are associated with a significant risk of systemic embolization, therefore the threshold for the initiation of anticoagulation treatment should be low.

### Sudden death and risk stratification

Sudden death is the most devastating consequence of hypertrophic cardiomyopathy and often occurs in otherwise healthy individuals. Reported annual mor-

tality rates from sudden death are 1% to 2% and are greatest in adolescents and young adults. Sudden death occurs most commonly at rest or during mild exertion, but is not infrequently related to physical exertion. Ventricular tachyarrhythmia appears to be the final common pathway for sudden death in most patients [20]. The exact trigger for this arrhythmia is unknown, although myocardial ischemia, diastolic dysfunction, outflow tract obstruction, inappropriate systemic arterial vasodilatation, or supraventricular tachyarrhythmias may contribute. Bradyarrhythmias as a result of sinus node dysfunction or atrioventricular block may also be responsible in some patients.

Patients who have survived a cardiac arrest are at greatest risk [21]. Most other patients at risk can be identified by noninvasive assessment, which should include history, 48-hour Holter monitoring, and cardiopulmonary exercise testing. Established risk markers for sudden death include nonsustained ventricular tachycardia, left ventricular wall thickness  $\geq 30$  mm, abnormal blood pressure response in those younger than 45 years, family history of sudden cardiac death, and recurrent unexplained syncope [22–26].

### Prevention of sudden cardiac death

Prophylactic treatment to prevent sudden cardiac death is most strongly warranted for patients with previous cardiac arrest or sustained spontaneous ventricular tachycardia. Patients with two or more risk factors have annual sudden death rates of 2% to 4% and should also be offered prophylactic treatment [27]. Although amiodarone has been used for prophylaxis, the implantable cardioverter defibrillator is increasingly seen as the preferred treatment in most high-risk patients [28–30]. Criteria for use of prophylactic treatment in patients with a single risk factor have not been established, and decisions should be made on an individual basis, taking into account the age of the patient, strength of the risk factor, and the level of risk acceptable to the patient and family.

### Screening

All first-degree relatives of affected patients should be offered screening; any identified affected family members should then undergo risk stratification. Currently, evaluation of family members relies on

history, examination, and echocardiographic and electrocardiographic evidence of left ventricular hypertrophy. In the future, however, gene testing will enable a more reliable and conclusive diagnosis to be made and prevent the need for continued clinical screening. ■

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# Metabolic imaging of hypertrophic cardiomyopathy

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### Abstract

To date, it has been generally accepted that impaired flow reserve is present in patients with hypertrophic cardiomyopathy. However, whether true ischemia at rest is present in patients with this condition and contributes to the pathogenesis has been controversial. In patients with hypertrophic cardiomyopathy, both oxidative and glucose metabolism are often impaired, particularly in the hypertrophic myocardium. Despite this, myocardial perfusion at rest may not be significantly decreased. In the nonhypertrophic myocardium, however, myocardial metabolism is preserved compared with that in the normal myocardium. From the metabolic point of view, primary metabolic impairment rather than resting ischemia is now considered to be dominant in hypertrophic cardiomyopathy. It has now been shown that hypertrophic cardiomyopathy exhibits a variety of metabolic patterns when assessed by positron emission tomography and single photon emission tomography. The first manifestation of metabolic abnormalities observed in hypertrophic cardiomyopathy is the reduction of free fatty acid uptake, followed by the impairment of oxidative metabolism. Finally, glucose uptake is reduced. Thus reduction of free fatty acid uptake is considered to be a sensitive indicator of metabolic abnormalities in patients with hypertrophic cardiomyopathy.

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**Keywords:** Free fatty acid metabolism, oxidative metabolism, glucose metabolism

The heart muscle can metabolize a variety of substrates, including free fatty acids, glucose, lactate, pyruvate, ketone bodies, and amino acids, depending on plasma substrate concentrations, hormonal conditions, and oxygen availability [1–4]. In the fasting state, long-chain fatty acids are known to account for approximately 70% of myocardial energy production; carbohydrate provides the majority of the remaining 30% of energy requirements. In contrast, after carbohydrate loading, the myocardium utilizes glucose as a primary energy source, as a result of the change in metabolic conditions. Although this metabolic diversity may complicate the assessment of myocardial metabolism, it can lead to unique patterns of substrate utilization that reflect cardiac pathophysiology. Preserved uptake of fluorine-18-fluorodeoxyglucose (FDG) in the segments with reduced

myocardial perfusion, known as perfusion-metabolism mismatch, has been proposed as a marker of ischemic but viable myocardium.

Patients with hypertrophic cardiomyopathy (HCM) often complain of chest pain. Exercise studies using thallium-201 have also suggested the existence of myocardial perfusion abnormalities, mainly in the hypertrophied myocardium in these patients [5, 6], and hemodynamic and metabolic evidence of pacing-induced myocardial ischemia has been reported [7, 8]. On the basis of positron emission tomography (PET) studies using <sup>13</sup>N-ammonia, it has also been suggested that coronary vasodilator reserve is impaired in this population of patients [9, 10]. Thus it is generally accepted that impairment of flow reserve is present in patients with HCM. However, whether true ischemia at rest is present in

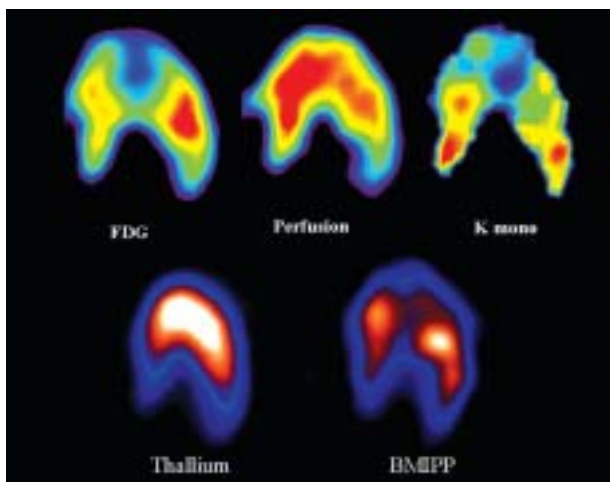


Figure 1. Horizontal long axis images of positron emission tomography (PET; top) and single photon emission computed tomography (SPECT; bottom) studies in a patient who had apical hypertrophy. Uptakes of 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) and fluorine-18-fluorodeoxyglucose (FDG) were decreased and the clearance rate constant for regional  $^{11}\text{C}$ -acetate (K mono) was also reduced in the hypertrophied apical region, indicating impaired metabolic activity, whereas perfusion was preserved.

these patients and contributes to the pathogenesis is controversial. Some investigations have used PET (with  $^{13}\text{N}$ -ammonia and FDG) to show the presence or absence of ischemia [11, 12]. In the PET studies using  $^{11}\text{C}$ -acetate and FDG [13, 14], however, both oxidative and glucose metabolism were often found to be impaired, particularly in the hypertrophic myocardium in the patients with hypertrophic cardiomyopathy, whereas myocardial perfusion at rest was not significantly decreased. In the non-hypertrophic myocardium, myocardial metabolism is preserved compared with that in the normal myocardium. These data indicate that absolute metabolic changes may exist mainly in the hypertrophic myocardium. Impairment of oxidative and glucose metabolism may precede decreased blood flow. Primary metabolic impairment, rather than resting ischemia, is considered to be dominant in hypertrophic myocardium [13, 14]. These discrepancies between the reports [11–14] may reflect that the disease process was at different stages at the time of study in the different groups. In the early stage, increased glucose metabolism may be observed in hypertrophied myocardium [12]. Further studies are

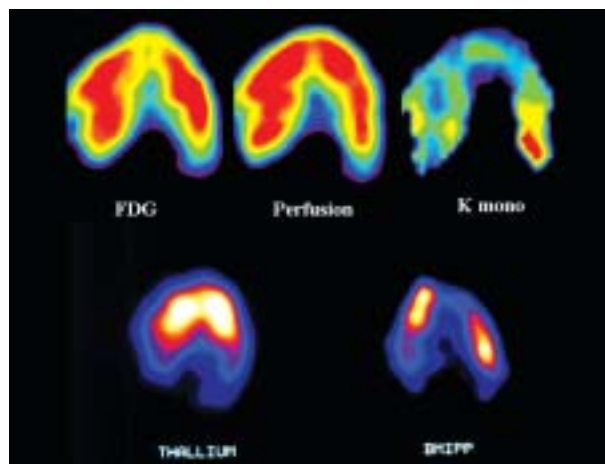


Figure 2. Horizontal long axis images of positron emission tomography (PET; top) and single photon emission computed tomography (SPECT; bottom) studies in a patient who had asymmetric septal hypertrophy. Hypertrophy was present from the antero-septal to the anterolateral region as shown in the thallium image, whereas apparent uptake of 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) was relatively homogenous. This indicated that BMIPP uptake was reduced in this hypertrophied region. The image for the clearance rate constant for regional  $^{11}\text{C}$ -acetate (K mono) showed that oxidative metabolism was impaired in this hypertrophic region, whereas uptake of fluorine-18-fluorodeoxyglucose (FDG) was almost maintained.

needed to determine if resting ischemia is related to the pathophysiology of the hypertrophic cardiomyopathy.

Grover-McKay et al [11] have demonstrated the reduced uptake of FDG and free fatty acid, using PET. Impaired regional fatty acid utilization has also been demonstrated using a radiolabeled long-chain fatty acid analog, iodine-123-labeled 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) [15, 16], in an experimental model of hypertrophic cardiomyopathy [17] and in human studies [18–20]. In order to clarify the relationships between oxidative metabolism, FDG uptake, and BMIPP uptake, combined PET imaging using FDG and  $^{11}\text{C}$ -acetate and SPECT imaging using thallium and BMIPP have been performed in patients with hypertrophic cardiomyopathy [21]. It was found that hypertrophic cardiomyopathy exhibited a variety of metabolic patterns. A myocardial tissue showing severe impairment of the clearance rate constant for regional  $^{11}\text{C}$ -acetate (K mono; a marker of oxidative

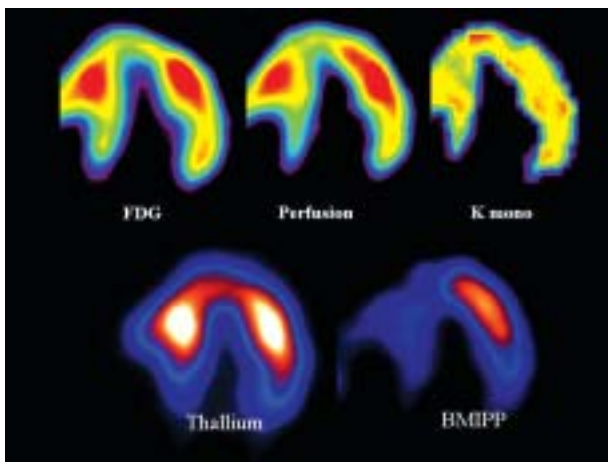


Figure 3. Horizontal long axis images of positron emission tomography (PET; top) and single photon emission computed tomography (SPECT; bottom) studies in a patient who had asymmetric septal hypertrophy. Uptake of 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) was reduced considerably in the hypertrophied septal region, whereas uptake of fluorine-18-fluorodeoxyglucose (FDG) and the clearance rate constant for regional  $^{11}\text{C}$ -acetate (K mono) were almost maintained.

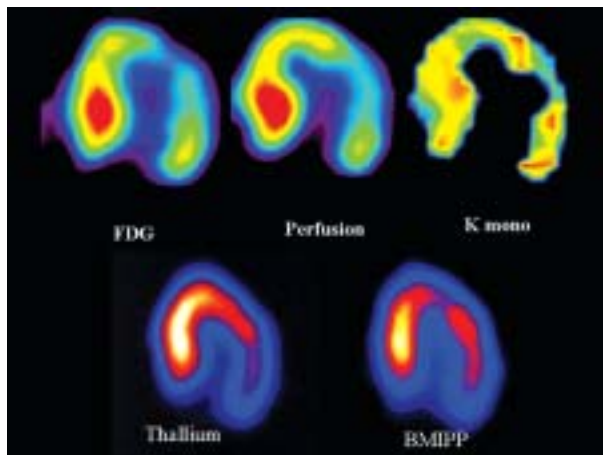


Figure 4. Horizontal long axis images of positron emission tomography (PET; top) and single photon emission computed tomography (SPECT; bottom) studies in a patient who had asymmetric septal hypertrophy. 15-(p-iodophenyl)-3-(R,S)-methylpentadecanoic acid (BMIPP) and fluorine-18-fluorodeoxyglucose (FDG) uptake were maintained, and the clearance rate constant for regional  $^{11}\text{C}$ -acetate (K mono) was also preserved in the hypertrophic septal region.

metabolism [22, 23]), FDG uptake, and BMIPP uptake is considered to be a fibrotic tissue, from the metabolic point of view (Figure 1). Interestingly, blood flow is preserved, in spite of impairment of every metabolic activity. Such a discrepancy between metabolism and blood flow is not usually observed in ischemic heart disease. Figure 2 shows reduced BMIPP uptake and impaired oxidative metabolism in the hypertrophied myocardium, but preserved uptake of FDG, suggesting that anaerobic glucose metabolism has a certain role in energy production in these segments. Figure 3 shows that uptake of BMIPP is reduced in the segments with relatively preserved K mono values and FDG uptake. In these segments, the primary energy source is converted from free fatty acid to glucose, even in fasting conditions. In addition, individuals were found in whom every metabolic parameter in the hypertrophic myocardium was preserved (Figure 4). However, these results suggest that the first manifestation of metabolic abnormalities observed in hypertrophic cardiomyopathy is the reduction of BMIPP uptake, followed by the impairment of K mono values, and that, finally, FDG uptake is reduced. Thus reduction of long-chain fatty acid

uptake is considered to be the most sensitive indicator of the metabolic abnormalities in patients with hypertrophic cardiomyopathy. ■

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# New therapeutic approaches to hypertrophic cardiomyopathy: alcohol ablation

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### Abstract

Percutaneous septal ablation (PTSMA) in hypertrophic obstructive cardiomyopathy (HOCM) aims to reduce thinning of the hypertrophied septum with consecutive increase of left ventricular outflow tract (LVOT) and reduction of LVOT gradients. The therapeutic aim can be achieved in >90% of the patients: up to 10% of the patients develop a complete heart block requiring pacemaker implantation. Follow-up studies could show ongoing hemodynamic and clinical improvement after successful ablation without increased risk of cardiac complications. Especially, no increased risk of sudden cardiac death could be observed. In conclusion, PTSMA is a new promising treatment option in symptomatic patients with HOCM.

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**Keywords:** Hypertrophic cardiomyopathy, alcohol ablation

### Introduction

Symptomatic patients with hypertrophic obstructive cardiomyopathy are treated to reduce symptoms, improve functional capacity, and provide better quality of life [1, 2]. Therefore, the extent of the outflow tract gradient and diastolic filling must be improved. Medical treatment, with the administration of negatively inotropic drugs – eg,  $\beta$ -blockers [3–5], verapamil [4, 6], or disopyramide ([7, 8] – is always the first line of treatment. However, a large number of patients with marked outflow tract obstruction have severe symptoms that are unresponsive to medical treatment [9]. In this group, surgical myectomy-myotomy has been the mainstay for decades, providing long-term relief of symptoms in a substantial proportion of patients. The high early postoperative mortality can be reduced to less than 1% to 2% in highly experienced centers [10–13]. Implantation of DDD pacemakers has not proved to be as efficacious in randomized trials, with most of the reported reduction in symptoms being attributed to a substantial placebo effect [14–16]. Percutaneous trans-

luminal septal myocardial ablation (PTSMA) through alcohol-induced occlusion of a septal branch aims directly to reduce the hypertrophied interventricular septum, with consecutive expansion of the left ventricular outflow tract and reduction of the left ventricular outflow tract gradient [17]. This is achieved through a circumscribed infarction of the area supplied by the occluded septal branch. In this report we give an update on the technique, indications, results, and perspective of this treatment.

### Technique

After initial studies had shown that temporary balloon occlusion of the first larger septal branch resulted in substantial reduction in the resting outflow gradient in a minority of patients [18, 19], Sigwart [18] was the first to report a successful nonsurgical myocardial reduction after occlusion of the septal branch using 96% alcohol.

The original technique of PTSMA has undergone several modifications, with the aim of improving the

identification of the target septal perforator branch, in order to achieve the optimal hemodynamic result with the least complications [18, 20, 21]. Nearly all operators agree that a temporary pacemaker should be placed in the right ventricle, because of the risk of trifascicular block during PTSMA. The echocardiography-guided ablation itself [17] is the one currently performed by most of the groups actively using PTSMA. We will discuss the advantage of this technique. Echocardiographic monitoring of the procedure was introduced [21, 22] in order to identify the target septal branch and to exclude unintentional injection of alcohol to an incorrect area, eg, papillary muscle or the left ventricular free wall. We have chosen Levovist instead of other echo contrast media, because of its superior visibility during the procedure. Finally, it must be underlined that monitoring of the patient's hemodynamic and rhythm status in the Critical Care Unit is required for at least 24 to 48 hours.

## Indications and contraindications

PTSMA is indicated clinically for symptomatic patients classified as at least New York Heart Association III/CCS III despite optimal drug treatment or with severe side effects of medication. They should have high outflow tract gradients ( $\geq 50$  mm Hg at rest or  $\geq 100$  mm Hg under stress). In individual patients with less severe symptoms, active treatment can be considered if they have high gradients and additional findings, such as recurrent exercise-induced syncope, abnormal blood pressure response at exercise, paroxysmal atrial fibrillation, or objective reduction in exercise capacity. These considerations are supported by data that have shown a correlation between death related to hypertrophic cardiomyopathy (HCM), in addition to progressive heart failure and a resting gradient of more than 30 mm Hg [23, 24].

Morphological indication for echocardiography-guided septal ablation is given in patients with both subaortic and midcavitary obstruction, previous, hemodynamically unsuccessful, surgical myectomy, or DDD pacemaker implantation. Patients with concomitant cardiac diseases indicating surgery eg, extensive coronary artery disease, valvular disease, and anatomical ailments of the mitral valve, in addition to papillary muscles responsible for gradient formation or mitral regur-

gitation should not be treated with interventional techniques. It must be noted, however, that, in individual patients with single-vessel disease amenable to dilatation and stenting, a combined percutaneous treatment (percutaneous transluminal coronary angioplasty and PTSMA) has been performed with success [25].

Finally, alcohol should not be injected when myocardial contrast echocardiography fails to identify a target septal branch or reveals opacification of any cardiac structure other than the target septal area, or when positioning of the balloon bears the risk of alcohol reflux during injection.

## Results

All operators report a reduction in acute left ventricular outflow tract gradient in about 90% of treated patients [17, 18, 20, 21, 26–34]. Younger patients achieved a lower reduction in gradient than did elderly patients [35], probably because they had greater septal thickness and additional structural deformities, such as abnormal papillary muscles. Nevertheless, about 50% of young patients in whom the acute result is inadequate show an improvement in gradient reduction at follow-up as a result of postinfarction remodeling and shrinkage of the ablated septal area. Patients of functional class IV showed acute results comparable to those in less symptomatic patients [36]. In patients with an insufficiently large PTSMA scar, the process of remodeling, which lasts up to 12 months, should be awaited. It is likely that, in the future, preintervention noninvasive estimation of the underlying histological substrate (fibrosis or muscle) and elongation of mitral leaflets will be helpful in excluding patients from PTSMA, in order to avoid realization of only limited hemodynamic success. Echo guidance with myocardial contrast echocardiography had a crucial impact on the selection of the ablated area in about 25% of our patients [17]. Echo contrast helped to identify an atypically originating septal branch as the target vessel, or to avoid misplacement of the alcohol by making it possible to change the selected vessel if there had been echo contrast opacification of the incorrect septal areas or other cardiac structures such as papillary muscles or ventricular free walls. Our findings were confirmed by those of an autopsy study by Singh et al [37].

# New therapeutic approaches

## Alcohol ablation of hypertrophic cardiomyopathy

Table 1. Acute results of percutaneous transluminal septal myocardial ablation (PTSMA).

Reference	Patients (n)	Success without complication (%)	Death (%)	Pacer (%)	Comments
[20]	25	88	4.0	20	No echo monitoring
[21]	91	97	2.2	11	Improvement of results by echo monitoring
[31]	50	NR	4.0	NR	12 reinterventions; no echo monitoring
[30]	29	NR	0	34	4 patients with only provokable gradients at dobutamine infusion
[26]	18	89	0	5*	1 patient: alcohol leakage down the LAD
[29]	9	100	0	22	Echo monitoring
[39]	172	NR	2.3	NR	No echo monitoring
[17]	290	90	1.0	5.5	DDD pacer rate with echo monitoring: 4.2%
[40]	50	NR	0	10	No echo monitoring; 2 septal branches in 6 patients
[41]	129	NR	3.1	26	No echo monitoring; comparable results in patients with and without resting obstruction
[42]	150	92	0.7	1.3	Echo monitoring

LAD, Left anterior descending coronary artery; NR, not reported. \*Six patients with pacemaker implantation before PTSMA.

Furthermore, echocardiographic monitoring also makes possible the interventional treatment of combined subaortic and midventricular obstruction, and of a pronounced midventricular obstruction, after reduction of its afterload by successful subaortic myectomy [38].

In-hospital death is the most significant complication observed to date, with a rate of up to 4% [31]. Our own experience with PTSMA in more than 600 patients showed hospital mortality of less than 1.0%, which is at least comparable to the results from experienced surgical myectomy centers (Table 1). These deaths have occurred only in elderly patients and during the period after an intervention, which underlines the importance of careful hospital monitoring. Particular attention should be paid to reports of delayed occurrence of complete heart block up to 10 days after the intervention, emphasizing the need for close monitoring for arrhythmias for several days after an intervention [43].

After the introduction of myocardial contrast echocardiography, the number of permanent pacemaker implantations because of permanent trifascicular block was reduced to less than 5% – almost the same as is achieved after operation [10]. Furthermore, the development of complete heart block after septal ablation can be predicted using a score that has been introduced by Faber et al [44]. In addition to

trifascicular blocks, the occurrence of bundle-branch block in about 50% of patients, predominantly involving the right bundle branch, has been reported by all groups. This is in contrast to the many patients who develop left bundle-branch block after surgical myectomy.

Unlike the occurrence of myocardial infarction as a result of coronary artery disease, the incidence of significant ventricular dysrhythmia during and after ablation is rare. Another serious complication that is reported is iatrogenic reflux of alcohol into the left anterior descending coronary artery, with transitory occlusion of the vessel and anterolateral ischemia [26, 34]. This can be avoided by some technical improvements, such as the use of a slightly oversized balloon, and at least 10 minutes of continuing balloon inflation after the last injection of alcohol.

Follow-up studies up to 6 years have shown no increased risk of sudden death or arrhythmic complications [45]. In contrast, an impressive continuing improvement in symptoms, accompanied by an increase in exercise capacity as judged by objective measures, has clearly been shown [17, 26, 40, 45, 46]. Echocardiographic measurements have demonstrated continuing and increasing reduction in the left ventricular outflow tract gradients [17, 45]: after a mean follow-up of 43 months, 90%

of the patients showed complete elimination of the outflow tract gradient. This should be judged as an expression of postintervention remodeling after an induced septal infarction, analogous to the remodeling that occurs after acute myocardial infarction. These findings also emphasize the correct reasoning behind our strategy of inducing a degree of septal necrosis by alcohol ablation, which, while sufficiently large, should nevertheless be as small as possible.

Remodeling after PTSMA results in reduction in both the ventricular septal thickness and the left ventricular posterior wall thickness [17, 45, 47]. As in surgical myectomy [48], these findings must be interpreted as a result of the elimination (or at least reduction) of the pressure overload. Negative effects of the induced septal infarction, in particular left ventricular enlargement, have not been described. Preliminary studies have shown a reduction in described risk factors for sudden cardiac death, such as exertional syncope, abnormal blood pressure response, and exercise-induced ischemia, after successful PTSMA [49].

## Perspectives

To date, no randomized trials comparing surgical and percutaneous treatment of septal reduction in hypertrophic obstructive cardiomyopathy have been published [50]. Nonrandomized trials have shown significant reductions in left ventricular outflow tract obstruction and improvement of symptoms in response to both treatment options [51–53]. Therefore, benefits and drawbacks for each method of treatment (*Table II*) must be counterbalanced when a decision is taken as to the treatment for left ventricular outflow tract obstruction. This decision has to take into consideration several clinical, morphological, and technical aspects. Although there are some reports of successful combined simultaneous or staged percutaneous treatment of hypertrophic obstructive cardiomyopathy and coronary artery disease [25], surgery should be considered primarily as the means of dealing with hypertrophic obstructive cardiomyopathy and coexistent cardiac diseases such as coronary artery disease and valve replacement. In patients with hypertrophic obstructive cardiomyopa-

*Table II. Advantages and potential drawbacks of percutaneous transluminal septal myocardial ablation and surgical myectomy.*

Percutaneous septal ablation	Surgical myectomy
<p><i>Advantages</i></p> <ul style="list-style-type: none"> <li>● Avoidance of cardiopulmonary bypass with attendant risks                             <ul style="list-style-type: none"> <li>– Elderly patients with concomitant noncardiac disease</li> </ul> </li> <li>● Treatment of patients with isolated midcavitary or combined subaortic and midcavitary obstruction</li> <li>● Short hospital stay</li> <li>● Short recovery time</li> <li>● Lower costs</li> </ul> <p><i>Potential drawbacks</i></p> <ul style="list-style-type: none"> <li>● Risk of damage to the left coronary artery with                             <ul style="list-style-type: none"> <li>– Emergency bypass surgery or left main/LAD stenting</li> </ul> </li> <li>● Technical impossibility of reaching or identifying a target septal branch</li> <li>● Lower success in patients with                             <ul style="list-style-type: none"> <li>– Mitral valve leaflet and papillary muscle abnormalities</li> <li>– Large septal thickness (younger patients)</li> </ul> </li> </ul>	<p><i>Advantages</i></p> <ul style="list-style-type: none"> <li>● Immediate and complete relief of resting and provoked obstruction and concomitant mitral regurgitation</li> <li>● Documented long-term results up to 30 years</li> </ul> <p>Ability to treat coexistent cardiac diseases</p> <ul style="list-style-type: none"> <li>– Coronary artery disease, valve disease</li> </ul> <ul style="list-style-type: none"> <li>● Additional treatment of papillary muscle in extended myectomy</li> </ul> <p><i>Potential drawbacks</i></p> <ul style="list-style-type: none"> <li>● Necessity for extensive individual surgical experience                             <ul style="list-style-type: none"> <li>– High surgical mortality in inexperienced centers</li> </ul> </li> <li>● Low risk of postoperative aortic regurgitation</li> <li>● LV deterioration after extended myectomy during long-term follow-up, possibly because of                             <ul style="list-style-type: none"> <li>– High incidence of left bundle-branch block</li> </ul> </li> <li>● More invasive approach requiring extracorporeal circulation</li> </ul>
<p>LAD, Left anterior descending coronary artery; LV, left ventricular.</p>	

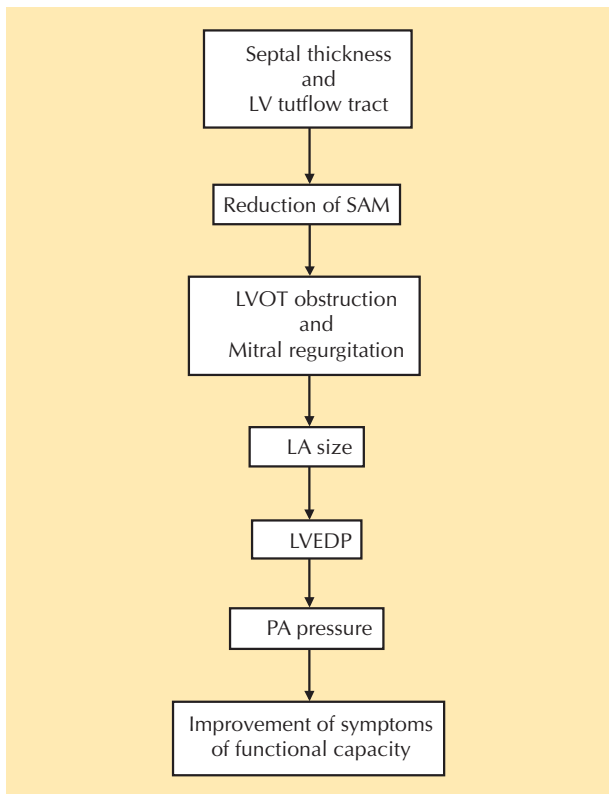


Figure 1. Morphologic, hemodynamic, and clinical effects of percutaneous septal ablation. ↓, Reduction; ↑, increase; LA, left atrium; LVEDP, left ventricular end-diastolic pressure; LVOT, left ventricular outflow tract; PA, pulmonary artery; SAM, systolic movement of the mitral valve apparatus.

thy and mitral regurgitation, pathomorphologic findings of the mitral valve apparatus should determine the preferred treatment option. Overall, surgery and percutaneous septal ablation should be seen as alternatives in hypertrophic obstructive cardiomyopathy. An individual decision must be made in each patient in order to achieve optimal results. Furthermore, in addition to the points mentioned above, the individual experience of the medical center should be taken into consideration.

## Summary

Nearly a decade after its introduction, percutaneous septal ablation is a promising treatment option for symptomatic patients with hypertrophic obstructive

cardiomyopathy refractory to medical treatment. The morphological, hemodynamic, and clinical effects (Figure 1) have been well described. Echocardiographic monitoring during the procedure results in optimization of the ablated septal area, with a reduction in peri-interventional complications and improvement in acute and mid-term hemodynamic results. However, possible complications and limited long-term effects mandate careful selection of patients. In order to avoid overuse of the technique, we would underline the importance of restricting the use of alcohol septal ablation in patients with hypertrophic obstructive cardiomyopathy to a few centers with large interventional and echocardiographic experience and knowledge of this uncommon disease. ■

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# Addressing the need for continuous round-the-clock cardioprotection with new Vastarel MR

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## Abstract

Most cardiovascular events are prone to occur in the early-morning hours with the renewal of daily activities, and this is accompanied by various neurohumoral stimuli. Precise knowledge of the circadian variations in angina paves the way to designing antianginal agents with an appropriate pharmacokinetic profile that ensures effective plasma concentrations at trough and a continuous anti-ischemic and cardioprotective effect. This was achieved with the new twice-daily formulation of the metabolic anti-ischemic agent, trimetazidine: Vastarel MR.

■ *Heart Metab.* 2003; 21:29–31.

**Keywords:** Cardiovascular events, circadian variations, trimetazidine, modified-release tablets, stable angina

## The circadian rhythm of angina

In patients with chronic stable angina, a marked early morning peak in the frequency of angina attacks and silent ischemic episodes has been demonstrated. Furthermore, 35% to 40% of episodes of sudden death [1], and acute coronary syndromes and stroke [2] occur between 6 AM and noon.

To the question: “Should we get up in the morning?” [3], came the answer: “It’s not a matter of time of awakening, but rather the standing position and daily activities” [4]; almost all ischemic events are preceded by an increase in heart rate. Silent and symptomatic episodes occur early in the morning, particularly within 2 hours after awakening (*Figures 1 and 2*) [5, 6]; waking up triggers an imbalance between myocardial oxygen supply and demand.

## Reduced oxygen supply to the heart

Reduction in oxygen supply is mainly the result of morning coronary vasoconstriction, caused by different mechanisms:

- sympathetic overactivity, a decrease in  $\beta_2$ -receptor sensitivity, or both [7]
- an increase in plasma concentrations of cortisol and angiotensin II
- an increase in blood viscosity [6].

In addition, increased heart rate leads to a decrease in supply through a shortening of diastole, but myocardial oxygen extraction cannot be further increased to compensate for the reduced supply.

# Focus on trimetazidine (Vastarel)

P. Meurin and T. Hénane

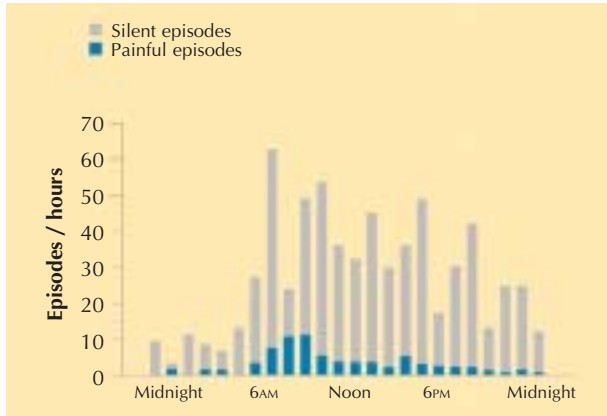


Figure 1. Circadian variation in the number of ischemic episodes (Adapted from Nademanee et al [5]).

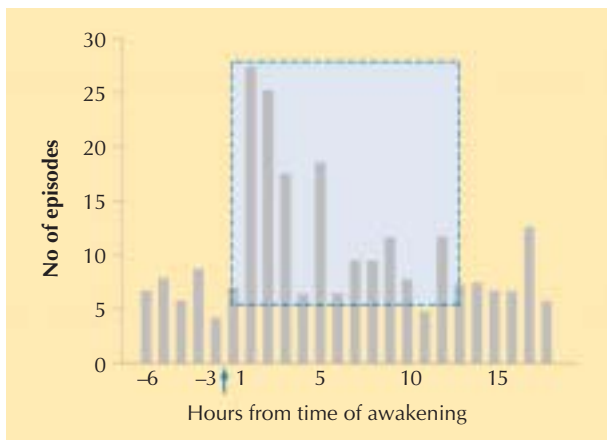


Figure 2. Number of ischemic episodes according to time after awakening (Adapted from Pepine [6]).

## Increased oxygen demand

In parallel, sympathetic overactivity is teamed with an increase in all determinants of myocardial oxygen consumption: heart rate, myocardial contractility, and left ventricular wall motion. In addition, early morning is known to be the time of the day when patients' treatment is less effective, as a result of low plasma concentration of the drugs (last intake 12 to 24 hours earlier, depending on the dosage plan).

This highlights the importance of developing antianginal drugs that provide effective blood

concentrations at trough and a sustained anti-ischemic effect throughout 24 hours.

## A new metabolic agent with an optimized pharmacokinetic profile

Vastarel MR (Modified Release) is a new twice-daily formulation of the metabolic anti-ischemic agent, trimetazidine. It was designed to be bioequivalent to the immediate-release formulation and to maintain high minimal plasma concentrations, while offering a twice-daily regimen to enhance patient compliance [8].

These aims have been achieved thanks to an innovative hydrophilic matrix that is the base of the new modified-release 35 mg tablet (Figure 3). When coming into contact with gastrointestinal fluids, the hypromellose matrix forms a gel that further triggers a controlled release of the active compound. As a result, Vastarel MR offers optimized pharmacokinetics, as demonstrated in a comparative trial in 12 healthy volunteers [8]. The pharmacokinetic profiles of modified-release and immediate-release tablets are compared in Figure 4.

There are three main advantages of the new formulation over the previous one:

- an increased minimal plasma concentration at trough (+31%)
- reduced fluctuations in plasma concentration

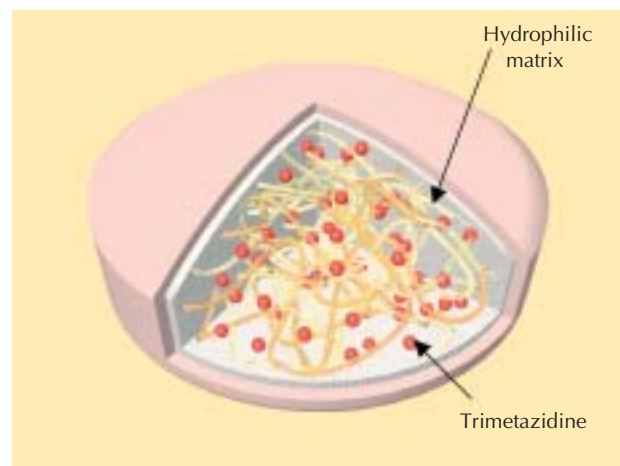


Figure 3. Section of a modified-release tablet of Vastarel MR.

# Focus on trimetazidine (Vastarel)

## 24-hour cardioprotection with Vastarel MR

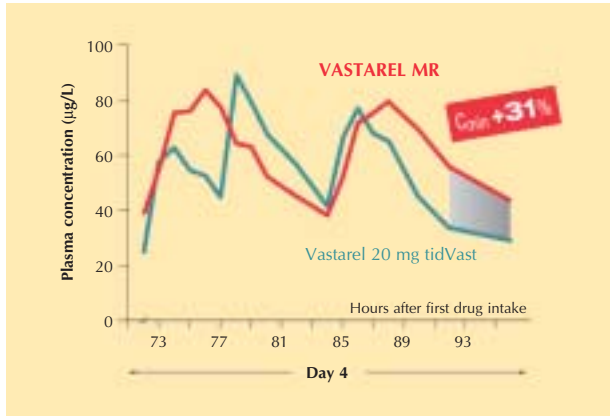


Figure 4. Comparative pharmacokinetic profiles of immediate-release trimetazidine (Vastarel 20 mg) and Vastarel MR.

- a prolongation of the concentration plateau (plasma concentrations remain greater than 75% of  $C_{max}$ ).

Vastarel MR provides coronary patients with sustained antianginal efficacy beyond 12 hours after the last drug intake, affording true round-the-clock cardioprotection.

Finally, Vastarel MR offers a simple daily dosage: one tablet twice daily (one in the morning and one in the evening), to be taken before, during or after meals,

as its absorption is not influenced by food. This great ease of use in daily practice should obviously favor patient compliance. ■

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# Hypertrophic cardiomyopathy

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### Abstract

Hypertrophic cardiomyopathy is the commonest genetic cardiovascular disease affecting 1 in 500 adults in the general population. It may be detected at any age and the majority of patients have a normal life expectancy. A small number are at risk and need to be identified. This case demonstrates the clinical approach to risk stratification and management and includes the interesting co-existence of Wolff-Parkinson-White syndrome which in turn needs to be risk stratified.

■ *Heart Metab.* 2003; 21:33–35

A 32-year-old man presented with a 3-week history of being aware of his heart racing with associated dizziness. His exercise ability was normal and he had experienced no syncopal episodes, but had noticed an increasing sensation of breathlessness. His father had recently undergone coronary artery bypass surgery, but there was no other family history of cardiac disease. His cholesterol was 6.4 mmol/L with an LDL 4.66 mmol/L. His family doctor heard a systolic murmur. He was on no medication, is single with a long-term partner and is a non-smoker. He drinks alcohol occasionally but less than 14 units per week.

Initial examination revealed him to be overweight (BMI 28 kg/m<sup>2</sup>), sinus rhythm, blood pressure 120/80 mm Hg, no evidence of cardiac failure, and clear lung fields. There was an impressive grade III/VI late systolic murmur best heard along the left sternal edge.

An echocardiogram identified severe hypertrophy affecting the whole of the left ventricle apart from the posterior wall with the septum worst affected at 31 mm thickness (upper limit of normal 1.1 cm). There was systolic anterior movement of the mitral valve and a calculated outflow gradient of 70 to 80 mm Hg. His resting ECG revealed Wolff-Parkinson-White (WPW) syndrome with a right-sided accessory pathway (*Figure 1*) and left ventricular hypertrophy. He underwent a Bruce protocol maximal exercise test managing an excellent 11 minutes, stopping because of general tiredness. The blood pressure response was normal and there were no arrhythmias. Immediately on

exercise the accessory pathway conduction disappeared indicating a "safe" accessory pathway (*Figure 2*).

He was referred to the dietician with regard to his hyperlipidemia and commenced on atenolol 50 mg daily for his cardiac symptoms. Arrangements were made to screen the family by echocardiography and fasting lipid profile.

He responded to the atenolol with fewer palpitations and no dizziness, and he was no longer breathless on exercise. He subsequently came to cardiac catheterization which revealed normal coronary arteries but confirmed hypertrophic obstructive cardiomyopathy. His post extrasystolic gradient was 87 mm Hg. After 50 mg intravenous disopyramide the gradient was reduced to 70 mm Hg post extrasystole. He was commenced on oral disopyramide retard 250 mg twice daily.

An invasive strategy to his WPW was not appropriate in view of the exercise test and he continued on medical therapy. His lipids failed to respond to diet and exercise but are controlled on atorvastatin 20 mg daily (LDL 2.6 mmol/L). He developed fatigue and postural symptoms which stopped when atenolol was discontinued, and he remains active and symptom-free on disopyramide. He was advised on the importance of genetic counseling, but his partner became pregnant before this was arranged. He understands the need for pediatric assessment on childbirth.

At follow-up, 48-hour ambulatory electrocardiography has identified no arrhythmias other than infrequent isolated ventricular extrasystoles.

# Case report

## Hypertrophic cardiomyopathy



Figure 1. Resting electrocardiogram (ECG) revealing Wolff-Parkinson-White and left ventricular hypertrophy.



Figure 2. Immediately on exercise accessory pathway conduction disappears.

### Discussion

Hypertrophic cardiomyopathy (HCM) affects 1 in 500 adults in the general population, and is therefore not rare, being the commonest genetic cardiovascular disease [1]. Many cases are undetected so that in a routine cardiac practice the incidence will be no more than 1% of the outpatient population. This limited clinical exposure should be supported by practical management guidelines, given the well-documented incidence of sudden death in the young, including young fit people [2,3]. Though sudden death is an obvious concern, overall the annual mortality is of the order of 1% and most patients are able to lead normal lives with a normal life expectancy. The question arises as to how to assess and identify those at risk, manage symptoms, and reduce the chance of sudden death.

HCM is inherited as an autosomal dominant trait caused by mutations in any of 10 genes encoding cardiac sarcomeric proteins [4]. The interest in this case is WPW. A genetic abnormality causing glycogen accumulation in myocytes is reported to cause familial WPW suggesting that the ventricular hypertrophy may reflect a metabolic storage disease rather than mutations in genes encoding sarcomeric proteins [5]. However, in this case the pattern on the echocardiogram suggests a coincidental WPW with a classical HCM appearance.

When presented with a case of HCM detected by chance (eg, on a routine medical a murmur is heard) or as a result of symptoms (atypical or exertional chest pain, dyspnea, palpitations, or syncope) it is essential to attempt to identify risk of sudden death as well as develop a treatment strategy to relieve symptoms [2,4]. Whilst sudden death is uncommon its occurrence in young people highlights its significance both to the families involved and the wider community. Though sudden death may be unpredictable higher risk subsets can be identified. Those at highest risk are summarized in *Table I* and lowest risk in *Table II*.

Table I. Highest risk of sudden death in hypertrophic cardiomyopathy (HCM).

Previous cardiac arrest
Sustained ventricular tachycardia (VT)
Family history of HCM sudden death
Syncope or near syncope
Repeated nonsustained VT on ambulatory ECGs
Hypotension on exercise testing
LVH > 30 mm
(Possibly degree of outflow obstruction)

ECG, Electrocardiogram; LVH, left ventricular hypertrophy.

Table II. Lowest risk of sudden death in hypertrophic cardiomyopathy (HCM).

No symptoms plus: -
No family history of HCM death or syncope
No VT on monitoring
No outflow gradient > 50 mm Hg
Wall thickness < 20 mm
Normal blood pressure on exercise

VT, Ventricular tachycardia

Risk stratification requires taking a good history, ECG and echocardiography, 48-hour ambulatory electrocardiography, and treadmill exercise electrocardiography with blood pressure monitoring. Invasive electrophysiologic testing with programmed ventricular stimulation has no clear role to play [6].

Symptomatic therapy usually begins with  $\beta$ -blockers but adverse effects may be limiting. Disopyramide has been extensively used in patients with significant outflow obstruction and its benefit may be predicted at catheterization by its effect on the induced postventricular extrasystole gradient increase [7]. There appears to be little evidence for prophylactic drug treatment in asymptomatic patients with HCM, even if they are judged as high-risk. Currently the most effective treatment for high-risk HCM appears to be the implantable cardioverter defibrillator (ICD) [8]. In addition avoiding intense physical exercise is both prudent and sensible. Amiodarone has a significant long-term side effect profile which limits its use in young people [4].

This particular case has demonstrated the classical symptomatic and echocardiographic features of HCM with the interesting coexistence of WPW. Though the septal thickness is in the high risk category, noninvasive testing has not identified a high-risk scenario. Symptomatic benefit and objective outflow gradient reduction has been seen with disopyramide which is being monitored to be certain it is sustained. There has been no evidence of atrial fibrillation (occurs in 20% and relates in part to left atrial enlargement) so anticoagulation is not indicated (his left atrium is slightly enlarged at 4.3 cm) but perhaps he should be on aspirin or clopidogrel. There is no evidence of cardiac failure and his ejection fraction was 90% before disopyramide. Surgical therapy or alcohol septal ablation are not indicated in the absence of limiting symptoms and the evidence for chronic dual chamber pacing is that it does not reduce sudden death or initiate remodeling of the left ventricle and even in the presence of symptoms the effects are unclear [4].

## Summary

HCM is a genetic condition caused by mutation of genes encoding sarcomeric proteins. Understanding the mechanism of the disease has not unfortunately translated into clear-cut clinical guidelines, though low- and high-risk patients can now be recognized. Symptomatic patients with outflow obstruction should initially be treated with  $\beta$ -blockers and/or disopyramide. A more aggressive approach is determined by symptoms failing to respond to medical therapy and includes alcohol septal ablation, surgery and possibly dual-chamber pacemaker therapy (debated). All patients should be risk stratified and this should include ambulatory electrocardiography and exercise testing. The majority of patients are low-risk and can be reassured. High-risk patients should be considered for ICD therapy as amiodarone cannot be recommended long term in young people because of the lack of a positive risk:benefit ratio when adverse effects are taken into account. ■

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# Genetics of hypertrophic cardiomyopathy

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## Abstract

Hypertrophic cardiomyopathy is a genetically heterogeneous disorder. More than 200 mutations have been described in 11 cardiac sarcomere protein genes and in one gene regulating muscle-specific gene expression. Inheritance is autosomal-dominant, with variable clinical expression. Although some mutations are more malignant than others, no particular phenotype is mutation-specific. Eighty percent of mutations occur in three cardiac sarcomere protein coding genes: *MYH7* gene ( $\beta$ -myosin heavy chain), *MYBPC3* gene (myosin binding protein C) and *TNNT2* gene (cardiac troponin T). A genetic diagnosis may be possible in about 60% of patients, even in "sporadic" cases. In severe manifestations of hypertrophic cardiomyopathy, more than one mutation should be sought.

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**Keywords:** Hypertrophic cardiomyopathy, genetic mutation, sarcomere protein, counseling.

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder, characterized by left ventricular hypertrophy, usually asymmetric in distribution, in the absence of other causes of hypertrophy (eg, systemic hypertension or aortic stenosis) [1]. It affects all ages, but usually becomes apparent from the age of adolescence, with a prevalence in young adults in the general population of 1 in 500 [2].

HCM is a genetically heterogeneous disease. Mutations have been detected in 11 cardiac sarcomere protein genes and in the *CRP3/MLP* gene coding for muscle-specific LIM protein [3–6]. HCM caused by sarcomere protein defects is characterized by cellular hypertrophy and myocyte disarray [3]. A hypertrophic appearance without these characteristics may be caused by disorders of storage disease, like Fabry's disease and a glycogen storage disease associated with the Wolff-Parkinson-White syndrome [3, 7].

The present review focuses on HCM caused by mutations in sarcomere protein genes. The cardiac sarcomere genes code for proteins building the structure of the sarcomere (*Figure 1*). At present, more than 200 different genetic mutations have been identified [3–5, 8]. All these mutations carry an autosomal-dominant inheritance pattern causing a

familial hypertrophic cardiomyopathy [3–5]. A family history may not always be apparent; in unselected populations, a positive family history may be found in 50% [9]. Not all genetically similarly affected family members will have the same (or any) degree of disease, and penetrance (percent of carriers of the mutation who also have the disease) for some of the investigated mutations is in the order of 60% to 90% and is age-dependent [10–12].

## Mutations in genes coding for sarcomere proteins

Three cardiac sarcomere protein genes are commonly (over 80%) mutated in hypertrophic cardiomyopathy: the  $\beta$ -myosin heavy chain, myosin-binding protein C, and cardiac troponin T genes [3, 5, 13]. The other genes account for a minority of cases of hypertrophic cardiomyopathy; they are summarized in *Table 1*, together with estimated frequencies of their occurrence.

The  $\beta$ -myosin heavy chain gene, *MYH7*, is the largest of the cardiac sarcomere genes. It is composed of 40 exons (protein-coding parts of the gene, as

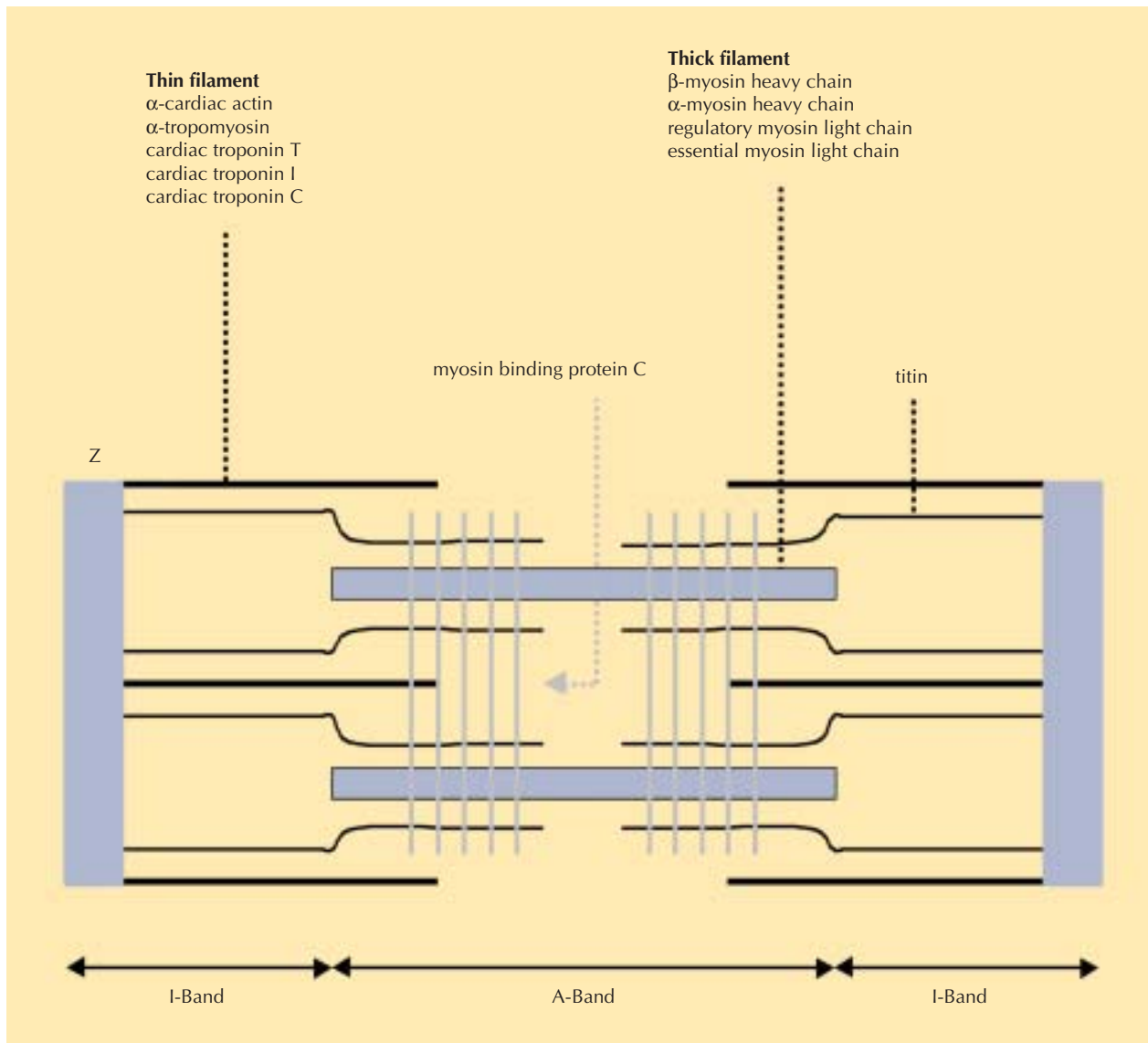


Figure 1. The cardiac sarcomere and its proteins.

opposed to introns, which are noncoding intervening parts between the exons), 38 of which are coding for a large protein of 1935 amino acids, carrying the myosin motor heads of the thick filaments [13]. The importance of the *MYH7* gene in hypertrophic cardiomyopathy is manifested in the finding of at least 70 mutations in families with hypertrophic cardiomyopathy, with an early onset and a high (~90%) penetrance of the disease [12–14]. Almost all the identified mutations in the *MYH7* gene are

missense mutations, resulting in a change of a single amino acid of the  $\beta$ -myosin heavy chain protein. The change may create a “poison peptide,” altering the function of the protein or its assembly into the sarcomere filaments [13]. Most mutations occur in the first part of the  $\beta$ -myosin heavy chain molecule, which contains the ATP binding site and the actin binding site, necessary for energy transfer and interaction between actin and myosin to enable contraction [13]. Arg403Gln and Arg719Gln muta-

## Refresher corner

### Genetics of hypertrophic cardiomyopathy

Table 1. Sarcomere proteins, genes and distribution of hypertrophic cardiomyopathy (HCM) genotypes. †Frequencies of HCM genotypes, as percentage of discovered genotypes, were obtained from Richard et al [5], who were able to explain HCM in 60% of 197 patients in France.

Protein	Gene	Number of exons	Chromosome locus	Frequency in HCM†
β-Myosin heavy chain	<i>MYH7</i>	40	14q11-q12	40%
α-Myosin heavy chain	<i>MYH6</i>	39	14q12	Low
Myosin binding protein C	<i>MYBPC3</i>	35	11p11.2	42%
Cardiac troponin T	<i>TNNT2</i>	17	1q3	6.5%
α-Tropomyosin	<i>TPM1</i>	10	15q22	Low
Cardiac troponin I	<i>TNNI3</i>	8	19p13-q13	6.5%
Regulatory myosin light chain	<i>MYL2</i>	7	12q23-q24	Low
Essential myosin light chain	<i>MYL3</i>	7	3p21.2	Low
α-Cardiac actin	<i>ACTC</i>	6	15q14	Low
Cardiac troponin C	<i>TNNC1</i>	6	3p21.3	Low
Titin	<i>TTN</i>	6	2q24.3	Low

tions have been associated with a greater frequency of premature death than have other mutations [12, 14, 15].

The myosin-binding protein C gene, *MYBPC3*, is also a large cardiac sarcomere protein gene. It contains 35 exons, of which 34 are coding for 1173 amino acids for myosin binding protein C, which binds the myosin heavy chains and titin [13]. Of the more than 60 described *MYBPC3* mutations, most occur in the latter part of the molecule, containing the major myosin and titin binding sites [5, 13]. In contrast to other gene mutations, *MYBPC3* mutations often are deletions or insertions that result in a frame shift during translation [16]. The expected result is the creation of “truncated proteins,” missing at least the myosin binding domain [16]. Mutations in *MYBPC3* have been characterized by a late onset and a mild phenotype [11, 17, 18].

The third most important gene, *TNNT2* for cardiac troponin T, is composed of 17 exons coding for a cardiac sarcomere protein with the function of binding tropomyosin to the troponin complex, troponin C and troponin I, necessary for crossbridge kinetics [13]. More than 20 mutations, most often missense mutations, were found in families with hypertrophic cardiomyopathy [19–21]. The disease caused by *TNNT2* mutations generally causes less severe hypertrophy, but has more severe myocyte disarray and carries a high risk of sudden cardiac death at young age [19–21].

Mutations that have been described in the eight other cardiac sarcomere genes, listed in Table 1, explain a minority of cases of hypertrophic cardiomyopathy. They are most often missense mutations [13]. The results of several genotype–phenotype studies, including those of the more common gene mutations, suggest that some of these mutations cause more severe disease than others with regard to sudden cardiac death [4, 12, 14, 18, 20]. However, there is a significant degree of variability in clinical expression of a same mutation, and no particular clinical phenotype is mutation-specific [22].

### Genetic counseling for patients with hypertrophic cardiomyopathy

When confronted with a patient with hypertrophic cardiomyopathy, a cardiologist should inform the patient concerning the nature of the disease, and its probable mode of inheritance. Some clues for risk assessment may be evident from making a pedigree, specifically asking about relatives with sudden cardiac death. Cardiologists should be aware of the diagnostic ability of genetic analysis, by which about 60% of genetic causes for hypertrophic cardiomyopathy may be determined, even in “sporadic” cases without an apparent family history [5, 23]. Other causes of hypertrophic cardiomyopathy-like disorders may have to be excluded such as hyperparathyroidism,

M. Fabry, von Recklinghausen neurofibromatosis, Friedreich's ataxia, mitochondrial cardiomyopathy, Noonan syndrome, and storage diseases such as hemochromatosis and amyloidosis [3]. Laboratory evaluation and sometimes neurological evaluation may therefore be of use when in doubt about the nature of cardiac hypertrophy.

As part of genetic counseling, patients and relatives should be well informed about the consequences of a possible genetic diagnosis [24]. When patients or their relatives consent to further genetic analysis, it is cost-effective first to screen the index patient for defects in the most frequently mutated genes, *MYH7* and *MYBPC3*. In severe cases of hypertrophic cardiomyopathy, compound heterozygotic mutations should be considered [25]. At present, the additional value of a genetic diagnosis is rather small, for example to reassure family members who do not possess the mutation, or to give advice on participation in competitive sports [24]. When sudden cardiac death occurs within a family with hypertrophic cardiomyopathy, the possible benefit from an implantable cardiac defibrillator must be considered in family members with the same genotype [26].

As protein defects in hypertrophic cardiomyopathy in themselves do not cause hypertrophy [27], lifestyle factors, modifier genes and polymorphisms that could modulate the phenotypic expression of the disease are being investigated [12, 22]. An early genetic diagnosis in a person with familial hypertrophic cardiomyopathy may therefore also be of value in enabling the institution, at younger age, of therapeutic strategies that include treatment with hydroxymethyl glutaryl-coenzyme A reductase inhibitors and angiotensin-converting enzyme inhibitors, which have shown promise in animal models of hypertrophic cardiomyopathy [28, 29]. ■

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# Featured research

### Abstracts and commentaries

#### Glucose-6-phosphate dehydrogenase modulates cytosolic redox status and contractile phenotype in adult cardiomyocytes

Jain M, Brenner DA, Cui L, et al. *Circ Res.* 2003;93:e9–e16.

The exquisite sensitivity of myocardium to oxidative injury is well established. This article reports the necessity of glucose-6-phosphate dehydrogenase (G6PD) as a critical component of the cellular antioxidant system in adult cardiomyocytes. Moreover and interestingly, the authors showed that hearts of mutant mice with significant G6PD deficiency exhibit progressive adverse structural remodeling and cardiac dysfunction over time. Echocardiographic studies performed in these mice indeed showed the development of hypertrophic cardiomyopathy with increased ventricular septal wall thickness and end-systolic chamber dimensions, as well as a significant decrease in fractional shortening relative to age-matched wild-type controls of same age.

#### Commentary

Glucose-6-phosphate dehydrogenase (G6PD) functions as the first and rate-limiting enzyme in the pentose phosphate pathway, responsible for the generation of NADPH in a reaction coupled to the oxidation of glucose-6-phosphate and de novo production of cellular ribose. The article by Jain et al demonstrates that G6PD activity in adult cardiomyocytes is rapidly increased in response to cellular oxidative stress. Furthermore, inhibition of GPD with DHA (dehydroepiandrosterone) altered cardiomyocyte redox status, resulting in marked depletion of cytosolic reduced glutathione levels which are important to protect against reactive oxygen species injury in cardiomyocytes. Importantly, G6PD activity correlated directly with levels of cytosolic reduced glutathione. Inhibition of G6PD also impaired cardiomyocyte contractility and calcium homeostasis. Rescue of contractile dysfunction in vitro with a

glutathione-generating compound or antioxidant treatment, along with the absence of any effect with ribose treatment, strongly supports the hypothesis that cellular dysfunction secondary to G6PD inhibition occurred as a result of depletion of cytosolic thiols and increased oxidative stress, rather than as a result of decreased end-product generation by the pentose phosphate pathway. Taken together, these data reveal an essential role of the enzyme G6PD for maintenance of cytosolic glutathione stores and subsequent protection against cellular reactive oxygen species. Furthermore, echocardiographic assessment of in vivo cardiac structure and function in G6PD deficient mice showed adverse structural remodeling and impaired contractile function over time. Obviously, the role that the enzyme G6PD may play in the protection against pathogenic alterations in cellular redox state should deserve further attention in future studies.

*Danielle Feuvray*

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#### Efficacy of perindopril in reduction in cardiovascular events among patients with stable coronary artery disease

*Lancet* 2003;362:782–788.

Angiotensin-converting enzyme (ACE) inhibitors are well established in the treatment of cardiac failure and diabetes reducing the risks of cardiovascular disease and renal damage. Their anti-inflammatory properties and hemodynamic benefits translating into reducing the risk of death, myocardial infarction, stroke, and deteriorating left ventricular function have mainly been in patients with heart failure or asymptomatic left ventricular dysfunction and/or diabetics. The European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) now extends the benefit to patients with coronary artery disease.

In EUROPA 12218 patients were randomized to either perindopril (titrated to 8 mg daily) or placebo.

Perindopril reduced the composite end point of cardiac death, myocardial infarction, and cardiac arrest at up to 4.2 years by 20% – 603 patients (9.9%) to 488 (8.0%) –  $P=0.0003$ . The findings were present in addition to therapy with aspirin 92%,  $\beta$ -blockers 62%, and lipid-lowering drugs 58%. Though left ventricular function is not described in the paper it is unlikely that it was impaired at baseline.

The results suggest an additive effect to prognostic therapy on plaque stability and improvement in endothelial function which may reduce the atherothrombosis risk. The risk reduction did not differ between hypertensives and normotensives though the blood pressure readings at entry were not categorised and related to outcome. Against hypotension being the mechanism of benefit was the greater effect on reduction in non fatal myocardial infarction (22%  $P=0.001$ ) versus stroke (7% not significant).

EUROPA suggests that independent of left ventricular function patients with coronary artery disease should be treated with an ACE inhibitor. These findings are not dissimilar to the HOPE trial involving ramipril – a long-acting ACE inhibitor like perindopril with similar significant tissue penetration [1]. Whether other ACE inhibitors will have similar properties depends on continuing research.

On prognostic grounds our patients with coronary artery disease will need to be considered for aspirin (or clopidogrol), a  $\beta$ -blocker, a statin, and an ACE inhibitor (or angiotensin II antagonist if not tolerated). Until further evidence is available perindopril and ramipril are the ACE inhibitors of first choice.

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*Graham Jackson*

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## Decreased energetics in murine hearts bearing the R92Q mutation in cardiac troponin T

Javadpour MM, Tardiff JC, Pinz I, Ingwall JS. *J Clin Invest.* 2003;112:768–75.

The thin filament protein cardiac troponin T (cTnT) is an important regulator of myofilament activation. Here we report a significant change in cardiac energetics in transgenic mice bearing the missense mutation R92Q within the tropomyosin-binding domain of cTnT, a mutation associated with a clinically severe form of familial hypertrophic cardiomyopathy. This functional domain of cTnT has recently been shown to be a crucial modulator of contractile function despite the fact that it does not directly interact with the ATP hydrolysis site in the myosin head. Simultaneous measurements of cardiac energetics using  $^{31}\text{P}$  NMR spectroscopy and contractile performance of the intact beating heart revealed both a decrease in the free energy of ATP hydrolysis available to support contractile work and a marked inability to increase contractile performance upon acute inotropic challenge in hearts from R92Q mice. These results show that alterations in thin filament protein structure and function can lead to significant defects in myocardial energetics and contractile reserve.

## Commentary

Patients with familial hypertrophic cardiomyopathy (FHC) are susceptible to arrhythmias and sudden death. One of the most clinically malignant FHC mutations is a missense mutation in the gene for the thin filament protein cTnT. In this recent article published in the *Journal of Clinical Investigation*, Javadpour et al examined cardiac energetics in intact hearts from mice containing a R92Q mutation in cTnT. These authors show that there is a decreased energetic driving force within the cardiomyocytes of these hearts. This extends previous studies suggesting that this mutation enhances the activation of myofibrillar ATPase activity, resulting in an excessive energy utilization by the contractile proteins. It also raises the intriguing possibility that a mismatch in energy use by the heart may be one of the pathogenic mechanisms of familial hypertrophic cardiomyopathy. If this is the case, the possibility exists that optimizing energy production in the heart may be a

novel therapeutic approach to treating hypertrophic cardiomyopathy.

*Gary D. Lopaschuk*

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### **In vivo detection of cell death in the area at risk in acute myocardial infarction**

Thimister PW, Hofstra L, Liem IH, et al. *J Nucl Med.* 2003;44:391–396.

Annexin A5 is a phospholipid binding protein with high affinity for phosphatidyl-serine, which is externalized by cells undergoing programmed cell death. An increased programmed cell death rate has been reported in the heart after myocardial infarction (MI). The aim of this study was to correctly localize annexin A5 uptake in vivo and to determine the area at risk in humans with acute MI. **METHODS:** Nine patients were studied. Before reperfusion was achieved, (99m)Tc-sestamibi was injected intravenously. Myocardial (99m)Tc-sestamibi perfusion scintigraphy was performed after reperfusion. Thereafter, (99m)Tc-labeled annexin A5 was administered intravenously, followed by scintigraphic imaging of the heart. Myocardial (99m)Tc-sestamibi scintigraphy was repeated 1 to 3 weeks after the MI onset. (99m)Tc-Annexin uptake was also studied in the subacute phase of the MI in 2 patients. **RESULTS:** All patients clearly showed perfusion defects on (99m)Tc-sestamibi scintigraphy in concordance with the infarct location. Furthermore, all patients showed accumulation of (99m)Tc-annexin A5 at the infarct site, indicating that cardiomyocytes with externalized phosphatidyl-serine are present in the infarct area. (99m)Tc-sestamibi defects determined 1 to 3 weeks after the MI onset were significantly smaller than the defects in the acute phase. (99m)Tc-annexin uptake was absent in the 2 patients studied in the subacute phase. **CONCLUSION:** In acute MI, an increase of programmed cell death can be correctly localized in vivo in the area at risk. Furthermore, the decrease in (99m)Tc-sestamibi defect size in the subacute phase

of the MI further suggests that in parts of the area at risk, reversible myocardial damage rather than necrosis is present in cardiomyocytes.

### **Commentary**

The protein annexin A5 binds to a membrane protein phosphatidyl-serine. In normal myocytes phosphatidyl-serine is not expressed on the outer cellular membrane but one of the first events in apoptosis is the expression of this protein. Labeling of annexin A5 to a radiotracer like <sup>99m</sup>Tc allows noninvasive in-vivo assessment of the process of apoptosis.

Programmed cell death or apoptosis has been demonstrated in a number of cardiac diseases like heart failure, MI, reperfusion injury, and hypertrophy. Most interestingly, recent data have suggested that after infarction, cell death is not only due to necrosis of the ischemic myocytes, but that apoptosis may also play an important role. In other words, there may be an overkill of myocytes in the area of infarction, purely related to apoptotic pathway. This suggests that if the process of apoptosis is limited by pharmaceutical interventions this may lead to infarct size reduction and possibly preservation of residual left ventricular function.

To monitor the process of apoptosis in patients and possibly in future to study the effect of therapeutic interventions, imaging of the extent of apoptosis is required. The authors of this manuscript have successfully demonstrated that <sup>99m</sup>Tc-annexin A5 retention localizes in the area of infarction, whereas no retention was observed outside the infarct area or in a healthy volunteer. Although many important questions remain to be answered, like if the <sup>99m</sup>Tc-annexin A5 retention is really specific for apoptosis or merely a sign of necrosis, these kind of studies open the way for exploring the mechanisms of apoptosis or the effect of therapeutic interventions in patients.

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# Glossary

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### **Akt**

Akt, which is sometimes called protein kinase B (PKB) is an intracellular kinase that is important in a number of cellular functions, including regulation of glucose metabolism and cell growth. It is a kinase in the insulin signalling pathway, and insulin activation of Akt will result in GLUT 4 translocation to the cell membrane, thereby stimulating glucose uptake. Overexpression of Akt in the heart can cause a marked hypertrophy of the muscle.

### **Allele**

An allele is one of two or more alternative forms of a gene at the same site in a chromosome. This determines the alternative characteristic of the inheritance.

### **ATPase**

ATPase are proteins that cleave adenosine triphosphate (ATP) to adenosine diphosphate (ADP). This reaction releases energy, which is usually used to drive some other energy-requiring reaction mediated by the ATPase. For instance, Na/K-ATPase pumps Na<sup>+</sup> out of cells and K<sup>+</sup> into cells using the energy generated from the ATPase reaction. Another example is myosin ATPase, where the energy generated by the ATPase is used for muscle contraction.

### **Autophosphorylation**

Autophosphorylation refers to a situation where a kinase can phosphorylate an identical kinase.

### **Alpha-myosin heavy chain**

Muscle is made up of interacting thick and thin filaments that slide past each other to produce muscle contraction. The thick filaments consist mainly of myosin. Myosin is a very large

molecule made up of two identical heavy chains (alpha-myosin heavy chains) and four light chains. The alpha-myosin heavy chain consists of an alpha helical coiled rod and a globular region.

### **Calcineurin**

Calcineurin is a phosphatase that cleaves phosphate groups from proteins. This phosphatase has received a considerable research interest in cardiac hypertrophy, since activation of calcineurin can promote cell growth secondary to dephosphorylation of translocation nuclear factor of activated T-cell (NFAT). The dephosphorylated NFAT can then translocate to the nucleus and promote cell growth.

### **Calmodulin**

Calmodulin is an important molecule that binds calcium and stimulates the activity of calmodulin-dependent kinases. Calmodulin mediates many important reactions in the cell, including excitation contraction coupling of muscle cells.

### **CamKII**

Ca<sup>2+</sup>/calmodulin-dependent protein kinase II (CaMKII) is a kinase that is activated by Ca<sup>2+</sup>/calmodulin. This kinase regulates many cellular proteins, many of which are involved in the regulation of cellular calcium. Activation of CamKII has also been shown to induce cardiac hypertrophy.

### **Missense mutation**

Mutations in the nucleotide sequence of DNA can result in the coding of proteins with missense mutations in the amino acids. This can alter the primary amino acid sequence and protein structure of the protein. An example of missense

mutations are mutations of the  $\beta$ -myosin heavy chain (MHC) gene that can lead in a number of mutations in the protein that can lead to hypertrophic cardiomyopathy.

### **p38 and c-jun N-terminal and mitogen-activated protein kinases**

Mitogen-activated protein kinases (MAPK) are important components of signaling modules activated by neurotransmitters, cytokines, and growth factors, as well as chemical and mechanical stressors. p38 MAPK is one of these kinases that has diverse cellular function including mitogenic activity, control of glucose metabolism, and activation of apoptotic pathways. The c-Jun N-terminal kinase (JNK) branch of the MAPK signaling pathway also regulates cellular differentiation, stress responsiveness and apoptosis in multicellular eukaryotic organisms.

### **PRKAG2**

PRKAG2 is the gene that encodes the  $\gamma$ 2 subunit of AMP-activated protein kinase (AMPK). Mutations in PRKAG2 have recently been shown to cause cardiac hypertrophy, cardiac glycogen accumulation, Wolff-Parkinson-White syn-

drome, and conduction system disease causing pre-excitation.

### **SERCA**

SERCA stands for sarcoplasmic/endoplasmic reticulum calcium ATPase. SERCA is the enzyme primarily involved in the transport of calcium into intracellular sarcoplasmic reticulum and endoplasmic reticulum. The sarcoplasmic reticulum (SR) is an intracellular organelle in heart and skeletal muscle that stores calcium. During excitation-contraction coupling, release of calcium from the SR is the major source of calcium that initiates muscle contraction.

### **Signalling pathways**

In all cells, complex signalling pathways exist which mediate cell function. Many of these signalling pathways involve kinases that mediate numerous cellular actions, including the effects of hormones binding to receptors which translate into cellular actions. p38 and c-jun N-terminal mitogen-activated protein kinases and calmodulin dependent kinase (CamKII) are examples of kinases involved in important signalling pathways.