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Myocardial O utilization and energetics of the left ventricle in hypertrophic cardiomyopathy

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Chapter

1

General introduction and thesis outline

A word cloud of medical terms related to hypertrophic cardiomyopathy. The words are arranged in a roughly rectangular shape, with varying font sizes and orientations. The most prominent words are 'mutation', 'hypertrophy', 'patients', 'sarcomere', and 'septal'. Other visible words include 'dysfunction', 'myocardial', 'myectomy', 'hcm', 'magnetic', 'months', 'non-hypertrophic', 'obstructive', 'efficiency', 'energetic', 'energy', 'group', 'imaging', 'lv', 'positron', 'proteins', 'replacement', and 'serve'.

dysfunction efficiency energetic energy group hcm
hypertrophic hypertrophy imaging lv
magnetic months mutation myectomy
myocardial non-hypertrophic obstructive patients
positron proteins replacement sarcomere septal serve

Hypertrophic cardiomyopathy

This chapter will provide a brief and general introduction about the morphological and functional abnormalities of hypertrophic cardiomyopathy (HCM).

Morphological definition

HCM is primarily a myocardial disease causing left ventricular (LV) hypertrophy in the absence of increased loading conditions such as hypertension or aortic valve stenosis. An LV wall thickness of ≥ 15 mm at end-diastole in any segment is used as an obligatory criterium, although due to the genetic background of the disease (described below), in relatives of HCM patients a cut-off of 13 mm is used.¹

HCM morphology exhibits heterogeneity. The most common variant is asymmetric septal hypertrophy involving the septum, accounting for about two thirds of the spectrum (Figure 1C). Sigmoid shaped septum is more common in the elderly (Figure 1B). Other phenotypical variants include apical hypertrophy (Figure 1D), which is more frequent in the Japanese population ($\pm 25\%$ of HCM patients) compared to western countries ($\pm 2\%$ of HCM patients), or a more diffuse or concentric pattern of LV hypertrophy (Figure 1E).

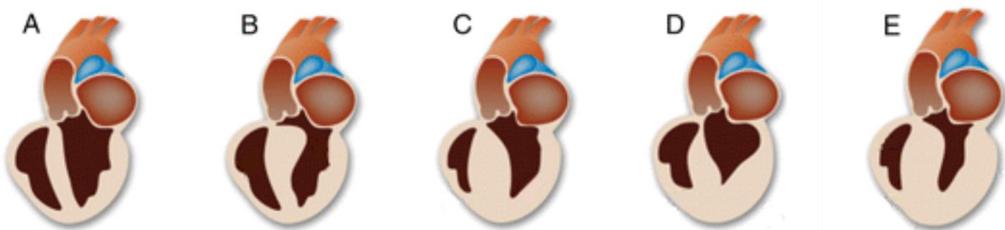


Figure 1. Phenotypical variants of HCM. A. Healthy heart B. Sigmoid-shaped septal hypertrophy C. Asymmetric septal hypertrophy D. Apical hypertrophy E. Diffuse concentric hypertrophy.

Epidemiology and genetics

HCM is the most common inherited cardiac disease with an estimated prevalence ranging from 1:500 to 1:200 in the normal population. HCM has an autosomal dominant pattern of inheritance, which indicates that offspring has a 50% chance to carry the mutant gene.¹⁻³

To date, more than 1400 HCM-associated mutations in more than 13 genes have been identified, that predominantly encode thick and thin myofilaments of the cardiac sarcomere.⁴ The most frequently affected thick filament genes are *MYBPC3*

(encoding cardiac myosin-binding protein C: cMyBP-C) and *MYH7* (encoding the sarcomeric protein β -myosin heavy chain: β -MyHC). The sarcomeric gene mutations can be detected in most HCM patients (genotype-positive patients); however, in approximately 30% of cases, no mutation is found (genotype-negative patients).^{4, 5}

The penetrance of these mutations differs substantially, even within families. Therefore, the phenotypic expression in HCM is highly variable, ranging from no cardiac phenotype to extreme LV hypertrophy. HCM patients may have no or mild symptoms throughout life, whereas a small proportion of patients develop progressive heart failure or sudden cardiac death at young age. Importantly, several clinical studies observed differences in disease onset between patients with mutations in *MYH7* and *MYBPC3*, indicative for gene-specific differences in the clinical course of HCM.⁶⁻⁸

Histopathological findings in HCM

The histopathological hallmarks of HCM are myocyte hypertrophy, myocyte disarray, small vessel disease and different types of fibrosis, which is mostly derived from several autopsy and transplant studies from HCM patients who suffered sudden cardiac death or progression to end-stage heart failure.⁹⁻¹¹ However, none of these findings are specific for HCM.

Myocyte disarray is characterised by regions of architectural disorganisation of hypertrophied myocytes (Figure 2A). The myocytes are non-parallel aligned in a chaotic manner. Myocyte disarray is not only confined to the septal region, but is also present in other segments of the LV.

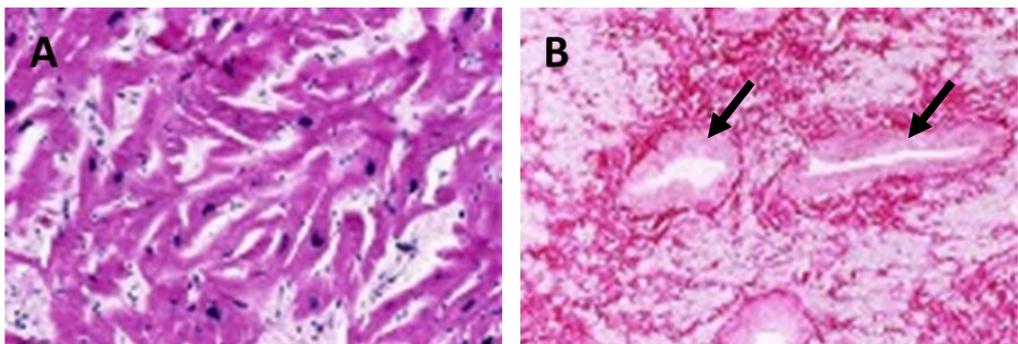


Figure 2. Histopathological findings in HCM. A. Photomicrograph of a section of LV myocardium of a HCM patient demonstrating marked myocyte hypertrophy and disorganization (Hematoxylin and eosin staining). B. Photomicrograph of a section of LV myocardium of a HCM patient showing abnormal intramural coronary arteries with thickened walls and narrowed lumens. (From Shirani J. "Abnormal Morphologic Features of Hypertrophic Cardiomyopathy")

Small vessel disease in HCM, or in other words microvascular dysfunction, is caused by thickening of the medial layer of intramural arterioles (Figure 2B), decreased luminal size and reduced capillary density. The mismatch between myocardial mass and coronary circulation is likely responsible for impaired coronary vasodilatory reserve and thus myocardial ischemia.^{20, 22}

Another important histopathologic feature of HCM is the presence of both dense replacement fibrosis (scar) and diffuse interstitial fibrosis, which forms a potential substrate for arrhythmias and heart failure. However, the precise triggers that lead to the development of fibrosis are unknown. Ho *et al.* found that interstitial fibrosis was already present in mutation carriers without signs of HCM.¹² This suggests that myocardial fibrosis is an early consequence of sarcomere mutations which may lead to irreversible changes within the myocardial extracellular matrix.

Clinical findings in HCM

LV outflow tract obstruction

LV outflow tract (LVOT) obstruction in HCM is caused by hypertrophy of the anteroseptal part of the LV, and its severity depends on the contractile state and filling status of the LV. Therefore, LVOT obstruction in HCM is dynamic, unlike the static LVOT obstruction due to aortic stenosis. The obstruction causes an intracavitary pressure gradient which pulls the mitral valve leaflet towards the septum by the Venturi effect, resulting in eccentric mitral regurgitation due to incomplete leaflet coaptation. The combination of LVOT obstruction, secondary mitral regurgitation and diastolic dysfunction leads to enlargement of the left atrium (LA). LA size is a determinant of the risk of atrial fibrillation, and its complications of thromboembolism and heart failure.

A LVOT pressure gradient over ≥ 30 mmHg is deemed to be obstructed. This is present in approximately 25% of HCM patients in rest. During exercise, LVOT gradient is generally higher due to increased LV contractility and reduced preload and afterload. An obstructive LVOT gradient may be undiagnosed at rest. Therefore, patient should be provoked by Valsalva manoeuvre to establish the absence or presence of an obstructive LVOT gradient.

Clinically, LVOT obstruction can cause dizziness and limited exercise tolerance due to diminished blood flow during systolic ejection. Previous studies performed in large HCM cohorts have shown that LVOT obstruction is an important predictor of disease progression and cardiovascular death.^{13, 14} At present, septal myectomy is the preferred treatment for symptomatic HCM patients with LVOT obstruction despite medical therapy. Septal myectomy can substantially reduce LVOT obstruction and secondary mitral regurgitation leading to significant improvement in symptoms and survival.^{15, 16}

Coronary microvascular dysfunction

Patients with HCM often have symptoms and signs of myocardial ischemia in the absence of epicardial coronary artery stenosis.^{17, 18} Previous functional studies in HCM patients using positron emission tomography demonstrated decreased hyperaemic myocardial perfusion and impaired coronary flow reserve (CFR), indicating coronary microvascular dysfunction (CMD).¹⁹⁻²¹ Decreased myocardial perfusion and CFR contribute negatively to symptoms and long-term outcome of patients with HCM.¹⁹ It has already been shown that CMD is mainly related to adverse remodelling of intramyocardial coronary arterioles, including medial hypertrophy, decreased luminal size and reduced capillary density.²²⁻²⁵ Recent evidence shows that genetic status might be related to the severity of CMD in HCM. Genotype-positive HCM patients were characterized by more severe CMD, increased prevalence of myocardial fibrosis and adverse outcome compared with genotype-negative ones.²⁰ These findings suggest a direct link between sarcomere gene mutations and adverse remodelling of the coronary microvasculature in HCM.

Diastolic dysfunction

Despite differences in phenotypic expression, almost all patients with HCM have some degree of diastolic dysfunction, in which impaired LV relaxation due to increased chamber stiffness leads to elevated LV end-diastolic pressures with reduced stroke volume and cardiac output. The cause of diastolic dysfunction in HCM is multifactorial, which is often the combined result of thickening of the heart, formation of fibrosis, myocardial disarray and ischemia due to arteriolar changes.

Diastolic dysfunction is also present in mutation carriers without LV hypertrophy. A higher degree of diffuse myocardial fibrosis was found not only in overt HCM, but also in mutation carriers without LV hypertrophy, which correlated with the severity of diastolic dysfunction.¹²

Arrhythmias

HCM is the most frequent cause of sudden cardiac death (SCD) in young adulthood and athletes. The arrhythmogenic substrate that leads to lethal ventricular tachyarrhythmias probably derives from the characteristic histopathological features, such as the presence of myocyte hypertrophy, myocyte disarray, small vessel disease and different types of fibrosis, as mentioned earlier.

The most common sustained arrhythmia in HCM is atrial fibrillation. Paroxysmal episodes or chronic atrial fibrillation ultimately occur in 20-25% of HCM patients, and are linked to LA enlargement and age. Atrial fibrillation is independently associated with heart failure-related death, occurrence of fatal and nonfatal stroke, and long-term disease progression.

Molecular pathogenesis of HCM

Disease mechanisms that ultimately lead to the clinical phenotype of HCM are still unclear. In this thesis, the energy depletion hypothesis will be discussed, which originally was shown to be of importance in the development of heart failure.^{26, 27} The association of energy depletion with HCM mutations^{28, 29} is based on observations in *in vivo* human studies. Using magnetic resonance spectroscopy, a reduction in the cardiac PCr to ATP ratio, a measure of energetic status, was found in HCM patients with LV hypertrophy.³⁰⁻³²

Interestingly, a reduction in PCr/ATP was already present in mutation carriers without LV hypertrophy.³⁰ Moreover, a recent study in *MYBPC3* mutation carriers without LV hypertrophy showed reduced myocardial efficiency compared with controls, evident from a reduced ratio between cardiac work and oxygen consumption.³³ To date, however, there is no direct proof of inefficient ATPase activity at the level of the cardiac sarcomere in human HCM. The assumption that increased ATP consumption of affected sarcomeres plays an important role in the development of HCM is still debatable.

Aim and outline of the thesis

Despite the discovery of multiple genetic defects, insights into the pathophysiological mechanisms that lead from sarcomere mutation to HCM phenotype are limited.

Therefore, the aim of this thesis was to provide insights into the pathophysiology of HCM, using positron emission tomography (PET) with acetate to assess myocardial oxygen consumption, and cardiovascular magnetic resonance imaging (CMR) to determine cardiac work in different stages of HCM. The combination of CMR/PET enables us to calculate myocardial efficiency non-invasively. In addition, *in vitro* measurements of myocardial efficiency were performed on muscle strips derived from myectomy specimens from patients with obstructive HCM.

To better understand the early and late consequences of sarcomere mutations and the effects of LV remodeling on cardiac energetics, CMR/PET parameters in mutation carriers without LV hypertrophy were compared with overt HCM patients and healthy subjects. In addition, patients with LV hypertrophy caused by aortic valve stenosis were subjected to these investigations as non-genetic control group with hypertrophy.

The list below summarizes the content of the various chapters of this thesis. The **second** chapter describes the rationale and study-design of the ENGINE study. (ENerGetIcs in hypertrophic cardiomyopathy: traNslation between MRI, PET and cardiac myofilament function). In the **third** chapter, a translational approach is used to study cardiac energetics in overt HCM and mutation carriers without LV hypertrophy harboring mutations in *MYBPC3* and *MYH7*. First, *in vitro* measurements of force development and ATPase activity were performed in HCM cardiac muscle strips. Secondly, *in vivo* measurements of myocardial efficiency were performed using [¹¹C]-acetate PET and CMR imaging. The **fourth** chapter concerns the evaluation of myocardial efficiency in patients with cardiac hypertrophy caused by aortic valve stenosis and the effects of aortic valve replacement on myocardial efficiency in relation to exercise capacity. The **fifth** chapter focuses on coronary microvascular dysfunction in HCM. The relation between capillary density with genetic status and LVOT gradient severity is evaluated by histological analysis of HCM cardiac samples. In chapter **six** disease stage-dependent changes in contractile performance and cardiac efficiency are investigated in HCM by comparing asymptomatic mutation carriers and overt HCM patients. The effect of surgery on cardiac efficiency is evaluated in HCM patients and aortic valve stenosis patients. Chapter **seven** and **eight** summarizes the findings of this thesis and discusses clinical implications and directions for future research in English and Dutch.

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