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

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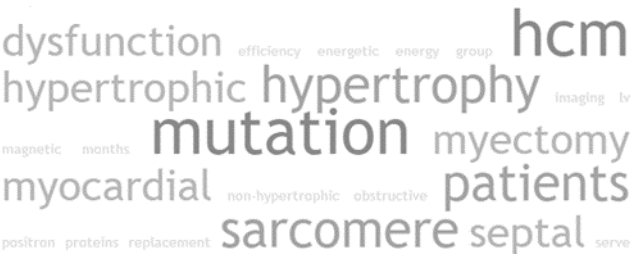
Chapter 7

Summary and future perspectives



Introduction

In this thesis, the aim was to gain insight into the complex pathophysiological processes resulting in the development of HCM. For this purpose, positron emission tomography (PET) with acetate and cardiovascular magnetic resonance imaging (CMR) was used in different stages of the disease process. The combination of PET/CMR allowed us to study cardiac energetics and function in HCM hearts. In addition, energetic cost of contraction was studied *ex vivo* by measurements of force development and ATPase activity in cardiac muscle strips derived from myectomy samples. The list below summarizes the results of the various chapters of this work.

Chapter 1 provides the general introduction of this thesis. An overview of histopathological and clinical findings in HCM is provided.

Chapter 2 describes the rationale and study design of the ENGINE-study. (ENerGetIcs in hypertrophic cardiomyopathy: traNslation between MRI, PET and cardiac myofilament function).[1] The aim of this study was to investigate to what extent disturbances of myocardial energy metabolism underlie disease progression in HCM. Results of the ENGINE-study are described in Chapter 3 to 6.

Chapter 3 discusses myocardial energy consumption and expenditure in overt HCM and mutation carriers without LV hypertrophy harboring mutations in genes encoding myosin-binding protein C (*MYBPC3*) and myosin heavy chain (*MYH7*).[2] This study provided direct evidence that sarcomere mutations perturb the energetic cost of cardiac contraction at the level of the sarcomere in human HCM. In line with these findings, a lower myocardial efficiency was observed *in vivo* with PET/CMR imaging studies in HCM hearts. Importantly, the reduction in myocardial efficiency was already present in mutation carriers and may be a primary trigger for development of the HCM phenotype. Both *in vivo* at the pre-hypertrophic stage (mutation carriers) and *ex vivo* in tissue from patients with manifest HCM, the degree of impaired efficiency of contraction depended on the affected gene. Myocardial efficiency was more reduced in *MYH7* mutation carriers compared with *MYBPC3* mutation carriers. These findings suggest that early initiation of metabolic treatment may be beneficial in particular in *MYH7* mutation carriers.

Chapter 4 shows the results of the effects of aortic valve replacement (AVR) on myocardial efficiency in aortic valve stenosis (AVS) patients without co-morbidities.[3] This study showed that myocardial efficiency is significantly reduced in patients with AVS induced hypertrophy. At 4-month follow-up, the detrimental effects of AVS

were partially reversed by AVR in patients with normal coronary arteries and preserved ejection fraction. This was evident from a regression of LV hypertrophy and improvement of myocardial efficiency. Interestingly, improvement of myocardial efficiency closely correlated with increased exercise capacity.

Chapter 5 explored whether cellular remodelling and reduced capillary density underlie decreased myocardial perfusion in HCM patients.[4] It was found that reduced capillary density is indeed a determinant of coronary microvascular dysfunction in HCM. Moreover, LVOT gradient, rather than genetic status, was associated with reduced capillary density in HCM. The significant relationship between resting LVOT gradient and capillary density suggests that septal reduction therapy in HCM patients with LVOT obstruction provides benefit by delaying deterioration of the microvasculature and preventing disease progression and heart failure.

Chapter 6 described the disease stage-dependent changes in contractile performance and cardiac efficiency in HCM by comparing asymptomatic mutation carriers and overt HCM patients. In addition, the effect of surgery on cardiac efficiency was evaluated in HCM and AVS patients. This study provided evidence that different mechanisms underlie reduced myocardial efficiency at the early and advanced stage of HCM. The initial increase and subsequent reduction in myocardial oxygen consumption (MVO_2) of the heart during disease progression indicates that energy deficiency is a primary mutation-related event, while mechanisms secondary to disease remodelling underlie low myocardial efficiency at advanced disease stage. Our data highlight that the benefit of therapies to improve energetic status of the heart may vary depending on disease stage, and treatment should be initiated before cardiac remodelling.

Conclusion and future perspectives

To date, the hypertrophic response in HCM cannot be stopped, because the pathogenesis is unclear. Therefore, the treatment of HCM focuses solely on the relief of symptoms (with medication or septal myectomy) and the treatment of life-threatening cardiac arrhythmias with an intracardiac defibrillator.

The presented research is vital, because it gives us new insight into the pathophysiologic processes in HCM and reveals potential new therapeuthical targets. It has been found that cardiac energy metabolism is impaired in HCM patients compared to a control group. In fact, the efficiency of cardiac contraction was already impaired in carriers, which suggests that there is a causal role for energy deficiency in the pathophysiology of HCM.

Ideally, treatment of HCM patients should start in the early stages of the disease process, in order to influence the course of disease and to avoid serious consequences. This could be done for instance with metabolic modulators, such as perhexiline. Perhexiline treatment shifts metabolism from free fatty acids to glucose in the heart leading to a higher cardiac efficiency.[5, 6] Before applying this treatment in carriers, several subjects warrant further investigation.

First, the metabolism in HCM should be examined in the early and late stage of the disease process. This can be performed using PET tracers such as FDG-PET (glucose metabolism) and palmitate-PET (fatty acid metabolism). In this way, we can define whether there is an early mutation-effect on metabolism and whether adaptation occurs in the course of the disease process.

In addition, research on the mitochondria could provide us with valuable information. There is evidence that mitochondrial dysfunction may play a role in the pathogenesis of HCM.[7-9] Some mitochondrial diseases may give the same HCM phenotype, suggesting that the signaling pathways are the same in causing the hypertrophic response. Unraveling the exact mechanisms may stimulate the development of new experimental therapies.

Finally, our study provides evidence that the degree of impaired efficiency of contraction depends on the affected gene.[2] Next to the type of the mutation, the natural course of HCM could be influenced by the number and location of the underlying mutation. Future studies are needed to investigate the *in vivo* and *ex vivo* myocardial properties of different subtypes of mutations. This may affect the type and timing of gene-specific intervention.

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