Summary

Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disease associated with over 100 mutations in genes encoding for the myocardial contractile apparatus. HCM is the most common cause of sudden cardiac death (SCD) in young adulthood, and a major cause of heart failure at any age. Next to asymmetrical left ventricular (LV) hypertrophy, preliminary studies in the early 90’s showed that HCM is also characterized by alterations in myocardial perfusion and energy handling. These findings implied that the pathogenesis of HCM was not merely limited to hypertrophy and adverse cardiac remodeling. More recently, the development of positron emission tomography (PET) has introduced a new era of myocardial imaging in heart disease, by facilitating accurate, noninvasive quantification of myocardial perfusion and metabolism. However, although PET has provided tantalizing new insights, the pathophysiology of HCM is comprehensive and many aspects remain unelucidated. Hence, this thesis aimed to increase our knowledge of the disease mechanisms underlying HCM, by use of advanced noninvasive imaging techniques to investigate myocardial perfusion, metabolism and function in different stages of the disease process.

PART I of this thesis explored the presence and interrelations between microvascular dysfunction, impaired energetics and cardiac dysfunction on a global and regional level, in HCM patients and asymptomatic ‘carriers’. In Chapter 2, the presence of microvascular dysfunction was found to be widespread, also affecting non-hypertrophied myocardial segments. Perfusion defects could be linked to the presence of contractile dysfunction and myocardial scarring, on a regional level. These findings suggest that microvascular dysfunction constitutes a primary component of the HCM phenotype, and may explain why the degree of dysfunction serves as such major predictor of clinical deterioration and death in these subjects. In addition, patients with severe perfusion defects had more myocardial fibrosis, possibly making these subjects more susceptible to cardiac arrhythmias. Chapter 3 explored myocardial energy consumption and expenditure in HCM patients, and showed that the energy efficiency of the heart in HCM is significantly reduced, in comparison to healthy subjects. Furthermore, impaired energetics were not limited to the hypertrophied septum only, but also affected non-hypertrophied areas. Although an imbalance between oxidative metabolism and cardiac function is rather unspecific, it appears to be a sensitive marker of myocardial pathology. After all, a reduced energy efficiency of the heart is also seen in other cardiomyopathies, and is prognostically unfavourable. Major predictors of impaired myocardial efficiency were a high LV mass and small stroke volume (SV), suggesting a therapeutic potential for interventions aimed at reducing LV hypertrophy and
increasing SV. In **Chapter 4**, asymptomatic carriers (subjects without LV hypertrophy and clinical signs of HCM, yet carriers of a pathogenic HCM mutation) were studied with myocardial perfusion and metabolic imaging, to investigate the presence of microvascular dysfunction or impaired energetics as early markers of disease. It was found that myocardial perfusion was comparable to healthy subjects. However, the carriers already showed reduced generation of myocardial work in relation to oxygen consumption, suggesting that impairment of myocardial efficiency precedes the onset of the HCM phenotype, and may be a major determinant of HCM pathogenesis. Altogether, these findings in conjunction with previous studies, highlight the clinical relevance of early detection of myocardial perfusion and metabolic abnormalities in HCM for risk stratification and development and application of (new) therapeutics.

**PART II** discussed the effects of alcohol septal ablation (ASA) on myocardial perfusion and energy handling in HCM patients. ASA is thought to alleviate symptoms in symptomatic patients with LV outflow tract (LVOT) obstruction by restoring perfusion. Analysis of the exact mechanism of action, however, may improve the selection criteria for subjects that benefit from this intervention. **Chapter 5** specifically focused on endo- and epicardial microcirculatory function in HCM patients with LVOT obstruction, before and after ASA. It was found that myocardial perfusion is predominantly impaired in the subendocardial regions of the heart. Relief of LVOT obstruction was associated with a major improvement in perfusion, especially in these regions. Moreover, the reduction of the gradient across the LVOT directly related to the improvement in perfusion in absolute terms, altogether suggesting that LV strain and loading conditions are important determinants of myocardial perfusion in HCM. In addition, ASA improved myocardial energy efficiency, predominantly by reducing LV mass. **Chapter 6** revealed that the effects of ASA extend beyond the LV and favourably affect energetics of the right ventricle (RV) as well. These results suggest that increased RV energy consumption in HCM patients with LVOT obstruction is presumably mediated by increased RV afterload due to augmented LV loading conditions. Therefore, reducing RV workload by relief of LVOT obstruction could be an additional mode of action by which ASA may reduce symptoms in HCM patient, next to augmenting LV microvascular capacity.

**PART III** discussed several technical aspects of myocardial perfusion and metabolic imaging with PET. In **Chapter 7**, the potential of $[^{11}C]$acetate, a substrate-based tracer primarily used for metabolic imaging, was explored for implementation as a perfusion tracer. Four previously described methods were analyzed and compared to the gold standard, being $[^{15}O]$water. Myocardial perfusion could be determined in fairly good agreement with actual perfusion
values by use of $[^{11}\text{C}]$acetate, over physiological flow ranges under baseline conditions. Of the four investigated methods, a single-tissue compartment model was most accurate. **Chapter 8** evaluated an alternative method for analyzing $[^{11}\text{C}]$acetate PET scans to improve noninvasive estimates of oxygen consumption. It was shown that a single-tissue compartment model with model-based corrections for the effects of spillover, partial volume and recirculating $[^{11}\text{C}]$ activity, yielded $[^{11}\text{C}]$acetate clearance rates in better agreement with myocardial oxidative metabolism, as compared to standard monoexponential curve fitting. This suggested that the non-invasive estimation of $\text{MVO}_2$ by use of $[^{11}\text{C}]$acetate could be improved by employing a compartment model, and its use should routinely be considered in cardiac study protocols using $[^{11}\text{C}]$acetate.

Finally, **Chapter 9** is a comprehensive review that discusses the findings of this thesis in combination with results in the literature regarding myocardial perfusion, metabolism and energy efficiency in HCM.

**Future Perspectives**

To date, microvascular dysfunction and impaired myocardial energetics are considered major determinants of HCM. Our findings of reduced myocardial efficiency in phenotype-negative HCM carriers even suggest a causative role for energy deficiency in the pathophysiology of HCM. Clinical trials focusing on long-term outcome are needed to determine the incremental prognostic value of myocardial energetics in HCM. Nonetheless, studies regarding metabolic and contractile properties of isolated mutated sarcomeres may provide additional insights into the macro-phenotype of HCM, and aid in elucidating its etiology. More specifically, by comparing energy handling of cardiomyocytes on a microscopic and macroscopic level (i.e., in-vitro tension cost versus in-vivo efficiency) intrindividually, translational research in HCM may shed new light on the HCM paradigm.

Similarly, going from bedside-to-bench by focusing on the pathologic basis of disease may enhance our understanding of current pharmacological treatments, and stimulate the development of new experimental therapies. Therapeutic strategies specifically aimed at improving myocardial perfusion and energy handling are a promising new avenue in the treatment of HCM. Evaluation of new treatment strategies in a relatively small number of patients can provide important insight and is a step toward testing interventions in larger clinical trials.

Finally, tangible evidence suggests that the natural course of disease is linked to the type, number, and location of the underlying mutation. Hence, future
delineation of specific HCM subgroups according their in-vitro and in-vivo myocardial properties is essential. Consequently, this may affect the type and timing of intervention in different subgroups, according to the pathogenic substrate and prognosis.