
Chapter 1

General Introduction & Thesis Outline

Introduction

Hypertrophic cardiomyopathy (HCM) is a relatively common genetic cardiac disease with an estimated prevalence of 1:500, and over 100 documented mutations.(1) HCM is the most common cause of sudden cardiac death (SCD) in young adulthood, and a major cause of heart failure at any age.(2) One of the hallmarks of HCM is asymmetrical left ventricular hypertrophy, predominantly involving the interventricular septum. Nonetheless, significant heterogeneity in phenotypic expression and clinical course has been documented. Intensive research has revealed that the pathogenesis of HCM is complex, and not merely limited to hypertrophy and adverse cardiac remodeling. For example, regional myocardial perfusion defects and abnormal energy handling were already noted more than two decades ago, by use of semi-quantitative imaging techniques.(3-5) Since then, myocardial perfusion and metabolic imaging has provided tantalizing new insights into the pathophysiology of HCM.

The introduction of positron emission tomography (PET) has greatly improved the quality of myocardial imaging in heart disease. PET facilitates accurate, non-invasive quantification of dynamic in-vivo tissue processes by use of radioactively labeled tracers. In addition, these parameters can be studied on a regional level, which is especially useful when investigating cardiac diseases in which regional disease expression is a hallmark, such as HCM.

For instance, PET studies in HCM have revealed that regional perfusion defects are the result of a reduced maximal myocardial perfusion due to microvascular dysfunction.(6) Microvascular dysfunction, in turn, represents a predisposing factor for myocardial ischemia, which may lead to scarring and the development of arrhythmias.(7) Subsequently, the degree of dysfunction has been shown to serve as a major predictor of death.(8) Myocardial metabolism and energetics in heart disease have been studied with similar interest since the development of substrate-based tracers, and growing evidence suggests that metabolic abnormalities play a central role in mechanical failure of the heart, regardless of the cardiomyopathies' etiology.(9,10) Although prognostic data related to an impaired energetic state in HCM are lacking, it is believed to hold strong prognostic relevance as well.(11,12) Correspondingly, microvascular dysfunction and abnormal myocardial energetics are to date considered as major determinants of the HCM pathogenesis.(13) Therefore, knowledge of the mechanism and causative factors of these determinants may significantly contribute to unraveling HCM's pathophysiology.

Obviously, treatment strategies aimed at improving myocardial perfusion and

energy handling are a promising new avenue in the treatment of HCM. Invasive septal reduction therapies such as alcohol septal ablation (ASA) alleviate symptoms in symptomatic HCM patients with LV outflow tract (LVOT) obstruction, and are thought to improve prognosis.(14) LVOT obstruction results from bulging of the hypertrophied septum during systole, and causes additional strain and workload on the LV. Relief of LVOT obstruction has previously been associated with improved myocardial perfusion.(15,16) However, the exact mechanism of action remains unelucidated. Furthermore, data regarding the effects of ASA on myocardial metabolism and efficiency are lacking. In this matter, PET may serve as a strong tool for better understanding the effect of such interventions and monitoring treatment response in patients.

Thesis outline

The main goal of this thesis is to contribute to a better understanding of the disease mechanisms underlying HCM, by use of advanced noninvasive imaging techniques to investigate myocardial perfusion, metabolism and function.

PART I summarizes the basics of myocardial perfusion and metabolic imaging, and aims to explore the pathophysiology of HCM with these techniques. In **Chapter 2**, myocardial perfusion defects in HCM are studied on a regional level, and linked to contractile dysfunction and myocardial scarring. **Chapter 3** explores myocardial energy consumption and expenditure in HCM patients, to determine the energy efficiency of the heart in comparison to healthy subjects. In **Chapter 4**, asymptomatic carriers of a HCM mutation are studied with myocardial perfusion and metabolic imaging to investigate whether perfusion defects and impaired energetics are early markers of disease.

PART II explores the effects of ASA on myocardial perfusion and energy handling. **Chapter 5** specifically focuses on endo- and epicardial microcirculatory function and myocardial energy handling of the left ventricle, after relief of LVOT obstruction. Complementary, **Chapter 6** describes the effect of ASA on myocardial energetics of the right ventricle in these patients.

PART III is devoted to technical aspects of myocardial perfusion and metabolic imaging. **Chapter 7** describes the potential of [¹¹C]acetate, a substrate-based tracer primarily used for metabolic imaging, as a myocardial perfusion tracer. **Chapter 8** introduces an alternative method for analyzing [¹¹C]acetate PET scans to improve noninvasive estimates of oxygen consumption.

Chapter 9 is comprehensive review that summarizes results in the literature regarding myocardial perfusion, metabolism and energy efficiency in HCM.

Rereference list

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