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## **Clinical assessment of the development of hypertrophic cardiomyopathy by cardiovascular magnetic resonance imaging**

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2014

### **document version**

Publisher's PDF, also known as Version of record

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### **citation for published version (APA)**

Brouwer, W. P. (2014). *Clinical assessment of the development of hypertrophic cardiomyopathy by cardiovascular magnetic resonance imaging*. [PhD-Thesis - Research and graduation internal, Vrije Universiteit Amsterdam].

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Hypertrophic cardiomyopathy (HCM) is an inheritable disease caused by mutations in genes that mainly encode for sacromeric proteins. Clinically, HCM is characterized by the development of heart failure, atrial fibrillation and sometimes potentially life threatening ventricular tachyarrhythmias. The molecular and macroscopic alterations that ultimately lead to the development of symptomatic HCM are still poorly understood.

In this thesis, the aim was to gain insight into the complex pathophysiological perturbations resulting in the development of hypertrophic cardiomyopathy. For this purpose, cardiovascular magnetic resonance imaging (CMR) was used in humans with various stages of disease and in a transgenic mouse model. The high spatial and temporal resolution of CMR allowed us to study in detail the morphological and functional changes of the pre-hypertrophic and manifest HCM heart.

## **Chapter 1**

Chapter one provides the general introduction of the thesis. An overview of HCM at a microscopical and macroscopical level is given. Besides, several state-of-the-art imaging techniques are described which are used in the work of this thesis. Finally, a brief overview of the clinical benefit of identifying patients at risk for developing manifest HCM is provided.

## **Chapter 2**

In this chapter, an overview was provided of the myocardial alterations that occur during the gradual process of LV wall thickening in HCM on the level of the myofilament. Besides, both structural and functional abnormalities that can be observed in genetically affected individuals prior to the development of HCM were described, using state of the art imaging techniques such as tissue Doppler

echocardiography (TDI) and CMR. In the final section, current and future therapeutic options were briefly discussed. Also, possible therapeutic options to reverse or prevent the hypertrophic disease process in HCM are described.

### **Chapter 3**

Chapter 3 shows the findings of a CMR study in pre-hypertrophic HCM mutation carriers, using tissue tagging. Data showed increased LV torsion in mutation carriers compared to healthy individuals. Torsion, which is the wringing motion of the heart, is the net result of contracting myofibers at the outer and inner parts of the LV wall. Apparently, the amount of torsion is enhanced in mutation carriers, possibly as a result of alterations in myofiber architecture.

### **Chapter 4**

This section shows the results of extensive characterization of crypts in mutation carriers and patients with different pathology. The incidence of crypts was significantly higher in the cohort of mutation carriers than in other pathological conditions and normal, which was expected. The main outcome of the study showed that mutation carriers typically show multiple crypts, which are predominantly located at the inferoseptum. The study also showed that a modification of standard two chamber cine images resulted in optimal detection of crypts.

### **Chapter 5**

Besides the observation that multiple crypts are highly specific for HCM mutation carriership (which is described in the previous chapter), this manuscript showed that crypts are a predictor for the hypertrophic response in these asymptomatic patients. Study subjects underwent serial CMR investigations with time-intervals of approximately 5 years. Results showed that both indexed LV mass and left atrial (LA) volumes increased significantly in this cohort of mutation carriers. The high

predictive value of crypts in this study may be used to select carriers at risk for developing manifest HCM. Therefore, it is advocated to use CMR as a first diagnostic tool, since this modality is capable of detecting crypts, which may be more difficult when using standard 2D echocardiography..

## **Chapter 6**

Previous imaging techniques used the contrast agent Gadolinium-DTPA to visualize regions with focal fibrosis in HCM. Autopsy studies revealed that HCM hearts also contain diffusely located interstitial fibrosis however. In chapter 6, a relatively new CMR technique, T1 mapping, has been used in patients with HCM phenotype. T1 mapping allows absolute T1 value measurements in any region of the myocardium, enabling the calculation of the myocardial extracellular volume fraction (ECV), representing the extent of interstitial fibrosis. Results of this work demonstrated that HCM patients have a similar ECV (e.g. interstitial fibrosis) in myocardium without focal fibrosis (e.g. LGE) as healthy controls. Therefore, the additional clinical value of T1 mapping in HCM seems limited, although future larger studies are needed to definitely establish potential of this technique in HCM.

## **Chapter 7**

In this chapter, results of the sole pre-clinical study in this thesis are presented. It is known that heterozygous cMyBP-C null mice have reduced full length protein expression (indicating haploinsufficiency), and typically show asymmetrical LV hypertrophy after a minimum lifespan of 9 months. Our data showed that especially the septum in these mice contains diminished protein levels, even before the presence of hypertrophy. Besides, the passive force of myofilaments was significantly higher in the septum than in the lateral LV free wall. We concluded that the unequally distributed pre-hypertrophic alterations in protein expression and

cardiomyofilament function may serve as triggers for the asymmetric hypertrophic response in HCM.

## **Future perspectives, directions for further research**

### ***From intervention towards prevention***

Although major advances have been made in the clinical management of HCM patients over the past decades, current treatment strategies solely focus on the alleviation of symptoms, which are often due to LV outflow tract obstruction, and the direct termination of HCM-related lethal arrhythmias (by virtue of ICD-discharges). Ideally, patients would receive (pharmacological) treatment at an earlier stage in the disease process, aimed to prevent the hypertrophic response and concomitant future adverse clinical events.

Several pharmacological agents, such as the anti-oxidant N-acetylcysteine [1,2], spironolactone [3] and ACE-inhibitors [4] already showed beneficial effects in the preclinical setting by reversing or preventing the development of hypertrophy and/or fibrosis. Recently, the use of ACE-inhibitors was extrapolated to humans and showed similar positive results [5,6]. Evenly promising might be the metabolic modulation of the HCM muscle [7]. Several studies showed inefficient ATP-utilization in transgenic animals [8] and HCM patients [9], and a study by Abozguia and co-workers [10] demonstrated that a restoration of impaired energy metabolism in HCM leads to improved functional outcome. Whether metabolic therapy is also capable of preventing or reversing HCM phenotype, needs further evaluation in future studies. Finally, modification of cardiomyofilament function in HCM may yield promising results. As described in chapter 2, therapeutic strategies aimed at

restoring sarcomeric dysfunction and  $\text{Ca}^{2+}$ -homeostasis might theoretically prevent or slow the (presumed) hypertrophic response.

### ***Optimization of patient selection***

The clinical field poses a large challenge to optimize the selection of patients at risk for developing adverse events in HCM. Currently, the SCD risk algorithm has been extensively studied and tested, aimed at optimizing patient selection for ICD implantation. Nevertheless, still a large number of patients receives inappropriate ICD-discharges, and there is an ongoing debate regarding the number of (major) risk factors necessary for ICD implantation [11,12]. As previously mentioned, a strategy aimed at preventing HCM phenotype is warranted in HCM. Unfortunately, risk factors for the development of LV wall thickening in HCM are largely unknown in HCM. Work of this thesis showed that crypts may have the potential to indicate mutation carriers at risk for developing asymmetrical hypertrophy. Therefore, a baseline CMR scan in every newly diagnosed mutation carrier may further establish the role of crypts as a predictor of disease progression in these patients. Large, multicentre, long-term studies are nevertheless needed to draw definite conclusions. In general, future research should maintain its focus on identifying new or additive risk factors for development of disease, ultimately leading to the prevention of the adverse events of HCM.

### ***Advances in cardiac imaging***

As stated earlier, cardiac imaging tools are a constant subject for further improvement. Within the field of CMR, emerging techniques such as T1 mapping have only just entered the field of research. The role of T1 mapping seems promising,

and may further improve our knowledge of the natural course of HCM. It seems plausible that new techniques may help to identify previously unknown predictors of disease progression, leading to optimization of patient selection. Furthermore, future research with hybrid imaging and the monitoring of biomarkers almost definitely will extend the current knowledge of the pathogenesis of HCM.

## References

1. Marian AJ, Senthil V, Chen SN, R.Lombardi R. Antifibrotic Effects of Antioxidant N-Acetylcysteine in a Mouse Model of Human Hypertrophic Cardiomyopathy Mutation. *J Am Coll Cardiol* 2006;47:827-834.
2. Lombardi, Rodriguez RG, Chen SN. Resolution of Established Cardiac Hypertrophy and Fibrosis and Prevention of Systolic Dysfunction in a Transgenic Rabbit Model of Human Cardiomyopathy Through Thiol-Sensitive Mechanisms. *Circulation* 2009;119:1398-1407.
3. Tsybouleva N, Zhang L, Chen SN et al. Aldosterone, Through Novel Signaling Proteins, Is a Fundamental Molecular Bridge Between the Genetic Defect and the Cardiac Phenotype of Hypertrophic Cardiomyopathy. *Circulation* 2004;109:1284-1291.
4. Lim DS, Lutucuta S, Bachireddy P et al. Angiotensin II Blockade Reverses Myocardial Fibrosis in a Transgenic Mouse Model of Human Hypertrophic Cardiomyopathy. *Circulation* 2001;6: 789-791.
5. Yamazaki T, Suzuki JI, Shimamoto R et al. A New Therapeutic Strategy for Hypertrophic Nonobstructive Cardiomyopathy in Humans. A Randomized and Prospective Study With an Angiotensin II Receptor Blocker. *Int Heart J* 2007;48:715-724.
6. Kawano H, Toda G, Nakamizo R, Koide Y, Seto S, and Yano K. Valsartan decreases type I collagen synthesis in patients with hypertrophic cardiomyopathy. *Circ J* 2005;69:1244-1248.
7. Ashrafian H, Redwood C, Blair E, and Watkins H. Hypertrophic cardiomyopathy: a paradigm for myocardial energy depletion. *Tr Gen* 2003;19:263-268.
8. Luedde M, Flögel U, Knorr M et al. Decreased contractility due to energy deprivation in a transgenic rat model of hypertrophic cardiomyopathy. *J Mol Med* 2009;87:411-422.
9. Crilley JG, Boehm EA, Blair E et al. Hypertrophic cardiomyopathy due to sarcomeric gene mutations is characterized by impaired energy metabolism irrespective of the degree of hypertrophy. *J Am Coll Cardiol* 2003;41:1776-1782.
10. Abozguia K, Elliott P, McKenna W et al. Metabolic Modulator Perhexiline Corrects Energy Deficiency and Improves Exercise Capacity in Symptomatic Hypertrophic Cardiomyopathy. *Circulation* 2010;122:1562-1569.
11. Elliott PM, Poloniecki J, Dickie S et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. *J Am Coll Cardiol* 2000;36:2212-2218.
12. Maron BJ. Sudden death in hypertrophic cardiomyopathy. *J Cardiovasc Transl Res* 2009;2:368-380.