New Insights in Morphology and Pathophysiology of Hypertrophic Cardiomyopathy by Magnetic Resonance Imaging

Germans, T.

2008

document version
Publisher's PDF, also known as Version of record

Summary and future perspectives

Tjeerd Germans

IX.I

SUMMARY

Cardiac magnetic resonance imaging (CMR) is an imaging modality that allows accurate assessment of mechanical function and tissue characterization with a high spatial resolution. In clinical practice, the diagnostic potential of CMR is employed in ischemic cardiomyopathy i.e. to detect ischemia and viability. In non-ischemic cardiomyopathy, CMR is used to determine the aetiology of non-ischemic cardiomyopathies.

In this thesis, the high spatial resolution of CMR and its capabilities to assess regional myocardial deformation by strain analysis have been applied to explore the cardiac changes in the development of hypertrophic cardiomyopathy (HCM), emphasizing morphology, left ventricular (LV) and left atrial (LA) volumes and diastolic function.

Chapter 1

In this chapter, an update of current literature on the genetic background, pathophysiological mechanisms and clinical management of HCM was provided. HCM has been associated with mutations in genes that mainly encode for sarcomeric proteins. Although the clinical course of HCM seems to be mutation specific, it is strongly influenced by other genetic and environmental factors. Since HCM usually develops in the first decades of life and patients may remain asymptomatic for years, identifying a causal mutation in a HCM patient allows to identify asymptomatic HCM mutation carriers without LV hypertrophy among first degree relatives. This enables close monitoring of these patients and timely initiation of therapy if necessary.

However, mutations are found in only 60 percent of HCM patients. In the remaining 40 percent, screening for asymptomatic HCM patients among family members is confined to cardiological evaluation using electrocardiography (ECG) and echocardiography. These diagnostic modalities have shown to only display non-specific abnormalities before the development of manifest HCM. Therefore, additional screening methods are warranted. The mutations seem to predominantly affect diastolic function in human HCM mutation carriers with borderline hypertrophy, but it is currently unknown whether the diastolic dysfunction results from the increased LV mass, or may be recognized as the trigger for the development of hypertrophy.

Chapter 2

CMR tissue tagging is a technique used to non-invasively assess regional deformation (strain) and strain rate of the myocardium, and torsion. In this chapter the underlying

technique and its clinical application are discussed. CMR tagging with strain analysis has been shown to provide highly reproducible and sensitive data, being more sensitive in detecting regional abnormalities than wall motion assessment. Indeed, strain analysis has already been shown to detect diastolic dysfunction in overt HCM patients, and may thus be considered an excellent tool to evaluate diastolic function in HCM mutation carriers with normal wall thickness.

Chapter 3

The diagnostic value of CMR in determining the aetiology of non-ischemic cardiomyopathies was discussed in this chapter. CMR cine imaging allows accurate determination of LV structure and can be used to easily diagnose non-compaction cardiomyopathy, which is a cardiomyopathy that may be difficult to differentiate from HCM by echocardiography. Also, the use of late Gadolinium enhancement (LGE) imaging and T2* measurement has proven to provide a unique possibility to differentiate between different causes of left ventricular hypertrophy, including familial HCM, amyloidosis, Anderson-Fabry disease and cardiac iron overload.

Chapter 4.1

Since planning of the image plane with CMR is not restricted by anatomical limitations, several methods can be applied to measure LA volume with CMR. In chapter 4.1, a 3D and biplane CMR method were validated and compared with several widely applied echocardiographic techniques to measure LA volumes. The 3D LA volume measurement method was found to have the lowest inter- and interobserver variability.

In addition, the acquisition is most likely less operator depended compared to the biplane techniques. Therefore, the 3D LA volume measurement method is optimal for research purposes when accurate measurement of LA volume is warranted. However, the time consuming acquisition and post processing time of the 3D LA volume method currently restrict its wider use in clinical practice.

Chapter 4.2

Before measuring LA volumes and function in HCM mutation carriers, the effect of normal ageing on the interaction between the LA and LV was evaluated in 19 younger and 19 middle aged healthy volunteers. With normal ageing, both absolute LA volumes and LA volumes relative to LV volumes increased, while the sum of LA volume and LV remained constant (total left heart volume). The shift of volumes of LA and LV in the older age group

correlated with the increase in LV mass-to-volume ratio (r=0.42, p<0.01), especially in males. In addition, the contribution of LA passive emptying to filling of the LV was lower in the older age group, which was compensated by a higher contribution of LA active emptying to LV filling. However, the largest contribution to LV filling in both age groups was made by the conduit volume, which is defined as the amount of blood that is directly 'sucked' into the LV from the pulmonary veins, thereby using the LA as a conduit.[1]. Indeed, conduit volume was shown to be lower in the older age group (p<0.05), which suggested that diastolic suction reduces with normal ageing.

Chapter 5

The LV structure of 16 HCM mutation carriers with normal LV wall thickness was compared with 16 age- and gender matched controls and described in chapter 5.1. In 13/16 (81%) of HCM mutation carriers, crypts could be observed in the inferoseptal basal and mid segments, which were discernable in end-diastole with CMR only, and not with echocardiography. This explains why these structural abnormalities have never been described previously in pathological studies, since post-mortem hearts are always contracted to some extent. Interestingly, the crypts were also visualized in 4 HCM mutation carriers with a normal ECG.

In an image report described in chapter 5.2 the very prominent crypts of one HCM mutation carrier were, although initially undetected in the study described in chapter 5.1, shown to be visible also on echocardiography and mimicked the appearance of non-compaction cardiomyopathy.

Whether non-compaction cardiomyopathy is a specific cardiomyopathy or a non-specific morphological trait is debated in a letter described in Chapter 5.3. Non-compaction has been related to HCM, but also to dilated cardiomyopathies. Also, many different genetic mutations that do not encode for one single specific structure of the cardiomyocyte have been associated with non-compaction cardiomyopathy. Therefore, further research on whether non-compaction cardiomyopathy may be regarded as a specific cardiomyopathy or as a striking, but non-specific morphological trait is necessary. Ideally, this should be performed with high resolution imaging techniques such as CMR.

Chapter 6

Regional diastolic and systolic dysfunction and LV and LA dimensions of 28 HCM mutation carriers with normal wall thickness, were compared with age and gender matched healthy volunteers. In the majority of these healthy volunteers, HCM mutation carriership was excluded.

Diastolic and systolic function were determined by regional peak diastolic circumferential strain rates and regional peak systolic circumferential strain. Also, LV morphology was assessed. It was found that the asymmetrical distribution of wall thickness, which is one of the hallmarks for HCM, was already present very early in the disease process. Systolic dysfunction was significant in the free LV wall, but diastolic dysfunction was present in almost every segment. After multivariate analysis, the magnitude of diastolic and systolic circumferential strain were positively related to an increase of end-diastolic wall radius in healthy volunteers due to the Frank-Starling mechanism. However, in HCM mutation carriers, both diastolic and systolic circumferential strain only minimally responded to increase of end-diastolic wall radius, suggesting a reduced efficacy of the Frank-Starling mechanism. This has been confirmed previously in experimental studies. Also, higher nt-proBNP levels were found in the HCM mutation carriers compared to controls.

Moreover, diastolic function deteriorated with increase of end-diastolic wall thickness, while systolic function was relatively preserved up to an end-diastolic wall thickness of 10 mm. The reduced diastolic function was also reflected in the larger LA volumes found in HCM mutation carriers. This study strongly suggests that in human HCM mutation carriers, functional abnormalities precede the development of hypertrophy, which is in line with the findings of experimental studies on HCM animal models. Of note, crypts were found in 23/28 HCM mutation carriers and not in controls.

Chapter 7

The effects of reduction of LV outflow tract (LVOT) obstruction by alcohol septal ablation (ASA) on the interaction between LA and LV was evaluated in 16 obstructive HCM patients. It was found that after ASA, LV mass and LA volumes were significantly reduced, which was independently related to improvement of diastolic function, as determined by lateral E/Ea ratio (r^2=0.59, p<0.001) and peak diastolic circumferential strain rate.

Despite reduction of end-diastolic wall thickness in both the septum and the lateral LV wall, improvement of diastolic function was only observed in the lateral LV wall. The diminished improvement of myocardial function in the septum was probably related to the presence of myocyte disarray within that LV region, or results from stiffening of the myocardium due the induced discrete infarct by ASA. Also, quantitatively assessed mitral regurgitation was demonstrated to be significantly reduced after ASA. In addition, nt-proBNP levels were found to strongly correlate with LA volumes (r^2=0.57, p<0.01) but not with LV mass. The importance of LA volume in HCM was further illustrated in chapter 8.

Chapter 8

The relation between LGE and LA volumes with atrial fibrillation (AF) in HCM patients was assessed in a multicenter study in 87 patients. It was found that HCM patients with AF had larger LA volumes than patients without AF (66±24 mL·m^{-2} versus 46±18 mL·m^{-2}, $p<0.001$) and displayed more LGE (12.4±14.5% versus 6.0±8.6%, $p<0.05$). Indeed, LGE significantly correlated with LA volume ($r=0.31$, $p<0.05$), which was the only independent determinant of AF. Also, it was found that the extent of LGE was higher in symptomatic than in asymptomatic HCM patients ($p<0.05$).

FUTURE PERSPECTIVES

Clinical implications

In HCM patients in whom no mutation is found, the first degree relatives should not only be screened for possible HCM mutation carriership solely by using ECG and echocardiography, but alternatively should undergo a CMR examination. This CMR examination should be focused on detecting crypt formation in the inferoseptum of the LV and presence of hypertrophy.

Although the positive predictive value of the crypts is presumably high, the specificity of the crypts to HCM mutation carriership still needs to be determined in a referral based population, but was found to be low among first degree relatives of HCM mutation carriers.

LA dilation seems to play a pivotal role in the development of atrial fibrillation in HCM patients and could be used to monitor the progression of disease. Moreover, LA volume may be used in clinical decision making, i.e. to perform LVOT obstruction reduction by ASA, while this has been demonstrated to significantly reduce LA volumes. As an alternative for LA volumes, nt-proBNP may also be used as a marker of progression of disease or to monitor the effect of therapy in HCM patients, since this biomarker strongly correlated to LA volume.

Directions for further research

The histological background of the crypts and their role in the development of HCM is currently unknown. We hypothesize that their presence may be related to extensive myocyte disarray, which is the histological hallmark of HCM. As such, the crypts may be one of the early morphological alterations of the LV that ultimately lead to overt HCM. To

confirm this hypothesis, long-term follow-up studies comparing the clinical course of HCM mutation carriers with and without crypts are ongoing.

It is unlikely that histology of the crypts can easily be obtained from human HCM mutation carriers, since SCD rate is fortunately extremely low in most HCM mutation carriers without hypertrophy. As an alternative, histology of HCM mouse models which are also known to develop asymmetric hypertrophy may be obtained in an early stage of disease.[2] First, it must be determined if the crypts are also detectable with CMR in these mouse models.[3, 4]

Afterload reduction by ASA causes reduction of LV mass in obstructive HCM patients. This suggests that afterload reduction by pharmacological treatment may reduce or even prevent the development of HCM in HCM mutation carriers without hypertrophy.[5] In HCM mouse models, angiotensin II and spironolactone have previously been shown to reduce the amount of interstitial fibrosis and improve diastolic function.[6, 7] Therefore, the effects of these agents on the development of hypertrophy in HCM mutation carriers should be further investigated in a randomized, double blinded, multicenter setting.

The results of the studies performed in this thesis demonstrate that CMR provides the unique possibility to accurately assess LV morphology and regional myocardial function, as well as global LV and LA volumes in HCM mutation carriers in a single acquisition. This indicates that CMR should be the imaging modality of choice to study the efficacy of these agents in preventing development of hypertrophy in HCM mutation carriers.

References

1. Bowman AW, Kovacs SJ. Left atrial conduit volume is generated by deviation from the constant-volume state of the left heart: a combined MRI-echocardiographic study. *Am J Physiol Heart Circ Physiol* 2004 June;286(6):H2416-H2424.

2. Carrier L, Knoll R, Vignier N, Keller DI, Bausero P, Prudhon B, Isnard R, Ambroisine ML, Fiszman M, Ross J, Jr., Schwartz K, Chien KR. Asymmetric septal hypertrophy in heterozygous cMyBP-C null mice. *Cardiovasc Res* 2004 August 1;63(2):293-304.

3. Feintuch A, Zhu Y, Bishop J, Davidson L, Dazai J, Bruneau BG, Henkelman RM. 4D cardiac MRI in the mouse. *NMR Biomed* 2007 May;20(3):360-5.

4. Chapon C, Herlihy AH, Bhakoo K. Assessment of myocardial infarction in mice by late gadolinium enhancement imaging using an inversion recovery pulse sequence at 9.4T. *J Cardiov Magnetic Resonance* 2008 January 24;10(6):1-10.

5. Takimoto E, Champion HC, Li M, Belardi D, Ren S, Rodriguez ER, Bedja D, Gabrielson KL, Wang Y, Kass DA. Chronic inhibition of cyclic GMP phosphodiesterase 5A prevents and reverses cardiac hypertrophy. *Nat Med* 2005 February;11(2):214-22.

6. Lim DS, Roberts R, Marian AJ. Expression profiling of cardiac genes in human hypertrophic cardiomyopathy: insight into the pathogenesis of phenotypes. *J Am Coll Cardiol* 2001 October;38(4):1175-80.

7. Tsybouleva N, Zhang L, Chen S, Patel R, Lutucuta S, Nemoto S, DeFreitas G, Entman M, Carabello BA, Roberts R, Marian AJ. Aldosterone, through novel signaling proteins, is a fundamental molecular bridge between the genetic defect and the cardiac phenotype of hypertrophic cardiomyopathy. *Circulation* 2004 March 16;109(10):1284-91.