Summary and future perspectives

Optimal cardiac pump function depends on contraction and relaxation of the myocardial fibers. In many cardiac diseases, decreased pump function is accompanied by distinct changes in the myocardial contraction pattern. Evaluation of myocardial deformation is therefore essential for understanding the (patho)physiology of the heart, and monitoring therapy. However, myocardial deformation is currently not often used as a clinical measure for cardiac function.

In this thesis, myocardial deformation is measured using magnetic resonance imaging (MRI) with tissue tagging. This technique allows for quantification of deformation with high spatial and temporal resolution. Myocardial mechanics are quantified by LV circumferential shortening and LV torsion, the opposite rotation of the base and apex, which are both measures closely related to the orientation of the myofibers.

Explicit measures of myocardial deformation, obtained by MRI, are introduced in healthy subjects and in patients with and without loss of cardiac pump function. The clinical usefulness of these measures is evaluated.

PART 1

The first part of the thesis explores the analysis of myocardial function by quantification of LV torsion, and proposes a standardized method that allows for proper data interpretation and comparison.

Chapter 1 reviews literature about non-invasive determination of LV torsion. LV torsion is a measure directly related to the structure and function of the myocardium and myocytes, and therefore a promising measure for qualitive, as well as quantitive detection of (sub)clinical (systolic and diastolic) dysfunction. Several reference values for LV torsion have been presented in literature. However, different definitions for calculation were used. LV torsion measurements should be comparable between hearts of different sizes, but also between different imaging techniques (e.g. MRI vs. ultrasound). The results obtained over the years are helpful for developing a standardized method to quantify LV torsion, and facilitate the interpretation and value of LV torsion before it can be used as a clinical tool. Based on mechanical considerations, it follows, that LV torsion should be quantified as the circumferential-longitudinal shear angle to be clinically most useful. In this way, length and radius of the heart are taken into account.

In Chapter 2, the LV torsion calculation method, which describes LV torsion as the circumferential-longitudinal (CL) shear angle, is implemented and tested. Torsion was analyzed in circumferential segments and in transmural layers, using an analytical model. In addition to this analysis, the axis of rotation was displaced. This resulted in a large variation in LV torsion over circumferential segments, whereas calculation in transmural layers was accurate. In a group of healthy subjects, results were in agreement with literature values. Hence, it is shown that LV torsion is a global measure of myocardial function and that it is unreliable to calculate torsion in different circumferential regions, due to its dependency on rotation axis.

Chapter 3 compares the standardized 2D torsion method, as described in Chapter 2, to extensive 3D strain analysis in healthy subjects. It was found, that both methods are highly correlated. However, the 2D method gives slightly larger values, inherent to the definition of the CL shear angle calculation. From the analysis, it is concluded that the faster 2D method is suitable for clinical practice.

PART 2

In the second part, myocardial strain and torsion in patients with severe heart failure who are candidates for cardiac resynchronization therapy (CRT) are studied. The underlying disease related changes in cardiac mechanics in these end-stage heart failure patients and mode of operation of CRT are still unclear. Analysis of myocardial deformation provides new information and will allow for better understanding and prediction of response to CRT.

Chapter 4 compares two methods for analysis of LV dyssynchrony in CRT candidates. Circumferential strain, assessed by MRI is compared to a newer, 3D echocardiography based regional volume method. A high correlation between both methods was observed. However, regional differences in time-delays were observed. The volume curve preceded the strain curve, but in the septum the difference was smaller than in the lateral wall. This obviously leads to discrepancies in the quantification of mechanical dyssynchrony between both methods, and is probably related to the method used for calculation of the regional volumes, which uses a non-fixed center line over time for the determination of regions. Therefore, both modalities might represent different measures of mechanical dyssynchrony and are not interchangable.

In Chapter 5, the patterns of circumferential strain are studied in relation to the acute hemodynamic response to CRT, measured by the relative increase in dP/dt_{max}. It is investigated whether mechanical dyssynchrony (regional differences in the timing of strain) or heterogeneity (regional differences in the amount of strain) are more predictive for response. The heterogeneity based measures were found to correlate better with acute response, but were similar to electrical dyssynchrony (QRS-width). A linear combination of the heterogeneity in strain measure and the electrical dyssynchrony resulted in a significant improvement of the relation to acute response. The results suggest that there is no one-to-one relationship between electrical and mechanical dyssynchrony and its influence on regional contraction.

Chapter 6 focuses on the torsional deformation of the LV myocardium in patients eligible for CRT. The majority of patients show a torsion pattern where the apical rotation direction is inverted, resulting in loss of opposite basal and apical rotation. The loss of opposite basal and apical rotation could be quantified by calculating the correlation coefficient between the basal and apical rotation curves. A positive correlation indicates loss of opposite rotation. Patients with this specific torsion pattern demonstrated a better acute and long-term response to CRT, as determined by relative increase in dP/dtmax and change in LV volume measured by echocardiography, respectively. Therefore, the patterns of LV torsion in the failing heart provide new insight in the disease and its therapeutic options. Loss of opposite basal and apical rotation is considered to be a very promising predictor for response to CRT.

PART 3

The third part of the thesis describes myocardial deformation in patients with a genetic mutation for hypertrophic cardiomyopathy (HCM) who still have normal wall thickness. This is important, since knowledge about the disease process might lead to possibilities for early detection and monitoring of the disease, as HCM is associated with heart failure and sudden cardiac death.

Chapter 7 studies regional circumferential strain in subjects with a genetic mutation for HCM (carriers), who still have normal wall thickness and normal pump function. The predictive value for the genotype is explored. Both peak systolic circumferential strain and peak diastolic circumferential strain rate were lower in carriers relative to control subjects, particularly in the basal lateral wall. Predominantly peak diastolic circumferential strain rate was found to be predictive for HCM mutation carriership.

In Chapter 8, LV torsion is examined in HCM carriers with normal wall thickness and pump function. Relative to normal subjects, torsion was increased, while subendocardial circumferential strain was normal. The change in ratio of torsion to subendocardial strain implies that the increase in LV torsion can be attributed to relatively impaired subendocardial function. All these abnormalities in the pattern of myocardial deformation in phenotype-negative HCM mutation carriers provide more insight in the disease and can be useful for early identification of patients with subclinical disease.

FUTURE PERSPECTIVES

This thesis provides new insights in measuring myocardial deformation and shows the mechanisms of deformation in heart failure and HCM carriership. It is once more underlined, that studying myocardial deformation is important for understanding and quantifying systolic and diastolic myocardial function. The introduction of these measurements in daily clinical practice is warranted, as quantifying myocardial function helps the clinician detect and follow the process and progress of a disease. Therefore, acquisition and processing of data should become more time efficient. Improvement of contour detection methods will result in more automated procedures, gaining clinical efficiency. Echocardiographic speckle tracking (1,2) is a very promising technique which is more widely available than MRI tagging. The use of speckle tracking could accelerate clinical application of quantification of myocardial deformation. However, additional comparative research is needed, since in echocardiography, image quality is inferior and imaging cannot be performed from any view. The development of 3D speckle tracking techniques will solve the problem of the missing reference coordinate system in echocardiography, such that standardized measurement methods can be used.

Furthermore, the exact physiology of normal and failing cardiac function should be further explored by studying myocardial deformation. In addition, a more comprehensive view on cardiac function can be obtained by the integration of various data. Although specific fundamental knowledge such as information about fiber structure (3,4) and electrical activation (5) is very old, little is known about its interaction. Only the combination of information about cardiac structure, function and electrical activation can bridge the gap in our current understanding of cardiac (patho)physiology.

An example of such integration can be seen in Fig. 1. Here, bulls-eye plots of electrical and mechanical activation of the LV of a healthy subject are shown. All data are acquired non-invasively. Mechanical activation was quantified by determining onset and peak times of circumferential strain using MRI tagging, whereas local myocardial electrical activation was measured by calculating the inverse of a 64 lead surface electrocardiogram, using anatomical information from MR images (6). It can be seen that electrical and mechanical activation propagate approximately opposite, whereas the time to peak circumferential strain shows a similar pattern as the electrical activation.

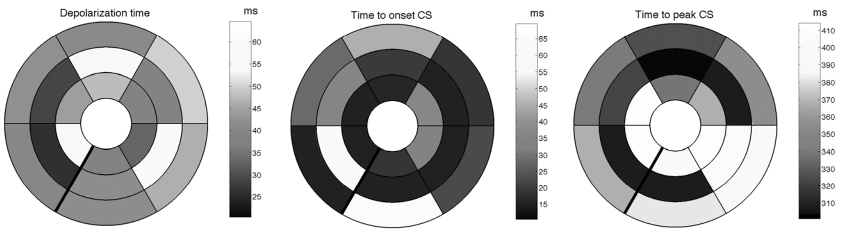

Figure 1. Bulls-eye plots of electrical and mechanical activation of the left ventricle in a healthy subject. CS: circumferential strain.

One can imagine that for a patient, additional information including tissue properties could be added. Also, due to improved data acquisition techniques, information is not limited to systole only, but diastolic function can be studied as well.

With combined information of cardiac structure, function and electrophysiology over time, all on a non-invasive basis, new ways to improve therapy are open.

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