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Summary
The present thesis describes effects of left bundle branch block (LBBB) on cardiac functioning. Assessment of mechanical dyssynchrony with real-time 3D echocardiography (RT3DE), tissue Doppler imaging (TDI) and cardiovascular magnetic resonance imaging (CMR) in left bundle branch block (LBBB) patients is described. Furthermore, effects of LBBB on right ventricular (RV) function and dimensions, acute hemodynamic response on biventricular pacing with respect to RT3DE derived mechanical dyssynchrony, the correlation between TDI derived mechanical dyssynchrony and RT3DE derived mechanical dyssynchrony and finally, a comparison of volume-time curves obtained by RT3DE with LV circumferential strain curves obtained by CMR is presented.

Chapter 1 exposes an update of current literature about LBBB and evaluation of mechanical dyssynchrony. LBBB is related to abnormal cardiac conduction and mechanical dyssynchrony (or asynchrony) and is associated with hypertension and coronary artery disease. Improved evaluation of left ventricular (LV) mechanical dyssynchrony is needed, because of the increasing number of patients with LBBB and heart failure. Therefore, results of evaluation of LBBB with TDI, strain (rate) imaging and tissue tracking in LBBB patients are described. With these modalities, a variety of patterns of mechanical activation can be observed in LBBB patients, with the majority of the included LBBB patients having symptomatic heart failure. In addition, RT3DE provides new regional information in relation to mechanical dyssynchrony. Using LV casts, derived volume-time curves and mechanical dyssynchrony projected on bull’s eye plots, this modality helps to display the spatial distribution of mechanical dyssynchrony fast and accurately. Finally, the potential of CMR imaging derived segmental time-to-peak circumferential strain curves is demonstrated. Detailed quantification, with high temporal resolution, of LV mechanical dyssynchrony is possible with CMR tissue tagging. Hence, effects of LBBB on regional and global cardiac function are impressive, myocardial involvement seems to play a role. With the help of novel imaging modalities, new insights concerning effects of LBBB of cardiac functioning continue to develop. Therefore, further studies are warranted.
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Chapter 2 of this thesis evaluates global LV function and mechanical dyssynchrony with RT3DE, in asymptomatic LBBB patients, healthy volunteers and patients with symptomatic heart failure and a LBBB. Furthermore, the relation between presence or absence of symptoms of heart failure and mechanical dyssynchrony was investigated. Therefore, RT3DE was performed in 16 healthy volunteers, 22 patients with an asymptomatic LBBB and 23 patients with symptomatic heart failure and a LBBB. Global LV function and the systolic dyssynchrony index (SDI) were measured. Healthy volunteers had the highest LV ejection fraction, closely followed by asymptomatic LBBB patients. Heart failure patients with a LBBB had impaired LV ejection fraction. Furthermore, mechanical dyssynchrony, represented by SDI, of asymptomatic LBBB patients was slightly more than SDI of healthy volunteers. However, heart failure patients with a LBBB had the highest SDI, which differed significantly with both other groups. A cut-off value for SDI for presence of symptoms of heart failure was obtained 10.8%.

Chapter 3 describes the assessment of RV dimensions and function in asymptomatic LBBB patients with mildly depressed LV function in whom coronary artery disease, hypertension, and valvular pathology was excluded. RV dimensions and function were studied because it was hypothesized that isolated LBBB may be an expression of idiopathic cardiomyopathy affecting both ventricles. Therefore, next to 15 asymptomatic LBBB patients, 15 healthy volunteers and 15 idiopathic dilated cardiomyopathy LBBB patients were studied. RV long axis and tricuspid annulus diameter were obtained, as were tricuspid annular plane systolic excursion (TAPSE) and peak systolic velocity (Sm) of the RV free wall annulus. Tricuspid regurgitation (TR) jets (peak TR jets) were used for RV pressure assessment. RV dimensions were comparable between asymptomatic LBBB patients and healthy volunteers. Also, RV function of asymptomatic LBBB patients and healthy volunteers were similar, whereas functional parameters in idiopathic dilated cardiomyopathy patients were significantly reduced. For the three groups combined, a significant inverse correlation between RV pressure (peak TR jets) and RV function (Sm) was observed.

In conclusion, patients with an asymptomatic LBBB demonstrated to have RV dimensions and function within normal range. Thereby suggesting that screening of RV functional parameters in asymptomatic LBBB patients is not useful for
identification of an early-stage cardiomyopathy. Furthermore, RV dysfunction is merely a consequence of increased RV loading conditions caused by left-sided heart failure and does not indicate a generalized cardiomyopathy affecting both ventricles.

In **Chapter 4**, CMR was used to evaluate the effect of LBBB on LV remodeling, mechanical dyssynchrony, functional mitral regurgitation (FMR) and deformation of the mitral valve apparatus (MVA) in LBBB patients at different stages of heart failure. In 12 LBBB patients with heart failure, 4 patients with isolated LBBB, and 4 controls, cine CMR was performed to measure LV remodeling, FMR grade and deformation of the MVA. CMR tissue tagging was used to measure septal-to-lateral onset of shortening delay and coefficient of circumferential strain variation to quantify dyssynchrony.

LV end-diastolic volume and end-systolic volume were largest in LBBB patients with heart failure. Patients with isolated LBBB tended to have a larger LV end-systolic volume and smaller LV ejection fraction compared to controls, QRS duration and septal-to-lateral-onset-of-shortening delay were comparable between LBBB patients with heart failure and isolated LBBB patients, circumferential strain variation was larger (98 ± 45% vs. 40 ± 4%, p < 0.05). MVA tenting and FMR were present both in LBBB patients with heart failure and patients with isolated LBBB and were not observed in controls.

The presence of a LBBB in asymptomatic patients is related to mechanical dyssynchrony and deformation of the MVA and may be associated with LV remodeling. If confirmed, close monitoring or even timely initiation of therapy may be warranted in patients with isolated LBBB. This advocates conducting a longitudinal CMR follow-up study on the clinical course in patients with isolated LBBB.

In **Chapter 5**, the utility of mechanical dyssynchrony by RT3DE for predicting systolic response to biventricular pacing, of which maximal rate of pressure rise (dP/dt$_{max}$) served as the gold-standard, was evaluated.

Seventeen consecutive heart failure patients ischemic cardiomyopathy, mean QRS duration 136 ± 32 ms, including LBBB and non-LBBB patients, underwent RT3DE and biventricular pacing. With the RT3DE post-processing software that already was described in Chapter 3, data of global LV function and SDI of 17 LV segments (SDI$_{17}$, %) for assessment of mechanical dyssynchrony were obtained. During biventricular
pacing, percentual change in \( \frac{dP}{dt_{\text{max}}} \) compared to the non-pacing mode, \( \Delta \frac{dP}{dt_{\text{max}}} \) was measured invasively with conductance catheters. LV ejection fraction was 31 ± 10\%, SDI\textsubscript{17} was 10.2 ± 4.2\% and percentual \( \Delta \frac{dP}{dt_{\text{max}}} \) during biventricular pacing was 14.5 ± 12.4\%. A significant correlation was found between SDI\textsubscript{17} and percentual \( \frac{dP}{dt_{\text{max}}} \), and between QRS duration and percentual \( \Delta \frac{dP}{dt_{\text{max}}} \).

Mechanical dyssynchrony measured by RT3DE shows a good correlation with invasively determined acute hemodynamic response to biventricular pacing in patients with symptomatic dilated cardiomyopathy. Future studies are needed to further define the clinical utility of RT3DE in identifying patients who are most likely to respond to cardiac resynchronization therapy.

**Chapter 6** compares mechanical dyssynchrony assessed with Tissue Doppler imaging and RT3DE. The hypothesis was that in participants with a wide range of LV ejection fractions, TDI equals RT3DE for assessment of presence and extent of mechanical dyssynchrony, particularly when both parameters are corrected for heart rate. Consequently, in 100 patients, TDI and RT3DE images were acquired and systolic dyssynchrony indexes were calculated. With TDI, standard deviation of time to peak systolic tissue velocity of 12 LV myocardial segments was assessed. With RT3DE, standard deviation of time from QRS onset to minimal volume of 12 and 16 LV subvolumes was assessed.

Adequate analysis and comparison of TDI and RT3DE derived dyssynchrony indices was possible in 90 of consecutive patients. The presence of mechanical dyssynchrony as detected by TDI was significantly greater than by RT3DE. A fair correlation could be observed between TDI-SDI and RT3DE-SDI of 12 LV segments as well as RT3DE-SDI of 16 LV segments. Correlations improved slightly when TDI-SDI was corrected for heart rate.

As a result, TDI and RT3DE derived dyssynchrony indices show a fair correlation. However, marked differences between techniques are found for presence of significant mechanical dyssynchrony.

**Chapter 7** compares regional LV volume curves obtained with RT3DE with LV circumferential strain curves obtained by CMR in cardiac resynchronization therapy candidates.
In twenty-one patients with chronic heart failure, RT3DE and tagged CMR were performed subsequently. During post-processing, regional LV volume was computed from the ultrasound images, with the post-processing software as described in Chapter 3. From the tagged CMR images, regional circumferential strain was calculated. Cross-correlations with time lags of 1% of the cardiac cycle were performed to compare the curves in corresponding LV segments and septal-to-lateral delays (as percentage of the cardiac cycle) were compared between modalities. CMR delayed contrast enhancement was used to detect scar tissue. The relation between the location of delayed contrast enhancement and the cross-correlation was explored.

High correlations were found between the curves, but regional differences in time delay between modalities were observed. In the septum, the volume curve was earlier than the strain curve (p = NS), while in the lateral wall, the volume curve was earlier (p < 0.01). There was a discrepancy between septal-to-lateral delays in the two modalities; however, the results were not significantly different. The presence of delayed contrast enhancement did not influence the cross-correlation.

High correlations were observed between circumferential strain and volume curves, but regional differences in time-delay occur in segments with abnormal strain curves. This possibly hampers the comparison of both measures for the quantification of dyssynchrony.

Chapter 8 reviews and discusses the principles of ventricular mechanical dyssynchrony and the acute and chronic effects of cardiac resynchronization therapy on systolic function, cardiac metabolism, and clinical parameters. Left bundle branch block occurs in a third of heart failure patients, and is accompanied by an adverse prognosis due to the detrimental effects of a dyssynchronous contraction pattern in the already failing heart. Simultaneously pacing the interventricular septum, i.e. RV apex and LV free wall (biventricular pacing) can partially restore ventricular synchrony (cardiac resynchronization therapy [CRT]). The latter result in acute improvement of cardiac performance, induces reverse remodeling, and translates into improved quality of life and reduced morbidity. The effects on mortality remain to be elucidated. Response to therapy is variable. Disparity between electrical (prolonged QRS width) and mechanical dyssynchrony is primarily responsible for the fact that 20–30% of patients do not respond to CRT. Imaging tools such as
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Echocardiography and magnetic resonance imaging can accurately visualize the mechanical activation sequence of the heart. Therefore, these techniques are useful in identifying patients with mechanical dyssynchrony who are most likely to respond to CRT. However, only 10% of patients with moderate-to-severe heart failure meet the current criteria for CRT.

Conclusions

LBBB has a subsequent impact on global and regional LV function and mechanical dyssynchrony. It is no surprise that a significant number of heart failure patients do have LBBB. Effects of LBBB on global and regional LV function can be displayed well with a novel imaging modality as RT3DE.

RT3DE evaluation of age-matched asymptomatic LBBB patients, healthy volunteers and symptomatic HF patients with a LBBB demonstrated that global LV function of asymptomatic LBBB patients already is slightly impaired with increased mechanical dyssynchrony, although not significantly, compared to healthy volunteers. However, patients with HF and a LBBB have the most severely impaired LV function and increased mechanical dyssynchrony. Substantial levels of mechanical dyssynchrony might coexist with symptoms of heart failure.

When RV dimensions and function of asymptomatic LBBB patients are studied, these dimensions and function are within normal range. In idiopathic dilated cardiomyopathy patients with a LBBB and symptomatic heart failure, RV dysfunction is observed regularly, which in turn is related to RV loading conditions. Therefore, screening of RV functional parameters in asymptomatic LBBB patients is not useful for identification of an early-stage cardiomyopathy, and RV dysfunction is merely a consequence of left-sided heart failure and does not indicate a generalized cardiomyopathy affecting both ventricles.

Cardiovascular magnetic resonance imaging demonstrated that LBBB in asymptomatic patients is related to mechanical dyssynchrony and deformation of the mitral valve apparatus and may be associated with LV remodeling, thereby necessitating close monitoring or even timely initiation of therapy in patients with asymptomatic LBBB.

As a relative novel imaging modality, RT3DE allows for a good correlation with invasively determined acute hemodynamic response to biventricular pacing in patients with symptomatic, primarily idiopathic dilated cardiomyopathy. Further
definition of the clinical utility of RT3DE in identifying patients who are most likely to respond to cardiac resynchronization therapy is necessary, but these first results are hopeful.

Compared to TDI, RT3DE derived mechanical dyssynchrony indices show a fair correlation in consecutive cardiac patients with a wide range of LV EF and different etiologies of cardiomyopathy. However, marked differences between RT3DE and TDI are found for presence of significant mechanical dyssynchrony when current cut-off values are applied. This also implicates future research to further define the clinical application of RT3DE for assessment of mechanical dyssynchrony and its predictive value for acute and long-term response to CRT.

Between CMR derived regional LV circumferential strain and RT3DE derived regional LV volume, high cross correlations were observed. However, regional differences in time delay between the curves were found, leading to discrepancies in the quantification of mechanical dyssynchrony. This could be ascribed to the poor correlation between regions with little or positive circumferential strain and the accompanying regional volume curves.

Different levels of global and regional cardiac dysfunction can be frequently observed in various patients with LBBB. One of the most promising imaging modalities is RT3DE, as RT3DE can be helpful in assessing, quantifying and displaying global and regional LV function and, therefore, might have the ability to predict a response to CRT.
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