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Chapter 1
General Introduction, Aim and Outline of the Thesis
INTRODUCTION

Heart failure is the fastest growing cardiovascular disease affecting over five million individuals annually. Despite advanced heart failure treatment, mortality rate remains high and more than 40% of patients diagnosed with heart failure die within 5 years. Furthermore, although heart failure hospitalization rate is decreasing both in Europe and the United States, heart failure still remains one of the most common causes for hospitalization.

Etiology of heart failure is multifactorial but the main causes in industrialized countries are hypertension and coronary artery disease. Specific patient populations are known to be at higher risk for heart failure, although often under-represented in heart failure randomized clinical trials. Elderly patients and patients with diabetes mellitus or chronic kidney disease are for example at increased risk of developing heart failure and the presence of these comorbidities is in turn well known to be associated with higher mortality among heart failure patients.

Implantation of a conventional pacemaker has also been related to an increased risk of left ventricular (LV) dysfunction, heart failure development and subsequently, mortality. Multiple factors may contribute to heart failure development or heart failure progression after pacemaker implantation. It is has been shown that right ventricular (RV) pacing results in an abnormal LV contraction with induction of intra- and inter-ventricular dyssynchrony, for which high percentages of RV pacing have been associated with heart failure events and worse long-term mortality. Furthermore, the mechanical presence of the RV lead through the tricuspid valve apparatus has been shown to lead to tricuspid regurgitation, which might play an additional role in heart failure development and progression after device implantation.

CARDIAC RESYNCHRONIZATION THERAPY

Cardiac resynchronization therapy (CRT) is an established therapy for heart failure patients with depressed LV ejection fraction (LVEF <35%), prolonged QRS duration (>120ms) and mild-to-severe heart failure symptoms despite optimal pharmacological therapy. The rationale behind CRT is the nullification of cardiac dyssynchrony by resynchronizing atrio-ventricular, inter-ventricular and intra (LV)-ventricular contraction. Large clinical trials have demonstrated improvement after CRT in clinical symptoms, LV function and mitral regurgitation as well as significant reduction in all-cause and cardiac mortality rates and heart failure hospitalizations. However, up to 40% of heart failure patients do not improve after CRT and the reasons for these relatively high non-response rates still remain unclear. Research has been
therefore focusing on identifying potential factors influencing response to CRT in order to further optimize patient selection or improve CRT efficacy. Of note, several specific patient populations, such as elderly patients, patients with diabetes or severe renal dysfunction, and presence of non-left bundle branch block QRS morphology are underrepresented in randomized clinical trials and the effects of CRT in these subpopulations remain unclear.

CARDIOVASCULAR IMAGING IN CRT

Cardiovascular imaging, including echocardiography, cardiac magnetic resonance (CMR) and nuclear imaging, is essential in the assessment of etiology, severity and prognosis of heart failure and has become therefore crucial also in the evaluation of patients referred for CRT. Particularly echocardiography, due to its wide availability and bed-side application, represents the first line imaging technique for the assessment of these patients.

LV volumes and function assessment

Echocardiography is the currently recommended imaging technique for quantification of LV systolic dimension and function. It is therefore also fundamental when referring patients for CRT considering the current indication criteria based on LVEF. In addition to the biplane Simpson technique to estimate LV dimensions and systolic function, it has been recommended to quantify LV volumes and LVEF using 3D imaging to provide more geometric-assumption free, accurate and reproducible measurements. Particularly, the excellent intra- and inter-operator variability of 3D echocardiography makes this modality also very suitable for the follow-up assessment. CMR is currently considered the gold standard for the quantification of LV volumes and LVEF but is not that often used in clinical practice.

LV dyssynchrony assessment

Quantification of mechanical LV dyssynchrony has been shown in single center studies to be useful in the prediction of response to CRT. Whether assessment of LV dyssynchrony might improve patient selection to CRT however is still highly debated. Recent guidelines include only QRS duration and morphology as criteria for CRT indication considering the inclusion criteria of the CRT randomized clinical trials. In particular, patients with left bundle branch block (LBBB) seem to have the largest benefit from CRT. However even among patients with LBBB, LV activation may change considerably as demonstrated by studies using 3D LV mapping which showed in these patients distinct patterns of LV dyssynchrony that may also influence CRT re-
Echocardiography permits characterization of these LV activation patterns using different indices of LV dyssynchrony. Indices such as septal-to-posterior wall motion delay using M-Mode or time-to-peak systolic velocity using tissue Doppler imaging (TDI) were initially proposed to quantify LV dyssynchrony and to identify the site of the latest activation. The Predictors of Response to CRT (PROSPECT) trial was the first multicenter prospective trial to explore the role of several echocardiographic cardiac dyssynchrony parameters to predict response to CRT, including the ones derived from M-mode, conventional Doppler and TDI. With 498 enrolled patients, the trial demonstrated a modest accuracy to predict response to CRT for all the echocardiographic LV dyssynchrony indices. However, the observational study design, the inclusion of patients with LVEF>35% or LV end-diastolic dimensions <65 mm, and technical related issues (different vendors, low reproducibility, and poor acoustic window) may have had significant impact on the study results. Furthermore, several pathophysiological factors, such as the presence of myocardial scar and LV lead position were not considered in the interpretation of the results. Further studies and small clinical trials have in fact later shown that an integrative approach, including assessment of LV dyssynchrony with speckle tracking strain-based more automated echocardiographic approaches, quantification of myocardial scar burden and targeting the site of latest activation without transmural scar for the LV lead position, may provide a more accurate selection of patients that will benefit from CRT.

Focus has been therefore shifted towards evaluation of active mechanical deformation with speckle tracking echocardiography and towards global evaluation with 3D imaging techniques to better characterize LV mechanical dispersion or dyssynchrony.

Tracking natural acoustic markers (“speckles”) in grey-scale images, information on regional myocardial deformation, known as ‘strain’ can be obtained in radial, longitudinal, and circumferential planes. Radial strain has shown to be a predictor of clinical benefit in patients with ischemic cardiomyopathy in terms of LV volumetric changes prognosis. At long-term follow-up, absence of LV dyssynchrony by radial strain was associated with poor outcomes in patients with QRS duration between 120-150 ms.

The 2D approach of speckle tracking echocardiography is based on the acquisition of several views during different cardiac cycles which provides still information on each LV segment, but may be limited by a potential beat-to-beat variability in its calculation and by a failure of tracking by a out-of-plane motion of the speckles. In this regard, the development of 3D imaging techniques has enabled the assessment of global LV mechanical dyssynchrony in one beat and could be of incremental value for selection of CRT candidates and optimization of CRT therapy.
One of the main LV dyssynchrony indices based on real-time 3D echocardiography was the systolic dyssynchrony index (SDI, Figure 1). From a LV 3D full volume dataset, LV endocardial border is semi-automatically defined at end-systole and end-diastole and a 3D LV model is derived. This model is subsequently divided into 16 or 17 segments and the LV mechanical dyssynchrony is quantified by calculating the standard deviation of time to minimum systolic volume of 16 sub-volumes (Tmsv16-SD). The LV mechanical dispersion can also be visualized on color-coded polar maps, with the earliest activated regions coded in blue and the latest activated areas coded in orange-red. In this example, the patient shows significant LV dyssynchrony (Tmsv16-SD 20.05%) and the lateral and posterior LV regions as the most delayed activated areas. The time-volume curves of the 16 regional sub-volumes are plotted in a graph providing also a visual estimation of LV dyssynchrony. Panel B: Assessment of LV dyssynchrony with triplane tissue synchronization imaging. The polar map shows the time to peak systolic velocity of 12 basal and mid-ventricular LV segments. LV dyssynchrony is calculated as the standard deviation of time to peak systolic velocity of the 12 segments. In this example, there is significant LV dyssynchrony (standard deviation: 47 ms) and the mid posterolateral segment is the most delayed activated area.
deviation of time to minimum regional volume of 16 or 17 LV sub-volumes and correcting it for the RR interval. A recent meta-analysis pooling data from 600 heart failure patients undergoing CRT implantation demonstrated a good accuracy of SDI to predict response to CRT. A weighted mean SDI of 9.8% predicted response to CRT with a sensitivity of 93% and a specificity of 75%.

Furthermore, from TDI, triplane LV echocardiographic data can be derived and LV dyssynchrony calculated as the standard deviation of time to peak velocity of 12 basal and mid ventricular segments. Particularly, tissue synchronization imaging has provided a rapid and intuitive visualization of LV mechanical dyssynchrony providing color-coded polar map plots of the LV activation. The earliest activated segments are color-coded in green whereas the latest activated segments are color-coded in orange (Figure 1). Using this methodology, van de Veire et al demonstrated that a standard deviation of time to peak systolic velocities ≥33 ms predicted response to CRT with 90% and 83% sensitivity and specificity, respectively.

Finally, the recently developed 3D speckle tracking has also permitted quantification of LV dyssynchrony. Future research evaluating this promising novel technique will show its additional value for clinical practice.

CMR and nuclear imaging can also be used for the quantification of LV dyssynchrony with dedicated software and in centers with the specific expertise.

LV myocardial scar
Coronary artery disease is the leading cause of heart failure and current evidence shows reduced CRT benefit among patients with ischemic heart failure as compared to patients with non-ischemic heart failure. The location of transmural scar and the extent or burden of myocardial scar has shown to be of important influence on the effects of CRT and particularly to target LV pacing lead position. Assessment of myocardial viability and scar with echocardiographic techniques is feasible. Particularly, speckle tracking echocardiographic techniques have been validated against contrast-enhanced CMR to identify transmural myocardial scar. Using speckle tracking radial strain echocardiography, a value of peak radial strain <16.5% has been proposed to identify regions of transmural myocardial scar. In 397 ischemic heart failure patients the presence of transmural scar as assessed with speckle tracking radial strain echocardiography at the area targeted by the LV lead was independently associated with poor outcome. The addition of myocardial scar in the segment targeted by the LV lead had incremental prognostic value over LV dyssynchrony, LV lead position and other well-known clinical prognostic markers. Although the impact of macroscopic myocardial scar has been described extensively, the potential role of diffuse myocardial fibrosis has not been explored. Recent advances in CMR techniques with T1 mapping now permit assessment of interstitial
myocardial fibrosis. This approach has shown a good agreement with histological biopsy studies.

AIM AND OUTLINE OF THE THESIS

The aim of this thesis was to study the role of pacing as potential cause but, most importantly beneficial therapy in heart failure. Particularly, it focused on optimization of selection and risk stratification of patients referred for CRT.

*Part I, Chapter 2* of the thesis describes the association between tricuspid regurgitation and the development of heart failure after pacemaker or implantable cardioverter-defibrillator (ICD) implantation.

*Part II* of the thesis focuses on CRT outcomes specifically in subpopulations underrepresented in randomized clinical trials in order to explore whether this therapy is still beneficial in these subgroups of patients. *Chapter 3* reviews the efficacy of CRT in populations underrepresented in randomized controlled trials. *Chapter 4* describes the impact of diabetes on cardiac function and long-term prognosis after CRT. In *Chapter 5*, the efficacy of CRT in chronic kidney disease stage 4 patients has been evaluated as compared to ICD implantation only. *Chapter 6* describes CRT response, device-related adverse events and long-term outcome after CRT in the elderly. *Chapter 7* focused on the changes in RV function and their impact on prognosis after CRT. In *Chapter 8*, predictors of long-term benefit of CRT in patients with right bundle branch block are evaluated.

In *Part III* of the thesis, novel approaches to optimize patient selection and risk stratification in CRT are evaluated. *Chapter 9* proposes a CRT-SCORE, a multifactorial risk stratification score for clinical shared decision-making for application and management of CRT. The role of 3D echocardiography LV dyssynchrony is evaluated for long-term prognosis after CRT in *Chapter 10*. *Chapter 11* describes myocardial contrast-enhanced $T_1$ mapping for assessment of interstitial myocardial fibrosis and its potential association with unfavorable LV reverse remodeling after CRT in non-ischemic cardiomyopathy patients.
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Chapter 1


