Left Ventricular Wall Motion Analysis to Guide Management of CRT Non-Responders

DISSERTATION

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Preface

This doctoral thesis intends to be considered for "Publikationspromotion". It consists of one scientific paper written by the doctoral candidate (lead author). The original manuscript was accepted for publication in February 2015 and got published in May 2015 as:

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Parts of the research project have been previously presented via poster and oral presentations at national and international conferences. Detailed information is presented in the List of Publications on page X. The content of the doctoral thesis is presented in three chapters. Chapter 1 introduces into heart failure, Cardiac Resynchronization Therapy and Real-time Three-dimensional Echocardiography in relation to the topic of the paper. It also deduces the rationale of the thesis. Chapter 2 consists of the original paper, its tables and figures as well as online published supplemental material. Chapter 3 contains a complementary discussion of the study results. Chapter 4 summarizes the research project under special consideration of its clinical impact.

This doctoral thesis was typeset with LaTeX.

Bettina Kirstein Dresden, May 28, 2017

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List of Abbreviations

2D	two-dimensional
3D	three-dimensional
6-MWD	six-minutes walking distance
ACC	American College of Cardiology
AF	atrial fibrillation
AHA	American Heart Association
AV	atrioventricular
CWD	continuous-wave Doppler
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy defibrillator
DCM	dilated cardiomyopathy
DICOM	Digital Imaging and Communications in Medicine
dP/dt_{max}	maximum systolic rate of change of pressure
ECG	electrocardiogram
ESC	European Society of Cardiology
GDMT	guideline-directed medical therapy
HF	heart failure
IQR	interquartile range
IVMD	interventricular mechanical delay
LAO	left anterior oblique projection
LBBB	left bundle branch block
LL	left lateral projection

LV	left ventricular / left ventricle
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
LVEDD	left ventricular end-diastolic diameter
LVEDV	left ventricular end-diastolic volume
LVESV	left ventricular end-systolic volume
LVMD	left ventricular mechanical dyssynchrony
MRI	magnetic resonance imaging
NYHA	New York Heart Association
PVC	premature ventricular contraction
pVO$_2$	peak oxygen consumption
PWD	pulsed-wave Doppler
QoL	quality of life
QRS	complex of ventricular excitation in the electrocardiogram
RAAS	renin-angiotensin-aldosterone-system
RAO	right anterior oblique projection
RT3DE	Real-time Three-dimensional Echocardiography
RV	right ventricular / right ventricle
SD	standard deviation
SDI	systolic dyssynchrony index
SLMA	site of latest mechanical activation
SNS	sympathetic nervous system
TDI	tissue Doppler imaging
T_{msv}	time to minimal systolic volume
$T_{s\varepsilon}$	time to peak systolic strain
T_{sv}	time to peak systolic velocity
VV	interventricular

1 Introduction

The following chapter introduces into heart failure (HF) with special focus on the development of left ventricular (LV) dyssynchrony. The value and challenges of Cardiac Resynchronization Therapy (CRT) for the management of LV dyssynchrony and the issue of CRT non-response are emphasized. Furthermore, Real-time Three-dimensional Echocardiography (RT3DE) is highlighted as a promising cardiac imaging technology for the evaluation of LV dyssynchrony and the optimization of CRT non-responders. The chapter closes with the deduction of the rationale of the thesis.

1.1 Heart Failure

Heart failure describes a complex syndrome with multi-organ affection rather than a disease of its own. It is defined as an abnormality in cardiac structure or function, which is leading to permanent insufficient delivery of blood to the metabolising tissues, at a rate non-commensurate with its requirements.[2] Frequently mistaken as a natural part of the aging process, only 3 % of the people are able to recognize typical signs and symptoms of HF like shortness of breath, reduced physical activity and congestion, which impair quality of life more than any other chronic medical condition.[3–5] Clinically, HF severity is classified by the New York Heart Association (NYHA) functional class. It ranges from asymptomatic LV dysfunction to severe impairment with symptoms at rest. The impairment of the left ventricular ejection fraction (LVEF) on echocardiography and the presence of structural abnormalities are used to classify the type and stage of HF. Clarification of the type, stage and pathology of HF is crucial because of different respective therapy regimes. Whereas heart failure with reduced ejection fraction (HFrEF) indicated by an LVEF $\leq$ 35 %, is known as systolic HF, heart failure with preserved ejection fraction (HFpEF) indicated by an LVEF $\geq$ 35 %, is known as diastolic HF. Furthermore, HF can be differentiated by the origin of the structural or functional damage, affecting only one or both ventricles, and by the time course of symptom onset, being acute or chronic with manifestation of symptoms within hours until days or within weeks until months, respectively. In this thesis left-sided chronic systolic HF in stage C-D with reduced LVEF and

symptoms of NYHA class III-IV is subject of discussion. The classification schemes of the NYHA classes and stages of HF are given in **Table 1.1**.

Table 1.1 Classification of heart failure taken from the European Society of Cardiology (ESC) Guidelines[2,6].

Classification of heart failure by symptomatic severity and functional capacity	
NYHA I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
NYHA II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
NYHA III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnea.
NYHA IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.
Classification of heart failure by structural abnormality (ACC/AHA)	
Stage A	At high risk for developing heart failure. No identified structural or functional abnormality; no signs or symptoms.
Stage B	Developed structural heart disease that is strongly associated with the development of heart failure, but without signs or symptoms.
Stage C	Symptomatic heart failure associated with underlying structural heart disease.
Stage D	Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy.

1.1.1 The Burden of Heart Failure

Every fifth person older than 65 years is expected to develop HF throughout their lifetime.[7] This unfavourable combination of high prevalence and incidence is further accompanied with a high morbidity and a poor prognosis. In industrialized countries, HF is the most frequent cause for an admission to the hospital, which often is prolonged and followed by a quick re-hospitalization using up 70 % of all HF-related health care expenditures.[8–11] Despite overall declining mortality, HF remains worse than many types of cancer. About 50 % of patients are dying within five years and presence of LV systolic dysfunction is of further negative prognostic value.[12–15] The most frequent cause of premature death in HF patients is due to pump failure or ventricular arrhythmia. Applying these data to Germany, approximately 1.8 million people are currently suffering from HF and 250.000 new cases will be diagnosed each year.[16] In 2012

a total of 386.550 patients were admitted to the hospitals due to HF, accounting for 2 % of all admissions in this year. The treatment required 1-2 % of all health care expenditures ranging about three billion Euro per annum. For several years HF has been the third most common cause of death in Germany after chronic ischemic heart disease and acute myocardial infarction.[17–20]

Summarizing the aforementioned statements, HF is one of the most common, life-threatening and cost-intensive chronic medical conditions in industrialized countries. The aging of the population, overall improved and prolonged survival after cardiac events as well as a wide distribution of precursors for the development of HF, will lead to a steep increase of HF patients over the next decades. Therefore, HF can be seen as the most rapidly growing public and economic health care challenge of the 21st century.

1.1.2 Pathophysiology of Heart Failure and Dyssynchrony

Heart failure is the terminal manifestation of nearly all kinds of heart diseases. It is mostly based on a myocardial disease, which leads to systolic ventricular dysfunction with reduced LVEF. However, it can also result from an abnormality of ventricular diastolic function, conduction, valves, heart rhythm, peri- or endocardium. In industrialized countries, about two-thirds of all HF cases are due to ischemic cardiomyopathy based on advanced coronary artery disease, followed by chronic arterial hypertension and dilated cardiomyopathy (DCM).[9,21]

Pathophysiology of Heart Failure

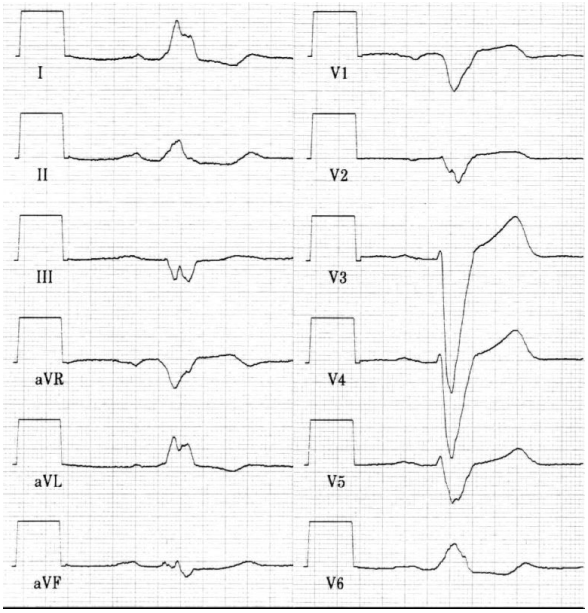
Pathophysiology of HF is characterized by a complex interaction of various compensatory mechanisms with systemic effects and multi-organ involvement. Despite the diversity of HF etiologies, the main pathophysiological pathways remain the same. Initiated by a cardiac event, which leads to a loss of myocardial contractility, cardiac output and organ perfusion are diminished. Consequently, various neurohormonal compensatory mechanisms, like the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone-system (RAAS) and other vasoactive substances, are naturally activated. Their systemic effect causes a combination of peripheral vasoconstriction, increased myocardial inotropy and chronotropy as well as additional extracellular fluid retention to increase end-diastolic preload to the heart. As a result, ventricular wall stretch is increased, which leads to a more forceful contraction of the left ventricle (LV) with a higher ejection of blood (Frank-Starling law of the heart). This restores cardiac output and maintains circulation with sufficient blood supply to the metabolizing tissues. While improving cardiac performance temporarily, a permanent activation of these mechanisms deteriorates

the hemodynamic situation. A chronic persistence of ischemia, inflammation and activation of the SNS and RAAS leads to myocardial hypertrophy, apoptosis and interstitial fibrosis with consecutive structural reconstruction of the heart, known as negative cardiac remodeling. The situation ends up in a vicious cycle with further progression of HF.

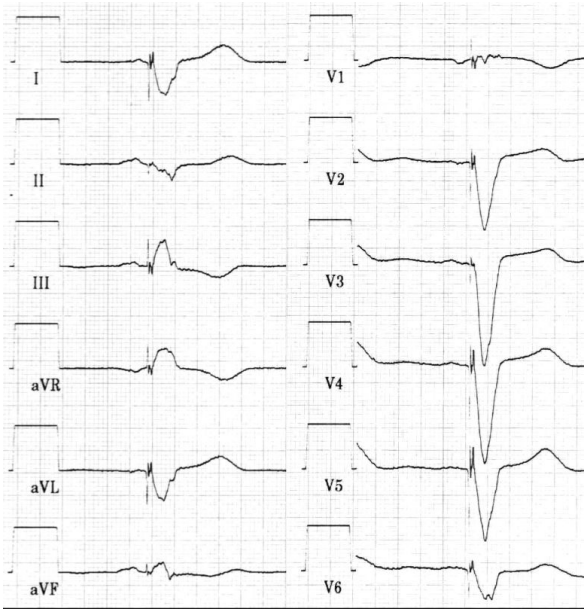
Pathophysiology of Left Ventricular Mechanical Dyssynchrony

The cardiac conduction system is vulnerable to the same pathophysiological processes. Physiologically, it ensures a rapid electrical activation of the myocardium in order to achieve a coordinated contraction of the heart chambers within 60-80 ms. If normal cardiac conduction is disturbed, delayed electromechanical activation of the myocytes leads to an abnormal timing of myocardial contraction with adverse effects on cardiac output. The co-existence of early and late activated myocardium with concomitant loss of coordinated contraction describes the pathological phenomenon of dyssynchrony, which can be present at different levels of the heart chambers. Atrio-ventricular dyssynchrony occurs if there is a delay between atrial and ventricular activation and contraction. Inter- and intraventricular dyssynchrony appear if there is a delay between the RV and the LV or within different parts of the LV itself, respectively. The different levels of dyssynchrony can be evaluated by echocardiography and are introduced in **Section 1.3**. Abnormal cardiac conduction is caused by a broad spectrum of conduction disturbances. Whereas focal lesions with an interruption in the proximal bundle of His lead to classic blocks in the left and/or right bundle branch, more diffuse lesions in different parts of the Purkinje fibre system are responsible of non-specific intraventricular conduction delays. Both occur frequently in HF and can be found in every third patient with DCM.[22–24] In the majority (25-36 %), they are based upon a left bundle branch block (LBBB), followed by right bundle branch block and non-specific intraventricular conduction delays in 4-6 % and 6 %, respectively.[25,26] This is of special relevance, because presence of an LBBB is an independent predictor of increased hospitalization due to progression of HF and worsening of prognosis.[27,28] However, in addition to baseline intraventricular dyssynchrony before initiation of CRT, LBBB is a strong predictor of CRT response with then improved survival.[29,30] **Figure 1.1** provides a 12-lead electrocardiogram (ECG) signal of a classical LBBB pattern in a patient before and after CRT implantation.

In LBBB, the LV is indirectly activated via the working myocardium of the RV and the interventricular septum rather than the normal conduction system.[31] This causes interventricular dyssynchrony with paradoxical septal motion, because the premature activation of the septum leads to a pre-stretch in the delayed activated segments of the lateral LV wall. If the delayed activated lateral LV wall then contracts, re-stretch is given to the now already relaxing septal



(**A**) ECG showing an LBBB with a QRS duration of 160 ms under intrinsic AV-nodal conduction.



(**B**) ECG showing a reduced QRS duration of 120 ms under biventricular stimulation by the CRT device.

Figure 1.1 Twelve-lead ECG of a patient before and after CRT implantation.

region. Consequently, blood is shifted between the opposing LV walls rather than being ejected effectively into the periphery. Full contribution of the myocardium to the pump function of the heart is lost and net cardiac output is lowered.[32] These processes are subsequently followed by delayed electromechanical activation with uncoordinated regional contraction in different LV segments, increasing intraventricular left ventricular mechanical dyssynchrony (LVMD). As a result, LVEF is further reduced, whereas end-diastolic and end-systolic volumes are increased. This promotes additional ventricular wall stretch and myocardial oxygen consumption. Uncoordinated papillary muscle activation further compromises overall LV performance by increasing the severity of mitral regurgitation. Further structural changes are initiated, such as ventricular dilatation and asymmetric hypertrophy with additional negative hemodynamic effects. If there is additional atrio-ventricular dyssynchrony, ventricular filling time is shortened, because atrial preload enhancement to the ventricle and LV stroke volume are diminished. Superimposition of atrial contraction on early passive LV filling leads to a premature inversion of the atrio-ventricular pressure gradient resulting in pre-systolic mitral regurgitation with further reduced end-diastolic volume (preload).

1.1.3 Management of Heart Failure

Modern management of chronic systolic HF is a track record of continuous research. It offers an innovative, guideline-based and stage-dependent therapy concept, which has been proven by landmark trials to reduce HF related signs and symptoms, improve quality of life (QoL) and exercise capacity, prevent disease progression and recurrent HF-related hospitalizations as well as reduce morbidity and mortality.[33–42] Whenever possible, the causing HF etiology has to be treated first. If absent, diuretics and glycosides are used to relieve signs and symptoms.[2] However, the aforementioned fundamental pathophysiological findings contributed to the development of disease-modifying drugs which are targeting the neurohumoral systems and led to the establishment of a guideline-directed medical therapy (GDMT) consisting of a combination of betablocker, angiotensinogen converting enzyme inhibitor or angiotensin receptor blocker, a mineralocorticoid receptor antagonist and the recently approved angiotensin receptor neprilysin inhibitor which accounts for an extension of conservative treatment options. Further disease progression despite optimal GDMT is handled by implantation of cardiac devices which have fundamentally enhanced HF therapy options. CRT, implantable cardioverter defibrillator and cardiac contractility modulation encounter LV dyssynchrony, malignant arrhythmias as well as loss of contractility in mild to severe symptomatic patients and prevent end-stage heart failure, in which treatment by a left ventricular assist device (LVAD) or heart transplant is required but limited due to complications, availability and the advanced age of the HF population. Considering these circumstances, CRT emerged as a milestone in HF therapy by filling a gap and being the therapeutic fulcrum for the majority of patients who are not eligible for LVAD or transplant.

1.2 Cardiac Resynchronization Therapy

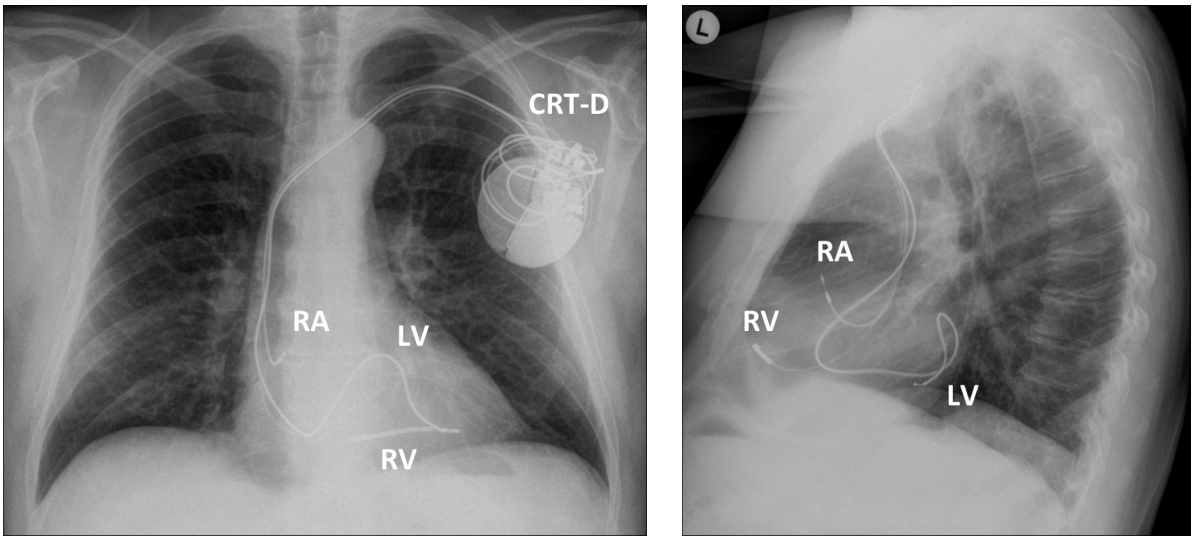
In the 1990s, first concepts were investigated to overcome the deleterious effects of desynchronized LV activation during LBBB as described in **Subsection 1.1.2**.[43–46] Simultaneous pacing by tiny electrodes at the right ventricle and the most delayed segments on the lateral free wall of the LV during LBBB revealed to be a promising concept to resynchronize LV activation. These fundamental findings led to the development of a new kind of cardiac device, known as Cardiac Resynchronization Therapy.

1.2.1 Components, Function and Indication of CRT

Today, CRT is an established therapy option for symptomatic HF patients, in NYHA functional class III - IV, with reduced LV systolic function $\leq$ 35 %, despite administration of GDMT and sinus rhythm, who suffer from an electrical delay in LV activation, as indicated by a QRS prolongation $\geq$ 120 ms in case of LBBB, and $\geq$ 150 ms independent of the kind of branch block morphology.[2,47] Several landmark trials confirmed CRT to improve HF symptoms and QoL, to reduce HF associated hospitalizations as well as improve morbidity and mortality of HF patients.[45,48–54] A modern CRT device consists of a metallic can which is implanted subcutaneously below the collarbone and contains a battery for energy supply as well as a miniaturized computer chip for proper device function. The connected electrodes are implanted transvenously into the right atrium, right ventricle and to the LV free wall over a coronary sinus vein to ensure therapy delivery to the heart. A chest X-ray image of an implanted CRT devices is depicted in **Figure 1.2**. Independent time-shifted biventricular pacing by the electrodes compensates for the differences of LV activation during LBBB and restores cardiac function. In contrast to a pacemaker or defibrillator, CRT is meant to support pacing of every single heartbeat. However, the antibradycardia and antitachycardia therapy option can be incorporated in the device function by either implanting a CRT pacemaker (CRT-P) or CRT defibrillator (CRT-D).

1.2.2 The Issue of CRT Non-Response

Since its introduction, CRT struggles with an enduring high rate of patients, who show no improvement of clinical and/or echocardiographic parameters within the first six months after implantation, the so-called CRT non-responders.[55] Approximately every third CRT recipient is affected by non-response, with lower rates (11 %) if clinical parameters and higher rates (46 %) if echocardiographic measurements are applied, respectively.[56] Despite intensive research, it



(**A**) Left-sided infraclavicular implanted CRT-D device with projection of three transvenously placed leads to the right atrium (RA), the right ventricle (RV) and the left ventricle (LV) via a coronary sinus vein

(**B**) Same investigation showing a classically implanted RA, RV and LV lead to a mid-ventricular position of an inferolateral coronary sinus vein.

Figure 1.2 Chest X-ray of an implanted CRT device in (A) anterior-posterior projection and (B) lateral projection.

has not been possible to lower the non-responder rate over the last 20 years. In absence of a clear non-response definition the term is applied if criteria for CRT response are not met. Frequently used response criteria encompass either clinical parameters like improved NYHA class by at least one class, QoL score, six-minutes walking distance (6-MWD) and $pVO_2 > 10$ % or echocardiographic parameters indicating reverse remodeling like reduced left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic volume (LVESV) by $\geq$ 15 % as well as improved LVEF by absolute $\geq$ 10 % and relative $\geq$ 25 %, respectively. Most often a combination of both is used.[56]

The reasons for CRT non-response are various and the most common ones are summarized in **Table 1.2**. Assuming a correct patient selection by current guidelines, stable sinus rhythm with effective biventricular stimulation $\geq$ 90 % and the delivery of GDMT, a mismatch between the LV lead placement and the site of latest mechanical activation (SLMA) can be responsible for CRT non-response. Historically, the LV lead is directed to a posterolateral vein of the coronary sinus but 30 % of eligible patients do not have their SLMA, as the target of CRT, in this area of the LV.[57] In some cases LV lead implantation concordant to the SLMA is anatomically restricted due to the absence of a suitable coronary vein. In light of this evidence it is important that such a discordant LV lead placement has been reported causative in every fourth to fifth non-responder patient.[58] Insufficient resynchronization of the altered LV wall motion, remaining

or even worsening of LV dyssynchrony with poor clinical and echocardiographic responses and potential effects on long-term outcome have been reported.[57,59]

Table 1.2 Reasons for CRT non-response.[58]

Reason	Characteristic
Etiology of HF[60]	ischemic
Heart rhythm[61,62]	AF, PVCs, competetive AV-nodal conduction
HF medical therapy[63]	incomplete GDMT, unadjusted after CRT
Electrical characteristics[64,65]	non-LBBB, QRS width $\leq$ 120 ms
Mechanical characteristics[29,66,67]	less LV dyssynchrony, scar burden $\geq$ 15 %
LV lead position[59,68]	apical position, discordant to the SLMA
Rate of biventricular stimulation[69,70]	$\leq$ 90-95 %
CRT device programming[71,72]	unadjusted AV/VV-delays

1.2.3 Management of CRT Non-Response

The management of CRT non-responders remains challenging and clinical data are lacking. So far, no gold standard method or guideline has been established.[73] Identification of the underlying reason for CRT non-response is crucial in order to administer the appropriate management option. Up-titration of the established HF medication, radiological re-evaluation of the LV lead positioning as well as re-assessment of BNP, hemoglobin and creatinine levels are helpful measurements to exclude other common causes like lead dislocation or disease aggravation by anemia or renal failure that can cause insufficient CRT delivery or HF progression during follow-up. Such a routine protocol-driven approach with multidisciplinary clinically, echocardiographic and radiological evaluation of ambulatory CRT non-responder patients in a special out-patient clinic has been successfully shown to be feasible and associated with fewer adverse events but may only be afforded by specialized CRT centers.[58]

A more applicable concept for the daily routine is the optimization of the CRT device programming. Modern devices allow variable re-programming of different parameters even after implantation. This feature is of major clinical relevance, because it provides an easy, quick and non-invasive adjustment of the CRT device to changed cardiac conditions such as LV remodeling during follow-up. The atrioventricular (AV)- and the interventricular (VV)-delay time interval are the main parameters of optimization. Whereas the AV-delay describes the timing between atrial and ventricular activation ranging from 80 ms to 200 ms, the VV-delay represents the time difference between the stimulation of the RV and LV by the corresponding ventricular leads ranging from biventricular simultaneous activation to sequential biventricular

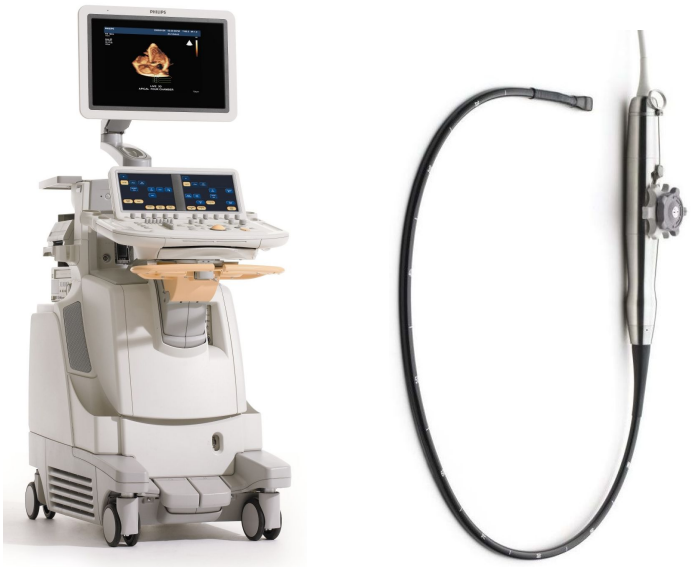
activation with either pre-activation of the RV or LV lead in an adjustable range of milliseconds. If programmed properly, optimal atrial and ventricular contribution to LV filling and cardiac output as well as minimization of atrio-, inter- and intraventricular LV dyssynchrony can be achieved. Empirically, the AV- and VV-delay are programmed to 120 ms and biventricular simultaneous activation, respectively.[74]

The optimization of the AV-/VV-delay can be guided by a plethora of methods as summarized in **Table 1.3**, which is not intented to be exhaustive. However, echocardiography is the preferred modality in clinical routine because of its non-invasive character and universal availability. Other management options are more invasive and riskier. They encompass second LV lead implantation concordant to the SLMA or, in case of large SLMAs, adjacent placement of an additional LV lead to the previously implanted one to provide full resynchronization.[75] Furthermore, total LV lead revision by either catheter intervention or surgical access with epicardial LV lead re-placement might be necessary. In case of premature ventricular contraction (PVC) or persistent atrial fibrillation, focal ablation or AV node ablation serve as the ultima ratio to achieve sufficient biventricular stimulation, albeit the latter consequently leads to pacemaker-dependency.

Table 1.3 Methods for the optimization of CRT device settings.[76–78]

Method Parameter	**AV-delay**	**VV-delay**
Echocardiography		
Iterative method – PWD transmitral flow pattern	×	
Ritter method – AV interval that bridges the end of the A-wave with closure of the mitral valve	×	
LVOT-VTI – LV outflow tract velocity time integral by PWD	×	×
AV-VTI – aortic valve velocity time integral by CWD	×	×
MI-VTI – mitral inflow velocity time integral by PWD	×	
Myocardial systolic velocity, atrioventricular displacement, strain, time to peak velocity derived by TDI	×	×
SDI – systolic dyssynchrony index derived by RT3DE		×
Endovascular micromanometry		
peak rise of left ventricular pressure change (LV dP/dt_{max})	×	×
Ultrasonic sonomicrometry		
ventricular stroke work (SW) calculated from LV pressure-volume loops	×	×
Intracardiac electrogram-based device algorithms		
St. Jude Medical QuickOpt™	×	×
Medtronic Adaptive Algorithm	×	×
Boston Scientific Smart Delay™	×	
Boston Scientific Expert Ease		×
Peak endocardial acceleration-based device algorithms		
Sorin Biomedica SonR	×	×
Finger Photoplethysmography		
greatest change of peripheral pulse pressure ($\triangle P$)	×	×
Radionuclide Ventriculography		
left ventricular ejection fraction (LVEF)		×
Impedance Cardiography		
cardiac output (CO) or stroke volume (SV) calculated from changes of thoracic impedance	×	×
Acoustic Cardiography		
electromechanical activation time (EMAT)	×	
Surface Electrocardiogram		
QRS duration		(×)

1.3 Real-time Three-dimensional Echocardiography



(**A**) Mobile ultrasound imaging machine iE33 by Philips Healthcare.

(**B**) Transesophageal matrix array transducer X7-t2 by Philips Healthcare.

Figure 1.3 Components of real-time three-dimensional echocardiography with corresponding software QLab 7.0 3DQ Advanced by Philips Healthcare (not depicted) for the evaluation of dyssynchrony. Original pictures, displayed with permission of Philips Healthcare.

Echocardiography is the most widely used non-invasive and non-radiative cardiac imaging technique for the diagnosis, management and follow-up of various heart diseases in daily clinical practice. In chronic systolic HF an easy assessment of LV parameters like end-diastolic and end-systolic LV diameters and LV volumes, LVEF as well as pathologies of the mitral valve and the myocardial tissue are of main interest. They are commonly evaluated by two-dimensional (2D) echocardiography as recommended by the guidelines.[79,80] Although before, but at least since the introduction of CRT, evaluation of LVMD as the main therapeutic target of resynchronization became more important. Intensive research and the development of new powerful imaging techniques established echocardiography as a feasible and reliable tool for the non-invasive measurement of LVMD in daily clinical practice. Meanwhile, various one-, two-, and three-dimensional echocardiographic methods and parameters for the assessment of LVMD are available. A selection is summarized in **Table 1.4**, also providing their cut-off values. Considering LVMD as a three-dimensional phenomenon[81] and common echocardiographic methods being limited to two dimensions and by additional aspects, the following section highlights why RT3DE was chosen for the evaluation and optimization in this study.

Table 1.4 Levels of dyssynchrony and common echocardiographic methods for the assessment of dyssynchrony.[81–83]

Parameter	Method	Cut-off
Atrioventricular Dyssynchrony		
diastolic filling ration (LVFT/RR)	PWD acquired transmitral flow velocity representing diastolic filling time (LVFT) as the sum of E-/A-wave duration corrected by the RR-interval	< 40 %
Interventricular Dyssynchrony		
interventricular mechanical delay (IVMD/ΔPEP)	PWD acquired difference between aortic and pulmonary flow velocities representing LV/RV pre-ejection periods (PEP)	≥ 40 ms
Intraventricular Dyssynchrony		
septal-to-posterior wall motion delay (SPWMD)	M-mode color-TDI acquired delay between systolic excursion of the septum and posterior LV wall	≥ 130 ms
mechanical dyssynchrony index (Yu Index)	2D color-TDI acquired longitudinal T_{sv}-SD of 12 LV segments	≥ 33 ms
anteroseptal-to-posterior wall delay (AS-P delay)	2D speckle tracking acquired radial $T_{s\varepsilon}$ of 2 LV segments and $T_{s\varepsilon}$-SD of 6 LV segments	≥ 130 ms > 76 ms
systolic dyssynchrony index (SDI)	RT3DE full volume acquired T_{msv}-SD of 16 LV segments corrected by the RR-interval	≥ 9.8 %

1.3.1 Components and Function of RT3DE

RT3DE is a unique non-invasive cardiac imaging technique and the state of the art in echocardiography. It consist of a special matrix array transducer for either transthoracic or transesophageal investigation connected to a standard ultrasound imaging machine as shown in **Figure 1.3**. To provide full potential of the components, the ultrasound machine is equipped with a comprehensive manufacturer-specific software, providing accurate analysis of LV parameters and LVMD. This special transducer differs from conventionally available ones by sending and receiving ultrasound waves from about 3000 active elements simultaneously. This allows investigation of

a 3D echocardiographic data set in real-time. The data set thus obtained encloses a pyramidal volume with a sector width of $30^\circ \times 50^\circ$, which can be widened up to $90^\circ \times 90^\circ$ if the acquisition of a full-volume data set is performed. This set consists of four smaller real-time volumes, acquired by the same transducer but from four consecutive cardiac cycles which are assembled afterwards. This ensures the correct assessment and analysis of the entire left ventricle, which can be challenging in patients with cardiomyopathy and enlarged left ventricles.

1.3.2 Assessment and Analysis of LV Mechanical Dyssynchrony by Real-time Three-dimensional Echocardiography

Assessment of RT3DE Images

Assessment of an LV full-volume can be performed from either a transthoracic or transesophageal approach with the patient lying in a left lateral decubitus position being connected to a machine-integrated multi-lead ECG. The acquisition starts with the proper positioning of the entire LV cavity and LV wall into the acquired cine loop using the "Angle" option in a standard two-dimensional apical 4-chamber view. After selection of the "4D" option, the depth should be adjusted to solely include the parts of the LV cavity from the apex down to the mitral annulus which optimizes the frame rate. By selecting the "Full-Volume" option a full-volume cine loop is acquired, consisting of four cardiac cycles triggered by the R wave and taken during a single breath-hold in end-expiration. The recorded full-volume cine loop is digitally stored in DICOM format and analysed using dedicated software (QLab 7.0 3DQ Advanced, Philips Healthcare, Best Netherlands).

Analysis of LV Dyssynchrony by RT3DE

Analysis of LVEF, LV volumes and LVMD can be performed directly on the ultrasound imaging machine (online) or on a different workstation after data transmission (offline). In a first step, the full-volume data set is reviewed for proper image quality including clear delineation of the endocardial boarder and inclusion of the entire LV wall. Next, three longitudinal planes of the LV within the full-volume data set are displayed and have to be manually adjusted to generate correct apical 4-chamber, 2-chamber and long-axis views to avoid LV foreshortening, if not fitting at all. The software then automatically generates the three standard views in an end-diastolic and end-systolic frame for further landmarking of the endocardial border at a septal, lateral, anterior and inferior mitral ring position as well as on the LV apex in each frame

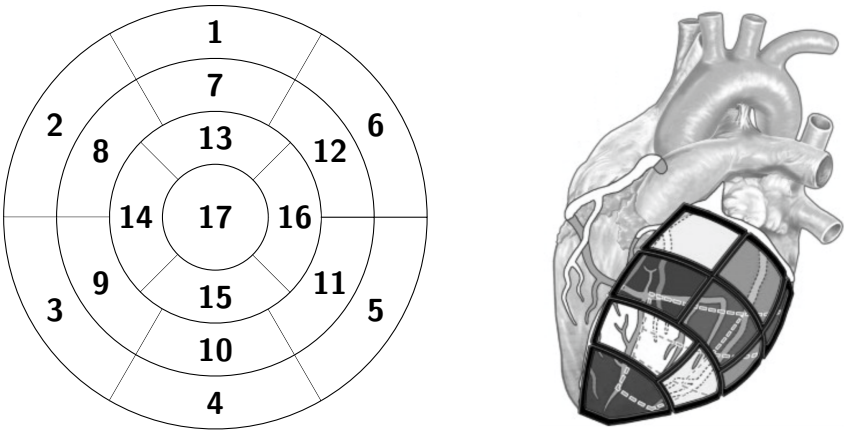
(see Figure 2B left column in the original paper). Semi-automated endocardial border tracking will be performed by the software which, if unsatisfying, can be manually edited afterwards.

Initial analysis shows quantification of global LVEF and LV volumes. For further analysis of regional and global LVMD the LV is subdivided into 16 pyramidal sub-volumes based around a non-fixed central point and one apical cap which, however, is excluded from further dyssynchrony analysis. The standardized structure of the LV segments and its nomenclature are given in **Figure 1.4**. For the whole LV and for each of the 16 segments time-volume curves are calculated assessing the global and regional time taken to reach the minimum systolic volume (T_{msv}). Out of the standard deviation of all these 16 sub-T_{msv} and its percentage of the cardiac cycle, a marker of global LV dyssynchrony is derived – called the systolic dyssynchrony index (SDI). In healthy subjects minimal and maximal systolic volumes are reached nearly simultaneously, indicating synchronous contraction. In patients with cardiomyopathy the time volume curves show an asynchronous pattern and the time to the minimal systolic volume of each segment is widely dispersed.[84] In a first modality, information about kineses of each segment is provided, which can be used to identify the presence and extension of scar tissue. Akinetic, dyskinetic, hypo- and normokinetic segments will be displayed as a flat curve without excursion, a curve with positive excursion and a curve with negative excursion, respectively. Akinetic and dyskinetic segments are not included in the calculation of the SDI. In a second modality, the time-volume curves for each segment are displayed and show when each segment reaches minimum systolic volume giving an impression of the most delayed segment. Furthermore, parametric motion imaging, derived by over 800 virtual waveforms, is performed and shows LV regional contraction timings (LV wall motion).

This qualitative analysis of the LVMD is visualized on a color-coded static two-dimensional polar map (bull's eye) using the global T_{msv} as a timing reference (see Figure 2B right column in the original paper). Segments with a T_{msv} similar to the global T_{msv} are displayed in green indicating synchronized activation. Segments with earlier and later T_{msv} than global T_{msv} are coded in blue and red color indicating early and late mechanical activation, respectively. This combination of time-volume curve analysis and parametric motion imaging helps to identify the SLMA.

Systolic Dyssynchrony Index

The SDI is the predominant parameter for quantification of LV dyssynchrony by RT3DE. It is defined as the standard deviation of the time to minimal systolic volume (T_{msv}) in 16 LV segments under exclusion of the apical cap. It is normalized to the corresponding RR-interval and expressed as a percentage of the duration of the entire cardiac cycle rather than in



Basal Segments		Mid-ventricular Segments		Apical Segments	
1	basal anterior	7	mid-ventricular anterior	13	apical anterior
2	basal anteroseptal	8	mid-ventricular anteroseptal	14	apical septal
3	basal inferoseptal	9	mid-ventricular inferoseptal	15	apical inferior
4	basal inferior	10	mid-ventricular inferior	16	apical lateral
5	basal inferolateral	11	mid-ventricular inferolateral	17	apex
6	basal anterolateral	12	mid-ventricular anterolateral		

Figure 1.4 Left: Reproduction of the standardized left ventricular segmentation and nomenclature (bottom table) for cardiac imaging using a 17-segment model as proposed by the American Heart Association (AHA) writing group on myocardial segmentation and registration for cardiac imaging.[85] Right: Pictorial representation of the 17-segment model on the heart anatomy by Craig Skaggs taken from Sengupta and Narula.[86]

milliseconds, which allows comparison between different individuals. Whereby, low SDI values indicate non-significant LV dyssynchrony, higher values indicate increasing LV dyssynchrony. Reference values of the SDI in different individuals are given in **Table 1.5**. In a meta-analysis, the SDI has been evaluated as a highly reproducible echocardiographic dyssynchrony parameter providing accurate assessment of intraventricular LVMD with good interobserver, intraobserver and interinstitutional reliability and feasibility in 94 % [95 % confidence interval: 92-95 %] of the patients.[83,87] More importantly, the SDI is highly predictive of clinical (NYHA class) and echocardiographic (LVEF, LVESV) response to CRT.[84]

Table 1.5 Reference values of the SDI in percentage (%) ± standard deviation (SD) for different individuals.[83]

Individual	**SDI** ± SD in %
healthy person	2.7 ± 0.9
heart failure patient	9.8 ± 3.9
patient eligible for CRT	10.7 ± 3.6

1.3.3 Advantages and Limitations of Real-time Three-dimensional Echocardigraphy

Advantages of RT3DE

Today, RT3DE is a widely available echocardiographic technique powered by good validation against other methods for a reliable measurement of LV volumes, LV function, LVMD and LV wall motion. If compared against hemodynamic monitoring and magnetic resonance imaging (MRI), the major advantages are its non-invasive character, the waiving of radiation and its feasibility even after implantation of a cardiac device, which allows repetitive measurements without re-exposure to complications and radiation. A composite measurement of radial, longitudinal and circumferential contraction in a single angle-independent 3D assessment is not only close to the nature of intraventricular dyssynchrony as a 3D phenomenon,[81] it also provides a more comprehensive and reproducible evaluation of LVMD than other echocardiographic techniques.[88] The acquisition of a dynamic full-volume dataset is fast and ensures the execution even if the LV is enlarged. With the use of additional software, highly automated quantitative and qualitative analysis of global and regional LVMD in the entire LV as well as in each of the 16 LV segments can be performed fast and simultaneously in one single recording, which is another major benefit especially over tissue Doppler imaging (TDI).

Limitations of RT3DE

Besides all these outstanding advantages, a realistic review of the limitations of RT3DE has to be addressed. One main restriction is its low spatial and temporal resolution (40-50 ms) with a frame rate of only about 20-30 frames per second (actual volumes per second)[81] in contrast to TDI with a frame rate of about 100 frames per second.[89] The acquisition of a full-volume data

set requires a relatively stable RR interval to minimize translation artefacts between the four acquired volumes, which restricts the assessment of LVMD in the presence of arrhythmias. In addition, the method is not able to discriminate between active and passive motion. Although possible, scar tissue can be better visualized by MRI. The analysis of a RT3DE data set is dependent on image quality and re-production of reliable measurement is subject to a learning curve. Furthermore, no standardized protocol for the assessments and analysis of LVMD by RT3DE is available.

Some of these limitations are ascribed to the development and establishment of every new technique and can be diminished by further research and critical involvement with the new technology. By more specific adjustment of echocardiographic settings before the acquisition of a full-volume data set, the frame rate can be increased up to 70-80 frames per second. These adjustments include working with fundamental rather than harmonic imaging, minimizing the depth below the mitral and aortic valve, because visualisation of the atria is not needed for analysis of LVMD, and reducing the width of the volumetric data set if the LV is not that enlarged.[89]

1.4 Rationale of the Thesis

Heart failure is the final pathway of various heart diseases and is associated with high morbidity and mortality, especially in evidence of LV dyssynchrony. CRT targets LV dyssynchrony and revolutionized the treatment of advanced, drug-refractory HF patients by improving both, HF-related as well as overall morbidity and mortality. Despite ongoing research, 30 % of CRT recipients show no clinical and/or echocardiographic improvement after device implantation, the so called CRT non-responders. If other causes can be excluded, a discordant LV lead position can be responsible for non-response causing insufficient reduction or even worsening of dyssynchrony. The management of a discordant LV lead placement is challenging and so far no gold standard or guideline has been established. Optimization of CRT device settings, such as the AV- and/or VV-delay is an approved concept, preferably performed by 2D echocardiography and guided by parameters of systolic function rather than dyssynchrony. Considering LV dyssynchrony as a 3D phenomenon, optimization by RT3DE might be a more adequate and promising opportunity since it has been proven to be reliable for the assessment of LV dyssynchrony as adequate as other imaging techniques.

Therefore, the presented study in this thesis investigates, whether an individualized optimization of CRT device settings using LV dyssynchrony analysis by RT3DE provides a feasible and safe concept for the management of CRT non-responders with a discordant LV lead position. In addition, the study analyzes the extent of improvement in clinical and echocardiographic parameters in these patients. To the current knowledge, this approach has never been studied before.

2 Publication

Title	**Left ventricular wall motion analysis to guide management of CRT non-responders**
Authors	Bettina Nitsche, Charlotte Eitel, Kerstin Bode, Ulrike Wetzel, Sergio Richter, Michael Döring, Gerhard Hindricks, Christopher Piorkowski and Thomas Gaspar
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The publication was based on a clinical, prospective, single center feasibility study, which was not randomized, blinded or controlled. It was investigated at the Department of Rhythmology at the Heart Center Leipzig, Strümpellstraße 39, 04289 Leipzig (Germany) between October 2009 and March 2014. The responsible project manager was Mr. PD Dr. med. Christopher Piorkowski. There was no financial support by industry or third party.

2.2 Supplemental Material

The following section provides supplemental material referring to the original paper, also published and available online.

In- and Exclusion Criteria of the Study

Patients were included if they had received a CRT device according to current guidelines[6] for at least 6 months without clinical and echocardiographic improvement or with even worsening of HF symptoms. Patients had to be on optimal medical therapy and in sinus rhythm or permanent right ventricular stimulation with effective biventricular stimulation ($\geq$ 90 % of all ventricular beats). Prior to all investigations, written and verbal informed consent of the patient was required. Because of established investigations, procedures and materials used in this study, an ethics committee vote was not necessary. Patients were excluded if clinical factors could be identified that would confound CRT efficiency and potentially contribute to an impaired clinical and echocardiographic response after CRT implantation. Pregnant patients were excluded, too.

Inclusion criteria were defined as:

(1) CRT implantation $\geq$ 6 months to current guideline[6]
(2) optimal medical HF therapy
(3) no improvement or worsening of HF symptoms
(4) sinus rhythm or permanent right ventricular stimulation
(5) effective biventricular stimulation $\geq$ 90 %
(6) written & verbal informed consent

Exclusion criteria were defined as:

(1) atrial arrhythmias
(2) acute HF decompensation
(3) acute angina pectoris, myocardial infarction or coronary intervention $\leq$ 3 months
(4) stroke $\leq$ 6 months
(5) severe pulmonary or kidney disease
(6) non-transplant HF surgery
(7) current pregnancy

Definition of Response

Clinical, echocardiographic and composite (clinical and echocardiographic) response was evaluated three months after optimization of the individual LV wall motion by either re-programming of the VV-delay or implantation of a second LV lead using the data obtained from the evaluation at baseline and follow-up. The response criteria were chosen, considering those of large clinical CRT trials as a benchmark[90] and defined as follows.

Clinical response was defined by one of the following criteria indicating improved physical exercise capacity:

(1) reduction of NYHA class $\geq$ 1 class, or
(2) improvement of 6-MWD $\geq$ 10 % or
(3) improvement of pVO_2 $\geq$ 10 %.

Echocardiographic response was defined by one of the following criteria indicating reverse remodeling:

(1) improvement of LVEF $\geq$ 10 % or
(2) reduction of LVESV $\geq$ 15 % or
(3) reduction of LVEDD $\geq$ 10 %.

Composite response was defined as response in at least one clinical and echocardiographic parameter.

3 Discussion

The following chapter is complementary to the discussion in the original paper. It addresses additional aspects in context of the thesis which had not been mentioned due to the journal's constraints.

3.1 Selection of CRT Candidates and Prediction of Response

CRT is the main therapeutic fulcrum for a substantial proportion of HF patients but struggles with a constantly high non-responder rate.[51] Presence of LV dyssynchrony is the main target of CRT and substantial reduction has been shown predicitve for CRT response.[29,91] In the current guidelines a prolongation of the QRS complex duration up to 120-150 ms is used as an indicator of LV dyssynchrony and criteria for the selection of CRT candidates. However, QRS duration and LV dyssynchrony are only poorly correlated and the QRS width has been shown of limited predictive value for the response to CRT.[92–94] This might be due to the fact, that the QRS duration reflects LV electrical activation rather than LV dyssynchrony which is a mechanical phenomenon further modulated by intracellular and biomolecular mechanisms. This phenomenon has been observed in the studied non-responder population of this thesis, too. In the majority of patients (13/17), the narrowest QRS width could be achieved by different VV-delay re-programmings, but were accompanied by unfavourable higher values of the SDI as mentioned on page 783 of the original paper.

Consequently, efforts were made to evaluate novel parameters upon QRS width, which provide a better patient selection as well as lower the rate of non-responders and improve the prediction of response beyond current guidelines. In this context, the assessment of LVMD by echocardiography has been found highly predictive for CRT response[29,91] and several dyssynchrony parameters assessed by different echocardiographic modalities have been successfully investigated for the selection of appropriate CRT candidates.[29,95–97] So far, none of these parameters has been incorporated into the current guidelines since the PROSPECT study showed that they have only a modest sensitivity and specificity for the improvement of CRT patient selection

beyond current guidelines.[98] Regarding this lack of evidence, the analysis of LVMD by RT3DE and the SDI emerged as an alternative echocardiographic method for a better selection of patients and prediction of response. Moreover, LVMD analysis by RT3DE has not been part of the evaluation in the PROSPECT study. Numerous studies compared RT3DE against different echocardiographic methods, especially TDI[99–103] and found, that RT3DE is comparable or even superior in the assessment of LV volumes, LV function and intraventricular LVMD. Other studies compared the assessment of LVMD by RT3DE against MRI and nuclear imaging. It was found, that the measurements correlate well with the values obtained from gated myocardial perfusion single photon emission computed tomography.[104] If compared to MRI excellent correlation for the assessment of LV volumes, LV mass and LVEF in healthy persons as well as in patients with cardiomyopathy was found.[105–110] Nevertheless, a comparison between RT3DE and MRI for the quantification of LVMD is controversial. While one study showed good correlation for both methods, especially in the basal and mid-ventricular LV segments[111] another study reported lacking evidence of correlation, which had been attributed to the presence of different measures of dyssynchrony between MRI and RT3DE.[112] However, the SDI obtained by RT3DE has been shown predictive for acute hemodynamic response because of a good correlation with the percentual increase in dP/dt_{max} under biventricular pacing.[88,113–115] It had also predicted clinical and echocardiographic response to CRT on short- and long-term follow-up. In general, a high baseline SDI and an SDI improvement $\geq$ 20 % during follow-up are the prerequisites for the prediction of response.[88,103,115–118] In a meta-analysis, an SDI of 9.8 % appeared as a cut-off value for the prediction of response with a high sensitivity and specificity of 93 % and 75 %, respectively.[83] In the studied population of this thesis a median SDI of 11.3 % indicated that suitable CRT candidates beyond the standard guideline criteria have been investigated who have significant response potential if the aforementioned aspects are applied. However, the mismatch of the LV lead and the SLMA impeded a significant reduction of the SDI and therefore CRT response as supported by the unchanged median SDI of 11.0 % during effective biventricular stimulation. Only after the individual VV-delay optimization by RT3DE analysis a significant reduction of the LVMD could be achieved, with a 50 % lowering of the SDI in comparison to the baseline value. This has been the prerequisite for clinical and echocardiographic response.

3.2 Evaluation of the Optimal Site for LV Lead Implantation

CRT is meant to restore physiological LV contraction which provides better cardiac function and improvement of HF symptoms. The optimal resynchronization can be achieved if those LV segments are paced that are the last to contract (SLMA). The impact of this concordance

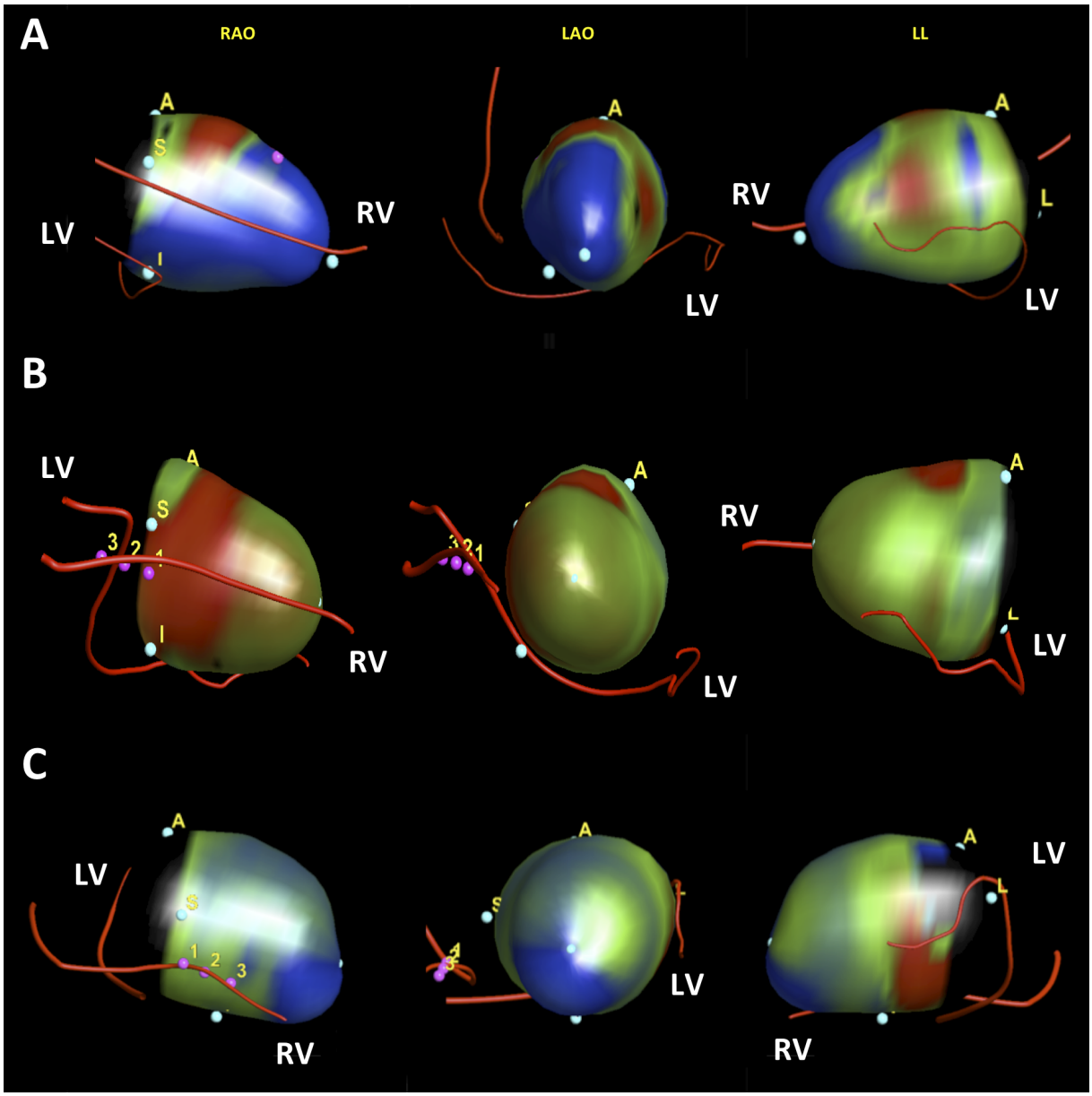

Figure 3.1 Integration of LV/RV lead position and LV wall motion – Examples of 3D LV models pictured in conventional projections showing individually different LV wall motion patterns in relation to the LV lead position. Pink dots with numbers denote integration landmarks, the red area indicates the site of latest mechanical activation (SLMA).

(**A**) Patient (No. 1) presenting with a *partly-concordant* LV lead at a mid-ventricular lateral position and multiple sites of latest mechanical activation on the anterior and lateral LV wall during intrinsic AV-nodal conduction.

(**B**) Patient (No. 4) presenting with a *discordant* LV lead at a mid-ventricular inferolateral position and site of latest mechanical activation on the anteroseptal LV wall during intrinsic AV-nodal conduction.

(**C**) Patient (No. 8) presenting with a *concordant* LV lead position and sites of latest mechanical activation on the basolateral LV wall during intrinsic AV-nodal conduction.

between the SLMA and the LV lead position has been intensively studied regarding outcome and response to CRT. The relationship was mostly investigated with different echocardiographic methods rather than RT3DE, but a concordant LV lead position always provided better clinical (improved NYHA class, 6-MWD, pVO_2, QoL) and echocardiographic (improved LVEF, LVESV, LVEDV) outcome with greater LV reverse remodeling,[57,59,66,97,119–123] lower rates of HF hospitalization and better prediction of long-term survival.[57,66,123] These mainly retrospectively assessed data later got reconfirmed by the TARGET study, a prospective trial using two-dimensional speckle tracking imaging.[59]

RT3DE provides a more comprehensive evaluation of the SLMA with better reliability and reproducibility than other echocardiographic methods.[124,125] In one sophisticated study,[126] a concordant LV lead placement was based on the preliminary analysis of the SLMA by RT3DE, which provided high response rates on mid-term follow-up and promising results even on long-term. The evaluation of the SLMA with RT3DE and subsequent concordant LV lead implantation was available in 37 of 38 (97 %) and 34 of 37 (92 %) patients, respectively. After a six months follow-up, highly significant changes in NYHA class, 6-MWD, pVO_2, LVEF (24 % vs. 39 %), LVESV (140 ml vs 103 ml) and SDI (13.7 % vs. 4.2 %) as compared with baseline were achieved providing excellent clinical (91 %) and echocardiographic (81 %) response accompanied by extensive LV reverse remodeling. Patients with a discordant LV lead position ($n = 3$) showed slight clinical but no significant echocardiographic improvement. Hard clinical endpoints such as HF hospitalization, death, assist device implantation, or heart transplantation were only experienced by one patient with a concordant LV lead position during further long-term follow-up (27 months).

Regarding these findings, RT3DE can not only be used for the accurate identification of the SLMA as the optimal site of LV lead implantation prior to CRT procedure, it can also be applied in CRT non-responders to evaluate the presence of a discordant LV lead position. **Figure 3.1** provides the 3D integration of exemplary cases showing a partly-concordant, discordant and concordant LV lead position in relation to LV wall motion as found in the study of this thesis. Subsequently, it can be utilized for the guidance of the second LV lead implantation if other options fail. The presented concept by Döring et al.[126] has been investigated by the same working group at the Heart Center Leipzig and served as a scientific idea for the rationale of this thesis.

3.3 Optimization of the CRT Device Programming

Modern CRT devices allow re-programming of different parameters after implantation. In clinical practice, optimization focuses on the AV/VV-delay time intervals. Empirically, they are programmed to 120 ms and biventricular simultaneous activation, respectively.[74] However, an individualized optimization of either the AV- or the VV-delay as well as a combined approach[71,72] have been superior to the empirical default programming, showing more pronounced improvement of LV hemodynamics, clinical and echocardiographic response on short-[45,127–129] as well as on long-term follow-up.[130–134] Echocardiography is the preferred method in clinical routine. Whereas Doppler echocardiography seems to be the best for AV-delay optimization, LV dyssynchrony analysis derived by RT3DE can guide VV-delay optimization. A combined approach using Doppler echocardiography derived aortic velocity time integral (AoVTI) and RT3DE derived SDI, respectively, achieved both, acute (24h after implantation)[135] and chronic (3 months)[136] improvement of LVEF, LV volumes and LVMD. The improvement was achieved subsequently to AV-delay optimization and followed by an improvement of LVMD especially after VV-delay optimization. Regarding the extent of acutely changed LVMD predicting improved response on long-term follow-up,[91] RT3DE is not only the preferred echocardiographic method for accurate assessment of LVMD it may also be a powerful tool to guide VV-delay optimization. This could revolutionize the optimization of CRT devices, because no gold standard has been established, so far. In real-world clinical practice, however, routine adjustment of the AV/VV-delay in every CRT recipient is performed infrequently[74] and controversially discussed since randomized trials[134,137,138] and a meta-analysis[139] had shown no or only a neutral effect of individual over empiric programming on outcome. However, in selected patients such as with a suboptimal LV lead position due to anatomy-limited LV lead delivery or extensive scar burden near the optimal pacing site as well as in CRT non-responders, an individually tailored optimization of CRT device settings is an useful feature to achieve optimal resynchronization and to enhance outcome. This is of additional value, because the optimal settings vary over time.[140] This aspect is supported by the results of the RESPONSE-HF trial, in which individually tailored VV-delay optimization with sequential biventricular pacing in CRT non-responders resulted in a 28.5 % higher conversion into responders after 6 months compared to maintenance of empiric programming.[141]

As proven by the aforementioned statements, VV-delay optimization guided by RT3DE LV dyssynchrony analysis has never been studied in CRT non-responders before. In light of the current evidence and the presented results of this study, management of a discordant LV lead by RT3DE was feasible and effective in inducing final CRT response. It also seems to be a promising technique to counter the scientific gap.

4 Summary

DISSERTATION

in partial fulfillment of the requirements for the degree of

Doctor medicinæ
(Dr. med.)

Left ventricular wall motion analysis to guide management of CRT non-responders

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submitted in:	June 2017

Heart Failure is the final pathway of various heart diseases and associated with high rates of morbidity and mortality. Due to demographic aging and improved survival after cardiac events, a rising number of new HF cases will be diagnosed in the near future, being responsible for one of the major public health challenges of the 21st century. Over the last decade, CRT a device-based, non-pharmacological therapy option, targeting LVMD revolutionized the treatment of advanced, drug-refractory HF patients, improving both HF-related as well as overall morbidity and mortality. However, and despite ongoing research, 30 % of patients show no improvement after implantation of a CRT device, the so-called CRT non-responders. Considering the side-effects of this invasive therapy and health economic aspects, CRT is a risky and costly business in these patients. The reasons for non-response are various. Assuming a correct patient selection

by current guidelines, stable sinus rhythm with effective biventricular device stimulation $\geq$ 90 % and further adjustment of guideline-directed medical therapy, a mismatch between the site of LV lead implantation and the SLMA on the left ventricle can cause for non-response. Insufficient reduction or even worsening of LVMD are two of the main pathological equivalents related to such a discordant LV lead position. Nevertheless, the LV lead is empirically implanted into a inferolateral mid-ventricular vein of the coronary sinus and the evaluation of LVMD or the pattern of LV wall motion prior to implantation of a CRT device is not recommended by the current guidelines. Optimization of CRT device settings is an approved concept for the management of CRT non-responders. Preferentially it is performed by two-dimensional echocardiography and guided by parameters of systolic function rather than LVMD. Considering LV dyssynchrony as a three-dimensional phenomenon, a three-dimensional approach guided by a dyssynchrony parameter or a combination of both parameters might be a more adequate and promising concept. With the development of RT3DE, a reliable and powerful non-invasive imaging technology for the accurate and radiation-independent assessment of LVMD and LV systolic function became available, which not only respects the three-dimensional nature of LVMD but also outperformed other imaging techniques.

Therefore, this doctoral thesis investigated whether an individualized optimization of CRT device settings using LVMD analysis by RT3DE provides a feasible and safe concept for the management of CRT non-responders due to a discordant LV lead position. As an additional research question, the patterns of LV wall motion, the LV lead position and their relationship to each other are scrutinized. To answer these questions, a prospective clinical feasibility study was conducted at the Heart Center Leipzig in the Department of Rhythmology between 2009 to 2014. Two-hundred and forty-six CRT outpatients were screened for non-response due to a discordant LV lead. An overall non-responder rate of 75 patients (30 %) was found, which is in line with reported data in literature. Seventeen of those patients had no obvious reason for non-response and were included in the study. Three-dimensional data of fluoroscopic rotation scan and RT3DE were integrated to analyze the individual LV wall motion in respect to the LV lead position. Optimization was guided by the SDI and LVEF during different VV-delay programming. If re-programming failed, implantation of a second LV lead was performed. As a result, a discordant or partly concordant LV lead position was found in nearly all patients (16/17, 94 %), which contributed to an unchanged baseline amount of LV dyssynchrony with either CRT on or off (SDI 11.3 % vs. 11.0 %; $p = 0.744$). Individually different LV wall motion patterns could be identified with two patients having multiple SLMAs. In general, the most delayed segments were widespread affecting a median of four LV segments (24 % of the surface). In the majority of patients (76 %) VV-delay re-programming achieved better resynchronization, 4/17 patients needed implantation of a second LV lead. After a three months follow-up, one patient received implantation of a left ventricular assist device and one patient

died. Nevertheless, significant improvement of NYHA functional class (1 class; $p = 0.004$), pVO_2 (10 vs. 13 ml/min/kg; $p = 0.008$), LVEF (27 % vs. 39 %; $p = 0.003$) and SDI (11.0 % vs. 5.8; $p = 0.02$) was observed. Clinical and echocardiographic response was found in 77 % and 59 %, respectively. Long-term follow-up in these 15 patients over a median of 45 months revealed two further deaths. Median LVEF remained stable at 38 % (IQR 28-41 %, $p = 0.721$). Overall, 36 hospitalizations with two per person and a time to first hospitalization for any reason and for HF of 14.5 months (IQR 5.5-22.5) and 17.5 months (IQR 11-30) occurred, respectively.

In conclusion, this tailored optimization concept revealed to be feasible and safe for the management of CRT non-responders with a discordant LV lead position. Leading to significant clinical and echocardiographic improvement with even good results on long-term is of valuable interest for the clinical physician. Despite these positive findings further research in a larger cohort of CRT non-responder patients is needed to test the concept for its solidity in a real world scenario. Since 2016, the presented concept is successfully implemented into daily clinical routine for the management of CRT non-responders at Heart Center Dresden.

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Contribution of Authors

Title	**Left ventricular wall motion analysis to guide management of CRT non-responders**
Bettina Nitsche (lead author)	Study protocol, screening, investigations at baseline & follow-up statistical analysis, writing and correction of the manuscript
Christopher Piorkowski	Project idea, study protocol, implantation of the second LV lead, reading and correction of the manuscript
Gerhard Hindricks	Reading and correction of the manuscript
Kerstin Bode Ulrike Wetzel Charlotte Eitel	Real-time Three-dimensional Echocardiography
Sergio Richter Michael Döring Thomas Gaspar	Implantation of second LV lead

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Ulrike Wetzel

Sergio Richter

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Gerhard Hindricks

Christopher Piorkowski

Thomas Gaspar

Declaration of Authorship

I hereby certify, to the best of my knowledge and belief, that the work presented in this thesis is entirely the result of my own original research. No third-party received direct or indirect payment or benefit-in-kind for any services which are related to the content of this thesis. The work on this thesis was done wholly or mainly while in candidature for a research degree at Leipzig University. It has not been submitted, either in part or whole, for a degree at this or any other university. All references, verbatim extracts and sources of information have been quoted. All main sources of help have been acknowledged. Current legal requirements, regarding the approval of clinical studies as well as the provisions of the Animal Welfare Law, the German Genetic Engineering Act and general data protection, have been observed. I assure, that I know and comply to the principles on safeguarding good scientific practice given by the statutes of Leipzig University.

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Bettina Kirstein Dresden, May 28, 2017

Curriculum Vitæ

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List of Publications

I Nitsche B, Eitel C, Bode K, Wetzel U, Richter S, Döring M, Hindricks G, Piorkowski C, and Gaspar T. Left ventricular wall motion analysis to guide management of CRT non-responders. Europace 2015;17:778–786

II Döring M, Braunschweig F, Eitel C, Gaspar T, Wetzel U, Nitsche B, Hindricks G, and Piorkowski C. Individually tailored left ventricular lead placement: lessons from multimodality integration between three-dimensional echocardiography and coronary sinus angiogram. Europace 2013;15:718–727

I confirm that parts of paper **I** have been presented as poster [1] or presentation [2] as indicated below. Paper **II** is not part of the thesis but has been developed while being part of the study group during the doctorate candidature.

Leipzig Course LC11 2010 | Leipzig, Germany [2]
Management of CRT non-responders: Interesting case studies (German)

77th Annual Meeting of the German Cardiac Society 2011 | Mannheim, Germany [2]
3D analysis of LV contraction pattern and optimization of LV lead position in CRT non-responders (German)

HRS Scientific Sessions 2011 | San Francisco, USA [1]
Analysis and optimization of Cardiac Resynchronization Therapy non-responders using 3-dimensional real-time echocardiography and non-invasive rotational angiography (English)

EHRA Europace 2011 | Madrid, Spain [2]
Optimization of CRT non-responders: A 3-dimensional approach using realtime 3D-TEE and rotational angiography (English) – Nominated for Young Investigator Award

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Bettina Kirstein Dresden, May 28, 2017

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