An electrocardiographic study in the patient eligible for cardiac resynchronization therapy

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Cover: median averaged left bundle branch block ECG (limb leads)

Ad tempus vitae

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An electrocardiographic study in the patient eligible for cardiac resynchronization therapy

Towards a better selection and response in the individual patient

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List of abbreviations

3D: three dimensional

ACC: American College of Cardiology

AF: atrial fibrillation

AHA: American Heart Association

AV: atrioventricular

CRT: cardiac resynchronization therapy

BV: biventricular

ECG: electrocardiogram

EDD: end diastolic diameter

EF: ejection fraction

EP: electrophysiology

ESC: European Society of Cardiology

ESD: end systolic diameter

HF: heart failure

HRS: Heart Rhythm Society

LAHB: left anterior hemiblock

LBBB: left bundle branch block

LPHB: left posterior hemiblock

LV: left ventricular / left ventricle

LVEF: left ventricular ejection fraction

NYHA: New York Heart Association Functional Classification

OMT: optimal medical treatment

QRSD: QRS duration

RV: right ventricular / right ventricle

SF: septal flash

SR: sinus rhythm

TTE: transthoracic echocardiogram

VCG: vectorcardiogram

VO2: maximal oxygen uptake

Part I

General Introduction

1. A synchronized heart beat

In healthy individuals, the mechanical contraction of the heart consists of an atrial contraction, followed by **a homogeneous contraction of both left (LV) and right ventricles (RV).** This synchronized contraction is controlled by the electrical conduction system of the heart (Figure I.1). During sinus rhythm, each heart beat is triggered by an electrical impulse travelling from the sinus node, through the atria causing an atrial contraction. After propagating through the atria, the electrical impulse reaches the atrioventricular node, where a delay in the electrical conduction occurs. This conduction delay in the atrioventricular node ensures the ventricles to have the necessary time to be filled with blood by the atria. After this atrioventricular delay, both left and right ventricles become activated through the electrical conduction system consisting of the His bundle, right and left bundle branches and eventually the Purkinje fibers. The infranodal conduction system allows fast electrical propagation, causing the right and left ventricle to depolarize and contract in a homogenous way. This fast and synchronized ventricular contraction causes an efficient ejection of blood towards the body (in case of the LV) and lungs (in case of the RV). After the repolarization of the ventricles, a new heart beat can occur by a new pulse form the sinus node[1].

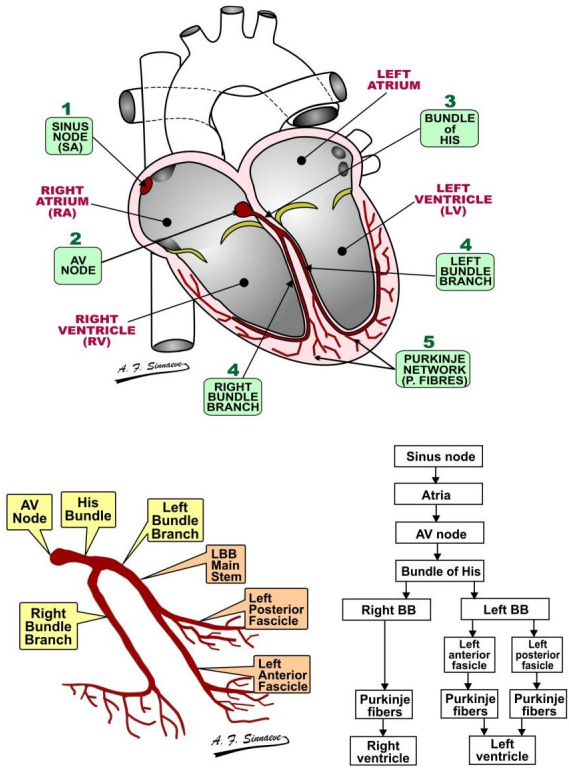

Figure I.1: *The electrical conduction system of the heart. (Reproduced with courtesy from "ECG from Basics to Essentials", Stroobandt et al., Wiley-Blackwell, 1st edition 2016).*

2. Registration of the electrical heart activity

The electrical activation of the heart can be registered by an electrocardiogram (ECG), using external skin electrodes. Traditionally, the electrical activation of the heart is registered by twelve electrodes (leads) placed on predefined anatomical landmarks. As such, the electrical activation of the heart can be visualized graphically by waves and segments, matching the electrical activation of the different parts of the heart (Figure I.2). The first wave, called the P-wave refers to electrical activation of the atria. The PR-interval, an iso-electric segment

occurring immediately after the P-wave, matches the conduction delay of the atrioventricular node. **The main deflection on the ECG, is called the QRS wave and represents the electrical activation of both ventricles.** At last, the repolarization of the ventricles is recorded by the ST-segment and T-wave on the surface ECG[1].

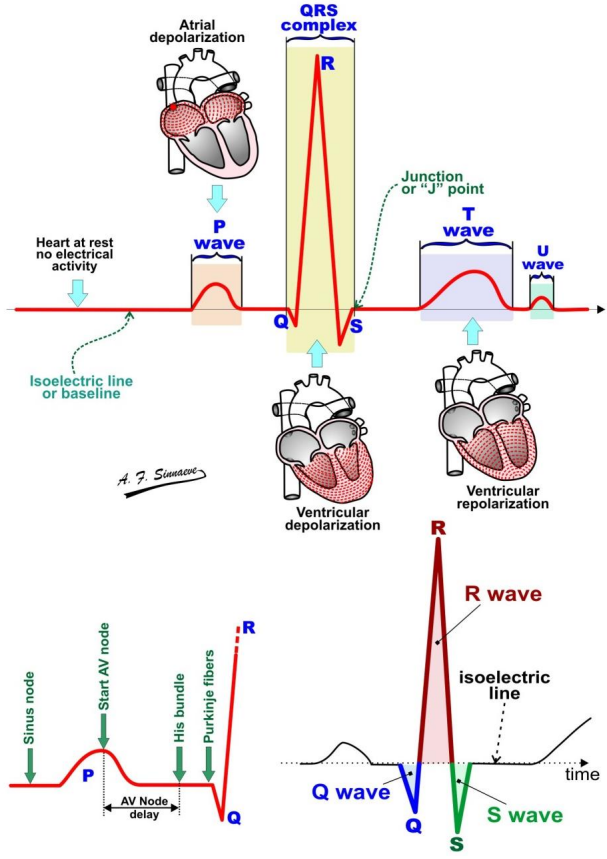

Figure I.2: *The electrical activation of the heart registered by the electrocardiogram (ECG). (Reproduced with courtesy from "ECG from Basics to Essentials", Stroobandt et al., Wiley-Blackwell, 1st edition 2016).*

3. Prolonged QRS duration: a marker of delayed ventricular activation

Electrical propagation delay in the ventricles can be caused by an infrahisian block, block in either the right or left bundle branch, or delayed cell to cell conduction. As the QRS complex represents the electrical activation of the ventricles, **delayed ventricular activation is characterized by a prolonged QRS duration (QRSD)**[1]. Wilson and colleagues defined, in their historical experiments in dogs, the upper limit of normal ventricular conduction as a QRSD <120ms[2]. Nowadays, it is accepted that normal conduction in adults is characterized by narrow QRSD <110ms, whereas QRSD ≥120ms is frequently used to define complete block in the bundle branches. A **prolonged QRSD is often referred to as electrical dyssynchrony,** as delayed activation of the ventricles can cause a less homogeneous cardiac contraction which may lead to impaired cardiac function. In fact, a prolonged QRSD is a marker of adverse outcome with an increased risk of pacemaker implantation, heart failure, cardiovascular and all-cause mortality[3-6].

On cellular level, cardiac conduction velocity delay finds its origin in fast response cells, typically located in the atrial and ventricular myocardium and His- and Purkinje system. These cells are characterized by a strong negative resting potential (between -80 and -90mV) and a high density of fast acting sodium channels. Influx of sodium ions through these channels causes fast depolarization during phase 0 of the action potential. The depolarization time of cardiac tissue is related to the maximal slope (dV/dt max) and amplitude of the action potential during phase 0. Under certain pathologic circumstances (ischemia, acidosis, hyperpotassemia,..) the resting potential of myocardial cells can become less negative and thereby causing a part of the sodium channels to become inactivated. As such, less sodium channels are available to allow influx of sodium ions as reaction on a depolarizing trigger. The maximum depolarization velocity and amplitude of the action potential decrease and conduction velocity within the myocardium becomes delayed. A second determinant of

conduction velocity is the junctional resistance between cells (gap junctions). The gap resistance is in normal circumstances low. However increasing calcium concentrations and decrease of intracellular pH, conditions typically occurring for ischemia or cellular hypoxia, cause an increase in gap resistance and contribute to a lower conduction velocity[1]. Gap junctions in cardiac cells consist of different connexin proteins and variations in connexin (mainly connexin 40 and 43) have been reported to be associated with cardiomyopathy, prolonged QRS duration and bundle branch bock[7, 8]. These findings suggest that prolonged QRS duration and even bundle branch bock can be modulated by genotype.

4. Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) involves the **electrical stimulation of both ventricles, so-called biventricular (BV) pacing** (Figure I.3). One of the earliest experiments with BV pacing was conducted in 1971 by Gibson et al. In patients, who underwent replacement of the aortic valve by a Starr-Edwards aortic valve prosthesis, "the rate of movement of the ball of the prosthesis" (ball travelling time) was greater when stimulating both ventricles simultaneously[9]. In 1994, Cazeau, a French cardiologist, implanted the first four chamber pacemaker in a 54-year old patient with severe congestive heart failure[10]. The patient improved markedly with "a weight loss of 17 kilograms, disappearance of peripheral edema and improvement in NYHA (New York Heart Association Functional Classification), from class IV to II". In 2005, CRT was included in the guidelines of the European Society of Cardiology (ESC) as recognized treatment of heart failure[11]. Currently, over 50 000 CRT devices are implanted in Europe[12].

With CRT, the RV is stimulated by a transvenously placed pacing electrode in the apex or septum of the RV. The LV is stimulated by a pacing electrode transvenously inserted in the

coronary sinus, preferentially in a posterior or posterolateral branch. Both ventricles can be paced simultaneously ("simultaneous biventricular pacing") or with a delay **to achieve the most synchronized contraction** ("sequential biventricular pacing"). Additionally, CRT can restore or secure the synchrony between the atrium and ventricles (AV-synchrony), by placing an atrial lead transvenously in the right atrium. To allow biventricular pacing with AV synchronization, the ventricular stimulation should occur before the intrinsic contraction of the ventricles, which can be achieved by programming a short sensed or paced atrioventricular delay[1, 13].

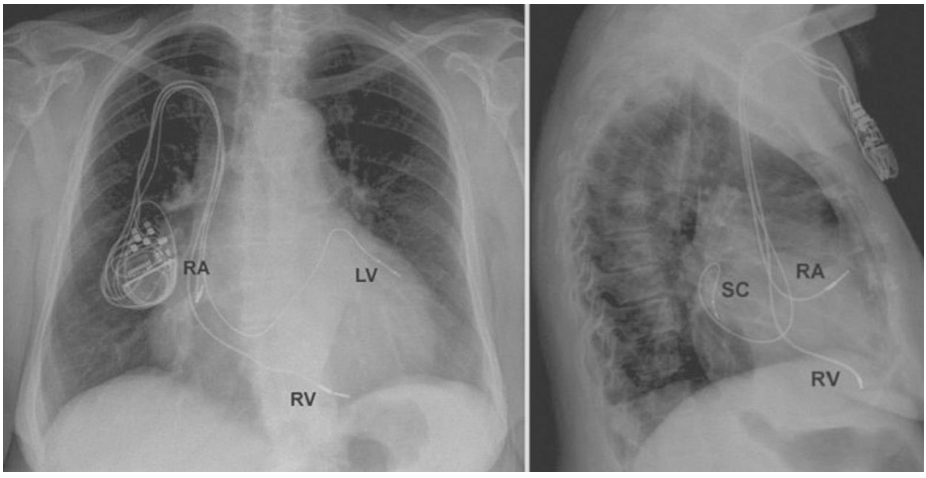

Figure I.3: *Anteroposterior and lateral chest radiography in a patient with a CRT pacemaker. RA: right atrial lead. RV: right ventricular lead. LV: left ventricular lead. (Reproduced with courtesy from "ECG uit of in het hoofd", Andries et al., Garant, 6th edition 2017).*

CRT has initiated a new era in the treatment of patients with heart failure. In the past decade, multiple randomized clinical trials have showed that CRT improves morbidity, functional status, quality of live and reduces hospitalizations and mortality in heart failure patients with prolonged QRSD[14-24]. Table I.1 gives an overview of the most important randomized clinical trials in the field of CRT. The large CRT trials included both patients with ischemic and non-

ischemic heart disease (Table I.1). The initial results from the COMPANION-trial showed similar outcome for both groups of patients in terms of all-cause mortality when comparing CRT-D (biventricular pacing with ICD) to optimal medical treatment[17]. However, Gasparini showed as first that reverse remodeling after CRT was greater in patients with non-ischemic cardiomyopathy compared to patients with ischemic cardiomyopathy[25]. This difference has been explained by the amount and transmurality of scar contributing to a lesser degree of CRT response in patients with ischemic cardiomyopathy[26]. When comparing the effect of CRT-P (biventricular pacing only) versus CRT-D, it seemed that only ischemic patients benefited from a CRT-D. This is explained as the arrhythmogenic substrate contributes more to all-cause mortality in patients with ischemic cardiomyopathy[27]. As such it becomes clear that the underlying heart disease impacts CRT efficacy with greater CRT response (in terms of reverse remodeling) in non-ischemic patients and a more prominent role for CRT with ICD backup (CRT-D) in patients with ischemic heart disease. Except for ischemic and non-ischemic cardiomyopathy, the effect of CRT in other cardiomyopathies is less well investigated. In patients with chronic RV-pacing and heart-failure upgrade to CRT might be considered according to recent pacing guidelines[28]. In patients with congenital heart disease the most frequent reason for CRT implant is chronic ventricular pacing rather than the presence of LBBB. The best CRT response in these patients is achieved in patients with a systemic left ventricle and chronic RV pacing who undergo upgrading to CRT[29]. The role of CRT in patients with chemotherapy-induced cardiomyopathy[30] or Chagas disease[31] remains less well established.

The precise mechanisms by which CRT improves patients with heart failure are yet incompletely understood, but probably multiple mechanisms might explain the clinical benefit of CRT. Potential mechanisms of effect include correction of inter- and intraventricular mechanical dyssynchrony, atrioventricular dyssynchrony, mitral regurgitation, diastolic

ventricular interaction and long-term effects on myocardial remodelling and prevention of bradycardia[32-35]. The recruitment of septal work (which is reduced in pure LBBB) may also be an important mechanism as part of "remodeling"[36]. Finally, CRT may attenuate or reverse the potential deleterious effects of RV pacing[37, 38].

Table I.1: Overview main CRT trials between 2000 and 2010.

Trial	Year	N	Age (yrs)	Females (%)	Study design	QRSD cutoff (ms)	NYHA	Etiology	LVEF (%)	SR/AF	Primary endpoint	Outcome
MUSTIC-SR	2001	58	63±10	25	CRT-P on versus off	≥150	III	Isch. and nonisch.	≤35	SR/AF	6-min walk distance	Favors CRT
MUSTIC-AF	2001	43	63±11	/	CRT-P versus VVI	≥200	III	Isch. and nonisch.	≤35	AF	6-min walk distance	Favors CRT
MIRACLE	2002	453	64±11	32	CRT-P on versus off	≥ 130	II/IV	Isch. and nonisch.	≤35	SR	NYHA Quality of live 6-min walk distance	Favors CRT Favors CRT Favors CRT
PATH CHF	2002	42	60±7	50	CRT-P on versus off	≥120	III/IV	Isch. and nonisch.	/	SR	Peak VO2 6-min walk distance	Favors CRT Favors CRT
MIRACLE ICD	2003	369	67±10	23	CRT-D on versus off	≥130	III/IV	Isch. and nonisch.	≤35	SR	NYHA Quality of live 6-min walk distance	Favors CRT Favors CRT No significant benefit
CONTAK CD	2003	490	67±11	23	CRT-D on versus off CRT-P on versus off	≥120	II/III/IV	Isch. and nonisch.	≤35	SR	Progression of heart failure (mortality, heart failure hospitalisation, ventricular arrhythmia)	No significant benefit No significant benefit
MIRACLE ICD II	2004	186	63±12	11	CRT-D on versus off	≥130	II	Isch. and nonisch.	≤35	SR	Peak VO2	No significant benefit
COMPANION	2004	1520	67	33	CRT-P versus OMT CRT-D versus OMT	≥120	III/IV	Isch. and nonisch.	≤35	SR	All-cause mortality or hospitalization	Favors CRT Favors CRT
CARE-HF	2004	813	67	26	CRT-P versus OMT	≥120	III/IV	Isch. and nonisch.	≤35	SR	All-cause mortality or unplanned cardiovascular hospitalization	Favors CRT
REVERSE	2008	610	62	20	CRT-D on versus off	≥120	I/II	Isch. and nonisch.	≤40	SR	Clinical composite score improvement	No significant benefit
MADIT-CRT	2009	1820	65±11	25	CRT-D versus ICD	≥130	I/II	Isch. and nonisch.	≤30	SR	All-cause mortality or nonfatal heart failure event	Favors CRT
RAFT	2010	1798	66±9	27	CRT-D versus ICD	≥120	II/III	Isch. and nonisch.	≤30	SR/AF/Paced	All-cause mortality or heart failure hospitalization	Favors CRT

N= number of patients. SR: sinus rhythm. AF: atrial fibrillation. CRT-P/CRT-D: cardiac resynchronization therapy pacemaker/defibrillator ICD: implantable cardioverter defibrillator. VVI: ventricular non tracking pacing modus. NYHA: New York Heart Association Functional Classification. Isch.: ischemic. Nonisch.: nonischemic, VO2: maximal oxygen uptake. OMT: optimal medical treatment. Yrs: years. QRSD: QRS duration.LVEF: Left ventricular ejection fraction.

5. Current selection criteria of CRT candidates

As can be deduced from Table I.1, QRSD has been a major enrollment criterion in clinical trials demonstrating the benefit of CRT. In these trials QRSD thresholds varied between 120-200ms and the likelihood of CRT response increases with wider QRSD[17, 21, 39]. Based on these findings, **QRSD is considered a major selection criterion** and international guidelines favor wide QRSD to implant CRT (Table I.2)[40, 41].

Interestingly, QRS morphology was never a primary selection criterion in large CRT trials. However, its role in the selection of CRT candidates has been established by subanalyses of the MADIT-CRT, REVERSE and RAFT trial showing the largest benefit of CRT occurring in patients with left bundle branch block (LBBB)[42-45], whereas patients with right bundle branch block (RBBB) or non-specific intraventricular conduction delay (NIVCD) showed only minor or even absent benefit from CRT[43, 45, 46]. Given the higher benefit of CRT in patients with LBBB, international **guidelines specify separate recommendations for patients with LBBB and non-LBBB morphology** (Table I.2) [40, 41].

Table I.2: 2016 ESC recommendations for cardiac resynchronization therapy implantation in patients with heart failure[40]

Class	Level	Indication
I	A	CRT ***is recommended*** for symptomatic patients with HF in sinus rhythm with a ***QRS duration ≥150ms*** and ***LBBB QRS morphology*** and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.
I	B	CRT ***is recommended*** for symptomatic patients with HF in sinus rhythm with a ***QRS duration of 130–149ms*** and ***LBBB QRS morphology*** and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.
IIa	B	CRT ***should be considered*** for symptomatic patients with HF in sinus rhythm with a ***QRS duration ≥150ms*** and ***non-LBBB QRS morphology*** and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.
IIb	B	CRT ***may be considered*** for symptomatic patients with HF in sinus rhythm with a ***QRS duration of 130–149ms*** and ***non-LBBB QRS morphology*** and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.
III	A	CRT is ***contra-indicated*** in patients with a ***QRS duration < 130ms***.

ESC: European Society of Cardiology. Class: class of recommendation. level: Level of evidence. HF: Heart failure. LBBB: left bundle branch block. LVEF: left ventricular ejection fraction. OMT: optimal medical treatment

6. Dyssynchrony: what's in a name?

As "new" diseases emerge, new therapeutics and techniques are developed and subsequently the optimal candidates need to be defined. Although large CRT trials demonstrated an overall benefit of CRT, up to 30% of the currently selected patients do not achieve the expected CRT response in clinical practice[28, 47, 48]. Given the increasing group of heart failure patients requiring CRT and the limited financial resources, research to better select patients and increase CRT response has gained a lot of interest.

As CRT aims to resynchronize the heart, cardiac dyssynchrony must first be present. In essence, **cardiac dyssynchrony refers to the lack of a homogeneous cardiac contraction**[49, 50]. However, the term dyssynchrony covers many different meanings. Cardiac dyssynchrony can be divided according to the anatomic level at which the dyssynchrony occurs[1]. Three categories are generally distinguished: atrioventricular (AV) dyssynchrony which refers to an unfavorable timing of the atrial and ventricular contraction. Interventricular dyssynchrony refers to a desynchronized activation of the left versus right ventricle. And last, intraventricular dyssynchrony is used to describe desynchronized contraction of different segments of the ventricular wall (generally applied to the left ventricle). Alternatively, dyssynchrony is often divided according to the underlying cause or pathophysiology. Depending whether electrical propagation problems or mechanical contraction heterogeneity are causing inhomogeneous cardiac contraction, the terms electrical and mechanical dyssynchrony are applied.

No consensus exists on how cardiac dyssynchrony should be best measured or quantified. Whereas electrical dyssynchrony is generally assessed by the duration of the QRS complex (QRSD), less consensus exists on how to optimally assess and quantify mechanical dyssynchrony. Several echocardiographic indices to assess mechanical dyssynchrony have been applied in the last decades[49]. Two echocardiographic techniques are frequently used: velocity imaging by tissue Doppler and strain imaging by speckle tracking. In essence, velocity imaging by tissue Doppler analyses differences in time to peak systolic velocity (not necessarily contraction) among different regions of the LV. Dyssynchrony is then defined as large differences in peak velocities between different LV segments. Similarly, speckle tracking techniques use differences in timing of regional peak strains (deformation) to qualify and quantify mechanical dyssynchrony. Single center studies, assessing mechanical dyssynchrony by echocardiography parameters, seemed promising and claimed a better selection of CRT candidates[51, 52]. However, the multicenter PROSPECT trial showed no additional clinical

benefit of these echocardiographic (tissue Doppler analyses) dyssynchrony assessments and was hampered by large observer variability among experts and centers[48]. Besides these results of the PROSPECT trial, other multicenter studies have shown that mechanical dyssynchrony alone is not the sole determinant of CRT response. Four randomized controlled trials (LESSER-EARTH, EchoCRT, RhetinQ and NARROW CRT) evaluated the effect of CRT in patients with narrow QRSD but with echocardiographic evidence for mechanical dyssynchrony[53-56]. Three of the four trials (LESSER-EARTH, EchoCRT, RhetinQ) did not show a benefit CRT compared to the control group[53, 55, 56]. Two studies (ECHO-CRT and LESSER-EARTH) were even stopped early due to safety concerns and futility[55, 56]. Based on the aforementioned trials, echocardiographic assessment of dyssynchrony is currently not considered in guidelines as CRT-selection parameter. Several explanations have been proposed for the poor predictive results of echocardiographic dyssynchrony assessment: large inter-observer variability, lack of validation of techniques on well-defined substrates, no differentiation between electrical and mechanical dyssynchrony, differences in cause-relationship of dyssynchrony and LV dysfunction[49]. So, it remained largely unclear what was exactly measured, and how it had to be measured.

Indeed, one of the key issues in the field of dyssynchrony is that **electrical dyssynchrony and mechanical dyssynchrony do not necessarily represent the same substrate or pathophysiology**[49]. Unfortunately the terms electrical and mechanical have been used interchangeably, or simplified to a common denominator “dyssynchrony”. Most patients with electrical dyssynchrony will also display mechanical dyssynchrony due to the altered ventricular activation caused by the conduction delay. However, this mechanical dyssynchrony may cover a wide heterogeneity in ventricular activation patterns depending on the location of the conduction delay (e.g. LBBB versus RBBB)[1], the anatomy of the bundle branches and the myocardial substrate. Conversely, mechanical dyssynchrony can occur independently of

electrical propagation problems due to myocardial scarring or regional myocardial dysfunction. Indeed, several studies have been conducted in patients with narrow QRSD ("no clear electrical substrate") but with echocardiographic evidence for "mechanical dyssynchrony"[53-56].

7. Left bundle branch block, towards the optimal CRT substrate…

Given the high CRT response rates among LBBB patients, CRT has triggered renewed interest in LBBB pathophysiology. In patients with LBBB, the RV is activated first by the (intact) right bundle branch. As the LV is no longer activated by the left bundle branch, electrical activation spreads from the right ventricle, through the septum towards the left ventricle. This right to left septal conduction does not occur by Purkinje fibers, but instead by slow cell to cell conduction. This results in a delayed activation of the LV, with a contraction pattern spreading from the septum towards the LV lateral wall. As the interventricular septum is activated before the LV lateral wall, coordinated ventricular contraction is lost leading to a decrease in LV ejection fraction and might eventually cause heart failure[1, 57-59]. The electrical conduction delay by LBBB, induces a dyssynchronous ventricular contraction, which is more amenable by CRT when compared to non-LBBB patients. This is generally explained as CRT corrects the underlying electrical substrate of LBBB patients by paced pre-excitation of the lateral LV when targeting a pacing lead to the delayed LV lateral wall. As such **LBBB seems to induce a typical substrate of electromechanical dyssynchrony which can be restored by CRT**.

LBBB can be diagnosed on the twelve lead ECG by distinct morphologic criteria reflecting the delayed activation of the LV[1]. However no uniform consensus on the diagnostic criteria to diagnose LBBB on the ECG exists among different institutions[60]. With the era of CRT, new criteria to diagnose LBBB morphology have been introduced including mid QRS notching and slurring[59, 61]. Even the historical QRSD cut-off of 120ms to diagnose bundle branch block has

been questioned as insights of computer models showed that QRSD cut-offs of 130 to 140ms may be required to diagnose complete LBBB. It has been shown that these stricter LBBB criteria allow better selection of LBBB patients who will respond to CRT[62, 63].

Although LBBB patients present delayed activation of the left ventricular wall, heterogeneity in LV activation patterns has been described among LBBB patients[57, 64]. Some patients show a so-called U-shaped depolarization pattern in which the activation pattern moves from the septum in a circumferential and longitudinal direction, passing over the apex towards the lateral basal LV[57]. Other LBBB patients showed early breakthrough sites in the septum and were associated with much shorter transseptal activation times[64]. In some LBBB patients, abnormal septal activation patterns are visualized on two-dimensional echocardiography as a rapid pre-ejection leftward motion of the septum, followed by a right ward motion[65]. This left inward phenomenon is called septal flash (SF) and can be easily assessed by visual "eyeballing". This presence of SF in LBBB patients strongly predicts reverse remodeling and CRT response[65-67]. Given the heterogeneous activation patterns among LBBB patients, it appears that not all LBBBs are created equally. This might be related to the variable anatomy of the left bundle, the site and/or the extent of conduction block in the left bundle or myocardial substrate modification.

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Part II

Aims and outline of the thesis

Aims and outline

The overall aim of the studies presented in this thesis, is to achieve a better selection and higher response rates among heart failure patients eligible for CRT.

- In **chapter 1** we studied the effect of different methods to measure QRSD. Although QRSD is a main parameter to select CRT candidates, guidelines do not recommend a preferred method to measure QRSD. QRSD can be measured manually or by automated computer-calculated QRSD assessments. The study focuses on variability among different QRSD measurements and potential clinical implications when selecting CRT candidates based on QRSD.

- In **chapter 2** we hypothesized that both the measurement of QRSD and its predictive value on CRT response are sensitive to the method by which QRSD is measured. The study focuses on global and single lead QRSD measurements. Additionally, the predictive value of shortening in QRSD with BV pacing is evaluated.

- Baseline QRS area, a parameter combining both QRSD and QRS morphology, has been proposed as a new parameter allowing better selection of CRT responders. However the value of paced QRS area to increase CRT response has not been investigated. **Chapter 3** evaluates the value of this paced QRS area in guiding CRT implantation and optimizing CRT within the individual patient.

- The patient presenting with both electrical and mechanical dyssynchrony, has been shown to have the most favorable substrate amendable by CRT. The study presented in

chapter 4 evaluated the prevalence of mechanical dyssynchrony in LBBB patients and non-LBBB patients. In **chapter 5**, we evaluated whether specific electrocardiographic markers of dyssynchrony are associated with the presence of mechanical dyssynchrony on echocardiography.

- Gender disparity in CRT selection and response has been reported with female patients being underrepresented and showing better CRT response compared to males. **Chapter 6** analyses gender differences in electromechanical characteristics of LBBB patients as a potential explanation for gender disparity in the field of CRT.

Part III

Methods

Methodology

The studies presented in chapter 1, 2, 4, 5 and 6 enrolled patients of the cardiac department of the UZ Gent. Patients in chapter 3 were recruited from a multicenter trial evaluating the benefit of multipoint pacing.

All studies analyzed digital ECGs, stored in either the MUSE Cardiology Information system (HL7 annotated electrograms sampling rates of 500Hz, GE Healthcare, Waukesha, WI, USA) or in the BARD® Labsystem (sampling rate 1 kHz). For digital analysis of ECGs and construction of vectorcardiograms (VCGs) custom made software (Matlab , Mathworks, MA, US) was developed at the cardiac department of University Hospital of Gent in collaboration with EMDT Europe Oy (Vantaa, Finland).

Detailed methodology of each study is specified separately within each chapter.

Studies were approved by the ethical board of Ghent University Hospital.

Part IV

Results

CHAPTER 1

Accuracy of computer-calculated and manual QRS duration assessments: clinical implications to select candidates for cardiac resynchronization therapy

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Abstract

Background:

QRS duration (QRSD) plays a key role in the field of cardiac resynchronization therapy (CRT). Computer-calculated QRSD assessments are widely used, however inter-manufacturer differences have not been investigated in CRT candidates.

Methods: *QRSD was assessed in 377 digitally stored ECGs: 139 narrow QRS, 140 LBBB and 98 ventricular paced ECGs. Manual QRSD was measured as global QRSD, using digital calipers, by two independent observers. Computer-calculated QRSD was assessed by Marquette™ 12SL™ (GE Healthcare, Waukesha, WI, USA) and SEMA3 (Schiller, Baar Switzerland).*

Results: *Inter-manufacturer differences of computer-calculated QRSD assessments vary among different QRS morphologies: narrow QRSD: 4[2-9]ms (Median,[IQR]), p=0.010; LBBB QRSD: 7[2-10]ms, p=0.003 and paced QRSD: 13[6-18]ms, p=0.007. Interobserver differences of manual QRSD assessments measured: narrow QRSD: 4[2-6]ms, p=non-significant; LBBB QRSD: 6[3-12]ms, p=0.006; paced QRSD: 8[4-18]ms, p=0.001. In LBBB ECGs, intraclass correlation coefficients (ICC) were comparable for inter-manufacturer and interobserver agreement (ICC 0.830 versus 0.837). When assessing paced QRSD, manual measurements showed higher ICC compared to inter-manufacturer agreement (ICC 0.902 versus 0.776). Using guidelines cutoffs of 130ms, up to 15% of the LBBB ECGs would be misclassified as <130ms or ≥130ms by at least one method. Using a cutoff of 150ms, this number increases to 33% of ECGs being misclassified.*

Conclusion: *Inter-manufacturer differences in computer-calculated QRSD assessments are significant and may compromise adequate selection of individual CRT candidates when using QRSD as sole parameter. Paced QRSD should preferentially be assessed by manual QRSD measurements.*

1. Introduction

QRS duration (QRSD) is a key parameter for selecting patients eligible for cardiac resynchronization therapy (CRT) according to both European and American guidelines.[1, 2] It has been shown that the magnitude of benefit with CRT declines in patients with shorter QRSD.[3] Recent guidelines recommend that cardiac resynchronization therapy (CRT) should not be used in patients with QRS duration <130ms.[4] Moreover, it has been shown that shortening in QRSD with biventricular (BV) pacing is associated with a favorable clinical and echocardiographic response, which can be used to tailor CRT in the individual patient [5-8].

Despite the major role for QRSD in selecting CRT patients and predicting CRT response, standardized measurements of QRSD are lacking and guidelines do not instruct clinicians how to measure QRSD. Some authors have reported large interobserver variability of manual QRSD assessments and suggest the use of automated computer-calculated QRSD assessments in CRT candidates [9, 10]. However, inter-manufacturer variability of computer-calculated QRSD measurements have not been thoroughly assessed in left bundle branch block (LBBB) and BV paced ECGs. This study aimed to analyze 1) inter-manufacturer variability of computer calculated QRSD measurements, 2) interobserver variability of manual QRSD measurements, 3) potential clinical implications of these differences when selecting CRT candidates and optimizing BV pacing based on QRSD.

2. Methods

2.1. ECG database

Standard 12-lead electrocardiograms (ECGs) of ambulatory patients were recorded at the department of cardiology at Ghent University Hospital between January 2014 and February 2015. All ECGs were recorded with MAC 5500 ECG recording devices (GE Healthcare, Waukesha, WI, USA) and stored digitally in a MUSE Cardiology Information system (GE

Healthcare, Waukesha, WI, USA) as HL7 annotated electrograms (aHL7 ECGs) with sampling rates of 500Hz.

A total of 377 ECGs were selected based on their QRS morphology: 1) narrow QRS ECGs without evidence for conduction delay (n= 139 ECGs), 2) LBBB ECGs (n=140) and 3) ventricular paced ECGs (n=98). LBBB was judged by experts according to the Strauss criteria: rS or QS morphology in lead V1, mid-QRS notching or slurring in 2 adjacent leads among leads V1-V2, V5-V6 or I-aVL[11]. LBBB assessment by the computer-based algorithm of the ECG recording device was performed automatically according to the programmed software. ECGs with ventricular extrasystoles were excluded. Paced ECGs included both right ventricular (RV) (n=52) and BV pacing (n=46) and all QRS complexes within the ECG had paced morphology. To assess QRSD variability between different ECG recordings, 120 ECGs of 60 patients (30 paced and 30 non-paced) recorded at 2 different time points (<1 month interval) were analyzed.

2.2. Computer calculated and manual QRSD assessments

Two independent experts, blinded to the study design, measured QRSD ($QRSD_{M1}$ and $QRSD_{M2}$ respectively) using digital calipers (custom-made software EAT4, EMDT Europe Oy, Vantaa, Finland). QRSD was measured as global QRSD, which is the interval between the first onset of the QRS in any lead until the latest offset in any lead, as recommended by guidelines.[12] This method has been validated to accurately assess QRSD in CRT patients with low inter- and intra-observer variability.[6] Global QRSD was assessed with sweep speeds of 50mm/s and amplitude calibration of 10mm/mV. The mean manual QRSD for each ECG ($QRSD_{MM}$) was calculated as the mean value of $QRSD_{M1}$ and $QRSD_{M2}$ and used as comparison with computer calculated QRSD measurements.

Computer based QRSD measurements were assessed by the Marquette^{TM} 12SL^{TM} algorithm (GE Healthcare, Waukesha, WI, USA) and SEMA3 software (Schiller, Baar Switzerland), ($QRSD_{A1}$ and $QRSD_{A2}$ respectively).

Both manual and computer calculated QRSD assessments did not take into account the pacing spike as onset of the QRS. As such, latency between the pacing spike and the true onset of the QRS could not influence paced QRSD.

To compare global QRSD assessment (using digital calipers) versus QRSD measurements on paper ECG recordings (paper speed 25mm/s), 60 ECGS (20 narrow QRS, 20 LBBB and 20 paced ECGs) were analyzed separately by two experts. The experts measured QRSD on paper recordings according to their routine practice.

2.3. Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Absolute differences in QRSD between different methods are expressed as median [quartile 1-quartile 3]. Comparison among groups was done by Mann-Whitney U test. Wilcoxon Signed Rank test and Friedman test were used for paired analysis between groups. Bland-Altman plots were used to analyze systematic bias among methods. Agreement between different methods was analyzed using intraclass correlation coefficients (ICC), (two-way mixed single measures, absolute agreement). Statistical significance was set at a 2-tailed probability level of <0.05. All statistical analysis was performed using SPSS software (Version 22.0, IBM, Armonk, NY, USA).

3. Results

3.1 QRSD in narrow QRS

Overall, mean QRSD of the narrow QRS group was comparable among all methods: $QRSD_{M1}$: 88±12ms, $QRSD_{M2}$: 89±12ms, $QRSD_{A1}$ 91±14ms and $QRSD_{A2}$ 90±14ms (p= non-significant, NS).

Analyzing QRSD within individual ECGs (pairwise), absolute differences in QRSD between the automated algorithms $QRSD_{A1}$ versus $QRSD_{A2}$ are 4 [2-9]ms (p=0.010) and between $QRSD_{M1}$ versus $QRSD_{M2}$ 4 [2-6]ms, p= NS. Absolute inter-manufacturer and interobserver variability were comparable in narrow QRS ECGs (4 [2-9]ms versus 4 [2-6], p=NS).

Agreement between $QRSD_{M1}$ and $QRSD_{M2}$ was comparable to agreement between $QRSD_{A1}$ and $QRSD_{A2}$ (ICC= 0.904 vs. 0.867, Figure 1.1). Likewise, Bland-Altman plots showed a comparable interval between the limits of agreement (LOA) of automated measurements $QRSD_{A1}$ and $QRSD_{A2}$ (LOA= -13:15ms) compared to manual measurements $QRSD_{M1}$ and $QRSD_{M2}$ (LOA= -11:13ms) (Figure 1.2).

Comparing manual versus automated QRSD measurements, absolute variability between $QRSD_{MM}$ and $QRSD_{A1}$ was 3 [1-5]ms, p=0.01 and between $QRSD_{MM}$ and $QRSD_{A2}$ was 5 [2-7]ms, p<0.001. Agreement analysis revealed comparable ICCs: $QRSD_{MM}$ versus $QRSD_{A1}$ (ICC= 0.857) and $QRSD_{MM}$ versus $QRSD_{A2}$ (ICC= 0.864). LOA are shown in Table 1.1.

Representative examples of QRSD assessment in narrow QRS ECGS are shown in Figure 1.3.

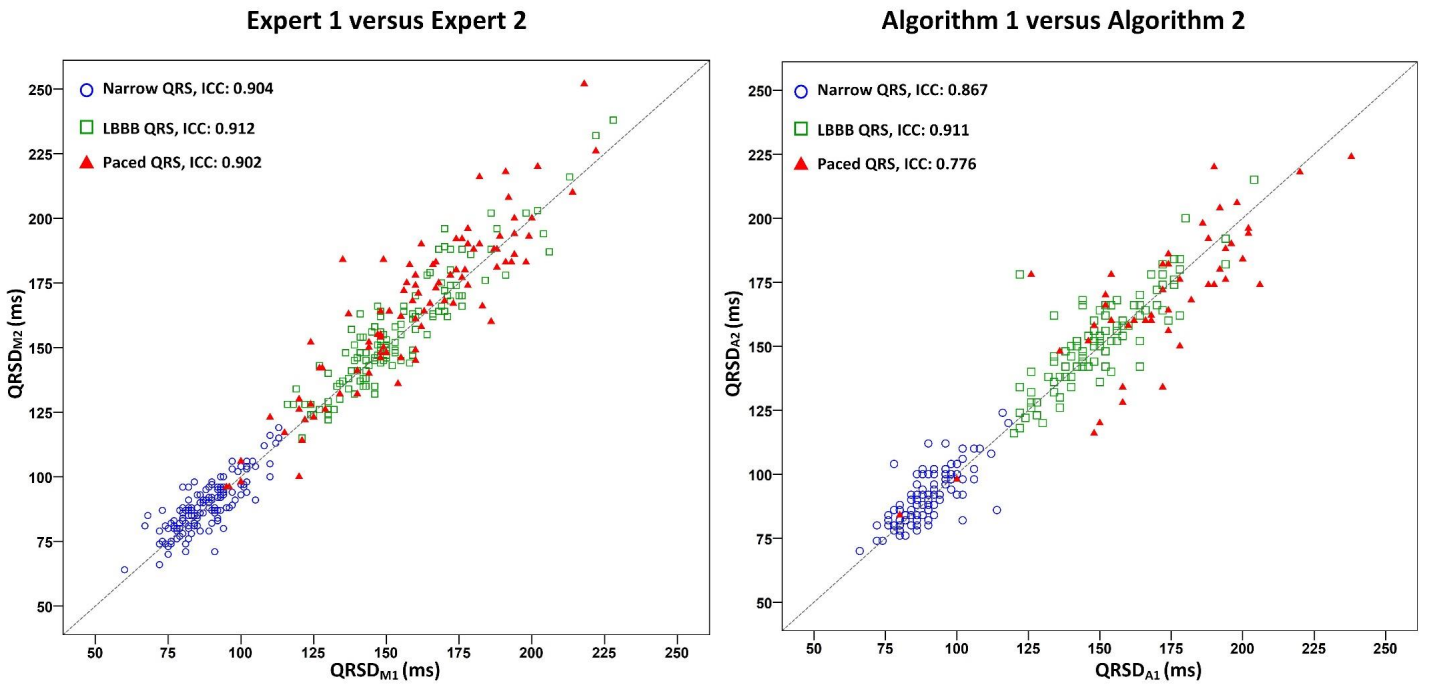


Figure 1.1: *Scatter plots of QRS duration (QRSD) measured by two experts ($QRSD_{M1}$ and $QRSD_{M2}$) and two automated computer-calculated QRSD assessments ($QRSD_{A1}$ and $QRSD_{A2}$). ICC: intraclass correlation coefficients.*

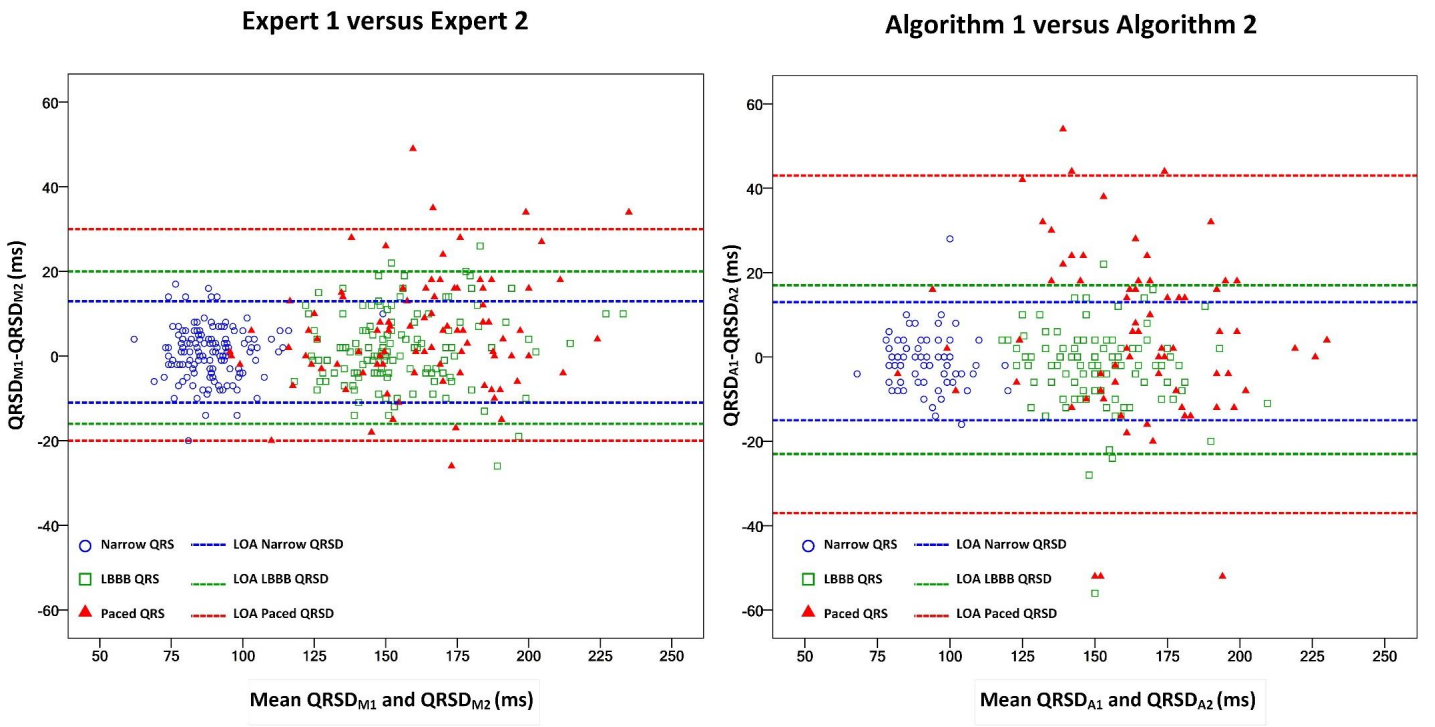
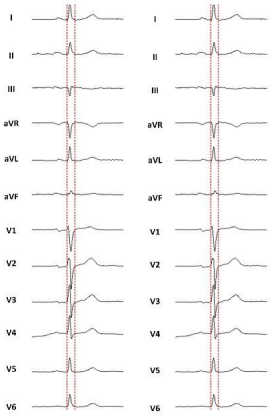


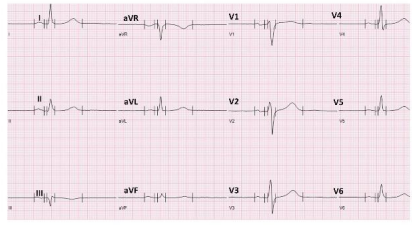
Figure 1.2: *Bland-Altman plots for manual QRS duration (QRSD) assessments ($QRSD_{M1}$ and $QRSD_{M2}$) and computer automated measurements ($QRSD_{A1}$ and $QRSD_{A2}$). LOA: limits of agreement defined as mean difference ± 1.96*standard deviation of the mean.*

Narrow QRS ECG (ECG nr 19)

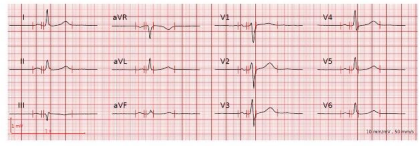


QRSDM$_1$: 91ms

QRSDM$_2$: 90ms

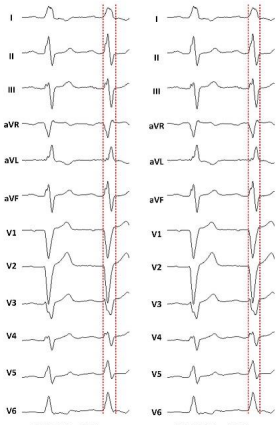


QRSDA$_1$: 88ms



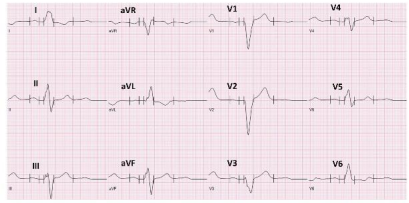
QRSDA$_2$: 94ms

LBBB ECG (ECG nr 47)

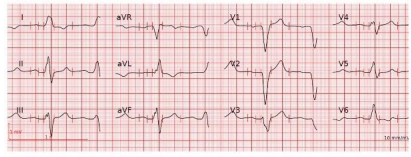


QRSDM$_1$: 125ms

QRSDM$_2$: 124ms

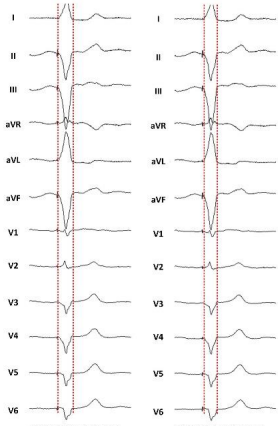


QRSDA$_1$: 122ms



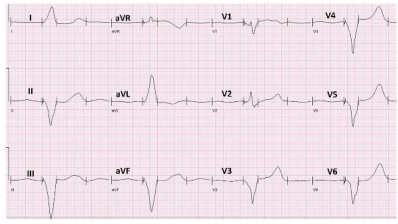
QRSDA$_2$: 134ms

Paced ECG (ECG nr 12)

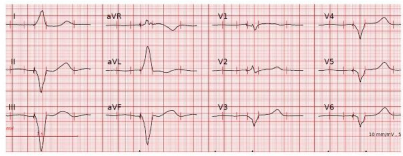


QRSDM$_1$: 171ms

QRSDM$_2$: 161ms



QRSDA$_1$: 178ms



QRSDA$_2$: 150ms

Figure 1.3: *Representative examples of QRSD assessment by four different methods in a narrow QRS, LBBB and ventricular paced ECGs. All ECG screenshots were calibrated at 50mm/s and 10mm/mV for figure clearness.* $QRSD_{M1}$ *and* $QRSD_{M2}$*: QRSD assessment by two different experts using digital calipers.* $QRSD_{A1}$ *and* $QRSD_{A2}$*: Automated computer-calculated QRSD by the Marquette™ 12SL™ algorithm (GE Healthcare, Waukesha, WI, USA) and SEMA3 software (Schiller, Baar Switzerland) respectively.*

Table 1.1: Limits of agreement among different methods to assess QRSD

QRS morphology	Comparison	Lower LOA (ms)	Upper LOA (ms)
Narrow QRSD	$QRSD_{M1}$ versus $QRSD_{M2}$	-11	13
	$QRSD_{A1}$ versus $QRSD_{A2}$	-15	13
	$QRSD_{MM}$ versus $QRSD_{A1}$	-10	14
	$QRSD_{MM}$ versus $QRSD_{A2}$	-8	16
LBBB QRSD	$QRSD_{M1}$ versus $QRSD_{M2}$	-16	20
	$QRSD_{A1}$ versus $QRSD_{A2}$	-23	17
	$QRSD_{MM}$ versus $QRSD_{A1}$	-31	21
	$QRSD_{MM}$ versus $QRSD_{A2}$	-19	17
Paced QRSD	$QRSD_{M1}$ versus $QRSD_{M2}$	-20	30
	$QRSD_{A1}$ versus $QRSD_{A2}$	-37	43
	$QRSD_{MM}$ versus $QRSD_{A1}$	-67	65
	$QRSD_{MM}$ versus $QRSD_{A2}$	-34	50

*QRSD: QRS duration. LBBB: left bundle branch block. LOA: limits of agreement defined as mean difference ± 1.96*SD of the difference*

3.2. QRSD assessments in LBBB QRS

Overall, mean QRSD of the LBBB ECG group was comparable among all methods: $QRSD_{M1}$: 158±22ms, $QRSD_{M2}$: 155±21ms, $QRSD_{A1}$: 151±18ms and $QRSD_{A}$:152±18ms (p=NS).

Analyzing QRSD within individual LBBB ECGs (pairwise), absolute differences in QRSD between the automated algorithms $QRSD_{A1}$ versus $QRSD_{A2}$ are 7 [2-10]ms (p=0.003), and between $QRSD_{M1}$ versus $QRSD_{M2}$ 6 [3-12]ms (p=0.006). In LBBB ECGs, absolute inter-manufacturer and interobserver variability was comparable (7 [2-10] versus 6 [3-12]ms, p=NS). Agreement between $QRSD_{M1}$ and $QRSD_{M2}$ was comparable to the agreement between $QRSD_{A1}$ and $QRSD_{A2}$ (ICC = 0.912 vs. 0.911, Figure 1.1). Bland-Altman plots showed a comparable interval between LOA of automated measurements $QRSD_{A1}$ and $QRSD_{A2}$ (LOA=-23:17ms) compared to manual measurements $QRSD_{M1}$ and $QRSD_{M2}$ (LOA= -16:20ms) (Figure 1.2).

Comparing manual versus automated QRSD measurements, absolute variability between $QRSD_{MM}$ and $QRSD_{A1}$ was 4[2-9]ms($p<0.001$) and between $QRSD_{MM}$ and $QRSD_{A2}$ was 7[3-10]ms (p=0.044). Agreement analysis revealed comparable ICCs between $QRSD_{MM}$ and $QRSD_{A1}$ versus $QRSD_{MM}$ and $QRSD_{A2}$ (ICC = 0.870 vs. 0.872). LOA are shown in table 1.1.

Representative examples of QRSD assessment in LBBB ECGS are shown in Figure 1.3.

3.3. Categorizing LBBB ECGs based on QRSD as sole parameter

When categorizing individual ECGs to QRSD <130ms or ≥130ms (guideline cutoff for CRT implant [1, 4]), 7% of the ECGs were differently categorized by $QRSD_{M1}$ and $QRSD_{M2}$ and 7% by $QRSD_{A1}$ and $QRSD_{A2}$. Taking into account all four methods ($QRSD_{M1}$, $QRSD_{M2}$, $QRSD_{A1}$ and $QRSD_{A2}$), 15% of the ECGs would be categorized differently by at least one measurement. Using a cutoff of 150ms (guideline cutoff for a class 1 indication regarding CRT implant [1, 2]) 21% of ECGs were categorized differently by $QRSD_{M1}$ and $QRSD_{M2}$ and 22% by $QRSD_{A1}$ and

$QRSD_{A2}$. Taking into account all four methods, 33% of the ECGs were categorized differently as having QRSD <150ms or ≥150ms by at least one measurement.

3.4. QRSD assessments in RV and BV paced QRS

Overall, mean QRSD of the paced QRS group was comparable among all methods: $QRSD_{M1}$: 165±32ms, $QRSD_{M2}$: 160±31ms, $QRSD_{A1}$: 163±31ms and $QRSD_{A2}$: 165±30ms (p=NS).

Analyzing QRSD within individual paced ECGs, absolute differences in QRSD between the automated algorithms $QRSD_{A1}$ and $QRSD_{A2}$ are 13 [6-18]ms, p=0.007 and between the manual measurements $QRSD_{M1}$ versus $QRSD_{M2}$ are 8 [4-18]ms, (p=0.001). In paced ECGs inter-manufacturer variability was significant larger compared to interobserver variability (13 [6-18] versus 8 [4-18]ms, p=0.035). No differences were found between RV and BV paced QRSD regarding inter-manufacturer or interobserver variability.

Correlation between $QRSD_{M1}$ and $QRSD_{M2}$ was higher compared to the correlation between $QRSD_{A1}$ and $QRSD_{A2}$ (ICC = 0.902 vs. 0.776, Figure 1.1). Bland-Altman plots showed a larger interval between LOA for the automated measurements $QRSD_{A1}$ and $QRSD_{A2}$ (LOA= -48:46ms) compared to the manual measurements $QRSD_{M1}$ and $QRSD_{M2}$ (LOA= -20:30ms) (Figure 1.2).

Comparing manual versus automated QRSD measurements, absolute variability between $QRSD_{MM}$ and $QRSD_{A1}$ was 14[7-25]ms (p=0.005) and between $QRSD_{MM}$ and $QRSD_{A2}$ was 14[4-23]ms, p=0.001. Agreement analysis revealed low ICCs both for $QRSD_{MM}$ versus $QRSD_{A1}$ (ICC = 0.666) and $QRSD_{MM}$ versus $QRSD_{A2}$ (ICC = 0.640). LOA are shown in Table 1.1. Representative examples of QRSD assessment in paced ECGS are shown in Figure 1.3.

3.5. Accuracy of paper-based QRSD assessments

Among all ECG categories, interobserver variability of manual QRSD measurements on standard paper printed ECGs (25mm/s paper speed) was larger compared to global QRSD assessment with digital calipers: narrow QRS ECGs: 20 [10-28]ms versus 4 [2-6] (p=0.008) , LBBB ECGs: 15 [0-38]ms versus 6 [3-12]ms (p=0.012) and paced ECGs: 13 [5-23]ms versus 8 [4-18]ms (p=0.022) respectively. Agreement of QRSD measurements on paper ECG recordings between experts was low: ICC for narrow QRS ECG: 0.290, ICC for LBBB ECGs: 0.121 and ICC for paced ECGs: 0.456. Of interest, the highest consistency between paper-based and automated QRSD measurements within one of the categories only reached an ICC of 0.745. In terms of intra-observer variability, global QRSD outperformed paper-based QRSD measurements: absolute intra-observer variability was 6 [2-11]ms versus 20 [2-40]ms (p=0.026) respectively. Intra-observer ICCs were low for paper-based QRSD assessments (ICC 0.640) compared to global QRSD (ICC 0.906).

3.6. Variability between ECG recordings within the same patient

Mean variability between 2 ECG recordings was comparable between methods: $QRSD_{MM}$: 7ms (range 0-15ms), $QRSD_{A1}$: 7ms (range 0-20ms) and $QRSD_{A2}$: 7ms (range 0-23ms) (p=NS). Of interest, variability between recordings was equal for LBBB and paced ECGs (mean variability respectively 5 versus 8ms for all methods, p=NS).

4. Discussion

4.1. Computer-calculated versus manual QRSD assessments

This study is the first to assess and quantify inter-manufacturer differences of computer-calculated QRSD assessments among varying QRS morphologies. Inter-manufacturer discrepancies in QRSD assessments are larger in LBBB QRSD compared to narrow QRSD. In

these groups, inter-manufacturer variability of computer-calculated QRSD assessments is comparable to interobserver variability of experts using a global QRSD approach. However, when considering paced QRSD, manual global QRSD assessments clearly show lower variability and better agreement compared to computer-based QRSD assessments.

The lack of gold standards to measure QRSD within the field of CRT complicates a straightforward recommendation for either manual or automated QRSD assessments. Global QRSD assessments among all leads are recommended by ECG guidelines as the preferred method to measure QRSD. [12] Low concordance rates have been reported between manual and computer-calculated QRSD assessments.[9, 10] Our data show that this disagreement between manual and automated computerized measurements is only significant when assessing paced QRSD. However, in narrow QRS and LBBB ECGs, agreement between manual and computer-calculated QRSD assessments is comparable with regard to inter-manufacturer and interobserver agreement, when manual measurements are performed by a global QRSD assessment.

4.2. Accuracy of manual QRSD measurements

Accuracy of QRSD measurements on paper-printed ECG recordings at 25 mm/s paper speed is low compared to global QRSD assessments using digital calipers. Other authors have reported similar interobserver variability (up to 35ms, range 20-50ms) and intra-observer variability (up to 25ms, range 10-50ms) when assessing QRSD on paper ECG recordings. [9, 10] Previously we have shown that global QRSD assessment is more accurate then single lead measurements.[6] As such, this study confirms the high accuracy of global QRSD assessments to measure QRSD among varying QRS morphologies.

The advantage of global QRSD assessment is that all leads are considered, whereas measurements of QRSD in individual leads may underestimate the QRSD because iso-electric

segments may occur due to a perpendicular projection of the lead orientation to the initial or terminal QRS vector. Moreover, the beginning and end of the QRS complex can be difficult to assess in an individual lead which might lead to a substantial inter-and intra-observer variability. Our data confirm that global QRSD assessment outperforms paper-based and single lead QRSD measurements in terms of inter- and intra-observer variability. Additionally, agreement with automated QRSD measurements is lower for paper-measured QRSD compared to global QRSD assessment using digital calipers.

4.3. Selecting CRT candidates by QRSD

On population level, mean QRSD assessed by different methods will not reveal significant differences, as no systematic bias could be appreciated between different methods. On the other hand, on individual basis, QRSD differences between methods become significant and clinical relevant when tailoring CRT based on a patients' QRSD alone. We show that a substantial number of LBBB patients could be wrongly withheld from CRT, because QRSD was scored below the 130ms cutoff by at least one method. As we reported mean absolute differences in LBBB QRSD up to 7ms, patients with a QRSD between 123 and 137ms may be considered equally with regard to CRT indication. Discrepancy rates of categorizing ECGs on QRSD alone become even more important when taking a QRSD cutoff of ≥150ms, which is a class 1 recommendation for CRT implant.[4] Our results show that up to one third of the patients would be misclassified as having a QRSD <150 or ≥150ms when using different methods.

However, in clinical practice the decision to implant a CRT cannot rely on QRSD alone. Indeed, clinical, echocardiographic and other ECG-criteria (as bundle branch block morphology) should be taken into account. Moreover, values of 130ms or 150ms are not even universally accepted within various guidelines and also different LBBB definitions can show variability. Therefore, our findings emphasize the need for a global approach (including clinical,

echocardiographic and electrocardiographic data) of the individual CRT patient and not to overemphasize the role of QRSD alone as both variability among methods and between ECG recordings may limit the use of QRSD as sole parameter.

4.4. Predicting CRT response by biventricular paced QRSD

Although paced QRSD cannot be used to select appropriate CRT candidates (as it requires the device already to be implanted), it can be instrumental to optimize CRT and improve response rates in individual patients. A recent meta-analysis showed that reduction in QRSD due to BV pacing is predictive of CRT response. [8] Likewise, some authors have reported that widening of QRSD with BV pacing is associated with adverse outcome. [13] Manual QRSD measurements, using global QRSD, show higher consistency rates and smaller absolute QRSD variability compared to computer-calculated QRSD assessments. A potential reason for this large disagreement in paced ECGS may be related to the pacing spike which makes automated computerized algorithms less accurate. Our findings clearly favor manual QRSD assessment to assess paced QRSD.

Global QRSD assessment does not include the pacing spike as onset of the paced QRS complex. This implicates that latency, defined as iso-electric segments in all leads [14], will not be taken into account for global QRSD assessment. The reason for this approach is that if every lead of the standard twelve lead ECG records an iso-electric segment, the amount of activated myocardium would be almost zero and therefore not included in paced QRSD[15]. If a small amount of myocardium is activated, we expect a small deflection to occur at least in one lead. Global QRSD assessment will capture a deflection in a single lead, as this method “scans” the earliest deflection in all leads to define the initiation of the QRS. As such, global QRSD assessments should be a reliable marker of pace-activated myocardium. In case the pacing spike causes immediate myocardial activation, there is no latency and the start of the paced QRSD is

set just behind the pacing spike. Given the short duration of a pacing spike (generally 0.4ms), this will not influence the paced QRSD.

A cutoff of 19ms shortening in QRSD has been reported to discriminate CRT responders from non-responders.[8] However, our study showed that even with the most accurate method, mean differences of 8ms are unavoidable. This may limit the use of QRSD shortening for predicting CRT response and optimizing CRT within the individual patient. Other ECG parameters of the paced QRS, such as QRS area, which shows less variability, may overcome this limitation. [16-18]

4.5. Variability between ECG recordings

QRSD variability between different ECG recordings in the same patient is approximate 7ms, irrespective of the method used. Interestingly, QRSD variability between ECG recordings applies both for LBBB and paced QRSD. These findings favor the use of repeat QRSD measurements to select appropriate CRT candidates and optimize CRT based on global QRSD.

5. Limitations

Manual measurements were performed with digital calipers using custom made software, which may not be available for every clinician. In this study, the expert was able to adapt sweep speeds in order to perform manual measurements as accurate as possible.

Differences between ECG recordings with different electrode positions in the same patient are not investigated.

This study compared only two computer-calculated QRSD assessments. As such, we cannot draw conclusions regarding other automated algorithms assessing QRSD. However, using another automated algorithm is expected to increase inter-manufacturer variation.

The authors were blinded to the QRSD onset and offset defined by the computer calculated QRSD, as such mechanisms for differences in QRSD remain largely unexplained.

6. Conclusion

Computer–calculated QRSD assessments in LBBB patients show significant inter-manufacturer variability and may influence adequate selection of individual CRT candidates when using QRSD as sole criterion. Paced QRSD should preferentially be measured by manual QRSD assessments. Our findings emphasize the need to standardize QRSD measurements within the field of CRT.

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CHAPTER 2

Different methods to measure QRS duration in CRT patients: impact on the predictive value of QRS duration parameters

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Abstract

Background: *Measurements of QRS duration (QRSD) in patients undergoing cardiac resynchronization therapy (CRT) are not standardized. We hypothesized that both the measurement of QRSD and its predictive value on CRT response are sensitive to the method by which QRSD is measured.*

Methods: *Electrocardiograms (ECGs) pre- and post-CRT from 52 CRT patients (66±12 years, 65% male) were retrospectively analysed. Custom-made software was developed to measure global QRSD ($QRSD_{global}$) and lead-specific QRSD ($QRSD_{I,II,III,aVR,aVL,aVF,V1,V2,V3,V4,V5,V6}$). QRSD was also assessed automatic by a routinely used ECG device. For each method we measured QRSD pre- and post-CRT and shortening of QRSD (ΔQRSD). Response to CRT at 6 months was defined as an improvement of ≥ 1 class in New York Heart Association (NYHA) classification and an increase by >7.5% in left ventricular ejection fraction.*

Results: *The CRT response rate was 77% (n=40). Different methods to measure QRSD show divergent nominal values before (median range 152-172ms, $p< 0.001$) and after CRT (130–152ms, $p<0.001$). The predictive value of QRSD measurements for CRT response also varies significantly according to the method used (range AUC pre-CRT QRSD 0.400-0.580, $p<0.05$; AUC post-CRT QRSD 0.447-0.768, $p<0.05$; AUC ΔQRSD 0.540-0.858, $p<0.05$). Global QRSD measurements revealed lower variability compared to lead-specific QRSD.*

Conclusion: *Different methods to measure QRSD yield not only different nominal values but also influence the value of QRSD in predicting CRT response. Measuring QRSD by a global method can help to standardize QRSD measurements in future studies.*

1. Introduction

In patients with left ventricular systolic dysfunction, prolongation of the QRS duration (QRSD) > 120ms is associated with dyssynchronous ventricular activation and is an independent predictor of all-cause mortality.[1, 2] In these patients cardiac resynchronization therapy (CRT) has proven symptomatic and prognostic benefits.[3, 4] However, up to one third of patients who undergo CRT implantation do not respond to this treatment.[5] Various echocardiographic parameters of cardiac dyssynchrony have been examined to improve CRT response rate, but showed limited success.[6, 7] Therefore QRSD remains the parameter of choice in selecting patients eligible for CRT according to the guidelines.[8] Methods of measuring QRSD are not standardized and no preferred technique is specified.[8-10] The American Heart Association, the American College of Cardiology Foundation and the Heart Rhythm Society (AHA/ACC/HRS) recommend for general electrocardiogram (ECG) interpretation the use of global QRSD measurements, in which the onset and ending of the QRS complex beyond all leads is used, above single lead measurements.[11] The lack of standardized QRSD measurement methods might cause inconsistency both in device prescription and in predicting CRT response. We hypothesized that both the measurement of QRSD and its predictive value on CRT response are sensitive to the method by which QRSD is measured.

2. Methods

2.1. Study subjects

We retrospectively analysed 52 patients (mean age 66±12yrs, 65% male) who underwent implantation of a CRT device at the Ghent University Hospital in Belgium. The study was approved by the ethical board of Ghent University. In all patients, 12-lead ECGs were recorded on the same day pre- and post-implantation of the CRT device. All patients had clinical and echocardiographic follow-up at 6 months post-CRT implantation.

Response to CRT was defined by an improvement of one class in New York Heart Association (NYHA) classification together with an increase in echocardiographic left ventricle ejection fraction (LVEF) of > 7.5 % (measured by biplane Simpson) between date of implantation and 6 months follow-up.[12, 13]

CRT devices were implanted transvenously by the same team of electrophysiologists targeting a lateral or posterolateral vein for the left ventricular lead. The right ventricular lead was placed preferentially at the apex. The sensed atrioventricular (AV) interval was set at 75% of the native PR interval.

2.2. Measurements of QRS duration

All patients had standard 12-lead ECG before (with intrinsic AV conduction) and after implant (during biventricular pacing). ECGs were recorded using the BARD® Labsystem (filtering 0.05-240 Hz, sampling rate 1 kHz). The QRS complexes were analysed at sweep speeds of 50 mm/s and magnified two times (20mm/mV). Using digital calipers (custom made Matlab software, Mathworks, MA, US) we calculated the global QRSD ($QRSD_{global}$) and the QRSD in each individual lead of the standard 12-lead ECG ($QRSD_{I, II, III, ...}$) pre- and post CRT. The $QRSD_{global}$ was defined as the interval between the earliest onset of the QRS waveform in any lead till the latest offset in any lead.[11] In case of paced beats, pacing spikes were not taken into account as the onset of QRS complex. For better visualization of the beginning and end of the $QRSD_{global}$, the 12-lead ECGs were aligned in a vertical manner (Figure 2.1). Measurements of both $QRSD_{global}$ and 12 lead-specific QRSD were performed by a single investigator who was blinded to clinical and echocardiographic response. Additionally, QRSD was assessed by an automatic computer-calculated measurement of a routinely used ECG device (AT-104, Schiller AG, Switzerland) ($QRSD_{routine}$). Differences in QRSD between pre- and post-CRT ($\Delta QRSD$ =

post-CRT minus pre-CRT QRSD) were evaluated for all QRSD measurement methods ($QRSD_{global}$, 12 lead-specific QRSD and $QRSD_{routine}$).

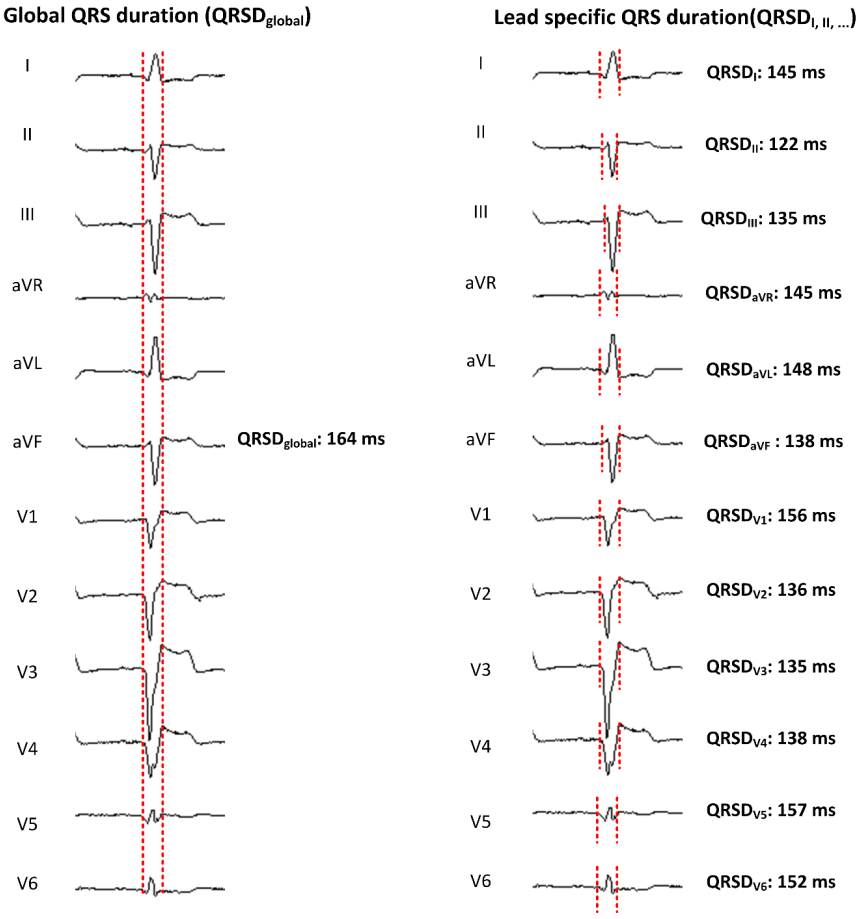


Figure 2.1. *ECG during sinus rhythm of a 69-year-old male patient with ischemic cardiomyopathy and reduced left ventricle ejection fraction. Right panel: global QRS duration ($QRSD_{global}$) measured by custom made software. Left panel: lead-specific QRS duration ($QRSD_{I, II, ...}$) measured by custom made software.*

2.3. Inter- and intra-observer variability

Inter-observer variability was evaluated to test the reproducibility of $QRSD_{global}$ and lead-specific QRSD. Four experts, blinded to the experimental design, measured QRSD in twelve randomly chosen ECGs (both pre-CRT and post-CRT) using the $QRSD_{global}$, one of the lead-specific QRSD in the frontal plane and one of the lead-specific QRSD in the horizontal plane. To test for intra-observer variability, the measurements were repeated by the same four experts two weeks later.

2.4. Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median [inter quartile range] if data were not Gaussian distributed. Categorical variables are expressed as absolute number with percentage (%). Comparison among groups was done by Mann-Whitney U test. Wilcoxon Signed Rank test and Friedman test were used for paired analysis. To compensate the problem of multiple comparisons the Bonferroni correction was applied where necessary. Categorical variables were compared by Chi-square tests. Statistical significance was set at a 2-tailed probability level of <0.05. Receiver operating characteristic (ROC) curves were constructed to compare the diagnostic accuracy and to determine optimal cutoff values of different methods of QRSD measurements. Inter- and intra-observer variability were analyzed by using the intraclass correlation coefficient (ICC). All statistical analysis was performed using SPSS software (Version 22.0, IBM, Armonk, NY, US).

3. Results

3.1. Patient characteristics

Based on the echocardiographic and clinical follow-up at 6 months, 40 (77%) patients were considered responders and 12 (23%) patients were considered non-responders. The patient

characteristics according to CRT response are summarized in Table 2.1. No significant differences were observed between responders and non-responders. By definition, responders had a greater increase in EF (14±7% vs. 2 ±3%, p<0.001) and improvement in NYHA class (2±1 vs. 1±1, p<0.001) compared to non-responders. No differences in pre-CRT $QRSD_{routine}$, post-CRT $QRSD_{routine}$ and $\Delta QRSD_{routine}$ were found between the two groups.

Table 2.1. Clinical characteristics (All patients, responders and non-responders)

	All (n= 52)	*Responders (n=40)*	*Non-responders (n=12)*	*p-value*
Age, yrs	66±12	67±12	64±11	NS
Gender, n (%)				
Male sex	34 (65%)	28 (70%)	6 (50%)	NS
Female sex	18 (35%)	12 (30%)	6 (50%)	
Etiology, n (%)				
Ischemic	23 (44%)	19 (48%)	4 (33%)	NS
Non-ischemic	29 (56%)	21 (52%)	8 (67%)	
Type of device, n (%)				
ICD	39 (75%)	29 (73%)	10 (83%)	NS
PM	13 (25%)	11 (27%)	2 (17%)	
Echocardiographic LVEF, (%)				
LVEF pre-CRT	27±8	27±8	26 ±6	NS
LVEF post-CRT	38±10	41±10	29±5	p<0.001
LVEF change	11±8	14±7	2±3	p<0.001
NYHA-score				
- pre-CRT	3±0	3±1	3±0	NS
- post-CRT	1±1	1±1	2±1	p<0.001
- change	2±1	2±1	1±1	p<0.001
$QRSD_{routine}$ pre-CRT (ms)	155±27	156±27	151±38	NS
$QRSD_{routine}$ post-CRT (ms)	155±29	156±28	152±33	NS
$\Delta QRSD_{routine}$ by CRT(ms)	1±33	1±36	1±22	NS
LBBB Morphology	48(92%)	37(93%)	11(92%)	NS

Values are expressed as mean±SD, or n (%). P-values comparing responders and non-responders. NS = Non-significant. ICD: implantable cardioverter defibrillator. PM: pacemaker. LVEF: left ventricle ejection fraction. NYHA: New York Heart Association. CRT: Cardiac resynchronization therapy. $QRSD_{routine}$: QRS duration measured by a routinely used ECG device. $\Delta QRSD_{routine}$: post-$CRT_{routine}$ minus pre-CRT $QRSD_{routine}$. LBBB: left bundle branch block.

3.2. Measurement of pre-CRT QRSD and its predictive value for CRT response: impact of the methodology

Pre-CRT QRSD for all patients was significantly different depending on the method (median values ranging from 152 to 172ms, p<0.001) (Table 2.2). Representative ECGs of a non-

responder and responder are given in figure 2.2 (Figure 2.2). Nominal values for pre-CRT QRSD vary according to the different methods, both for the responder patient (variation up to 28ms) and non-responder (variation up to 29ms). Overall, when compared to $QRSD_{global}$ (median=172ms), $QRSD_{I}$ (152ms), $QRSD_{II}$ (161ms), $QRSD_{III}$ (159ms), $QRSD_{aVR}$ (153ms), $QRSD_{aVL}$ (155ms), $QRSD_{aVF}$ (158ms), $QRSD_{V1}$ (161ms), $QRSD_{V2}$ (161ms), $QRSD_{V3}$ (160ms), $QRSD_{V6}$ (161ms) and $QRSD_{routine}$ (158ms) were significantly different ($p<0.01$ for all). No significant difference was observed when comparing $QRSD_{global}$ to $QRSD_{V4\ and\ V5}$.

Also ROC curves for predicting CRT response based on pre-CRT QRSD revealed different AUC values according to the method (AUC ranging from 0.400 to 0.580, $p< 0.05$) (Figure 2.3). Significant difference in predictive value for CRT response based on pre-CRT QRSD was observed between pre-CRT $QRSD_{global}$ (AUC=0.580) and each of pre-CRT $QRSD_{routine}$ (AUC=0.533, p=0.034), $QRSD_{V3}$ (AUC=0.458, p=0.011), $QRSD_{V4}$ (AUC=0.442, p=0.010), $QRSD_{II}$ (AUC=0.428, p=0.035), $QRSD_{III}$ (AUC=0.428, p=0.037), $QRSD_{I}$ (AUC=0.415, p=0.040), $QRSD_{aVF}$ (AUC=0.413, p=0.010), $QRSD_{aVR}$ (AUC=0.400, p=0.009). In contrast there was no significant difference observed in AUC when comparing pre-CRT $QRSD_{global}$ to each of $QRSD_{aVL,V1,V2,V5,V6}$.

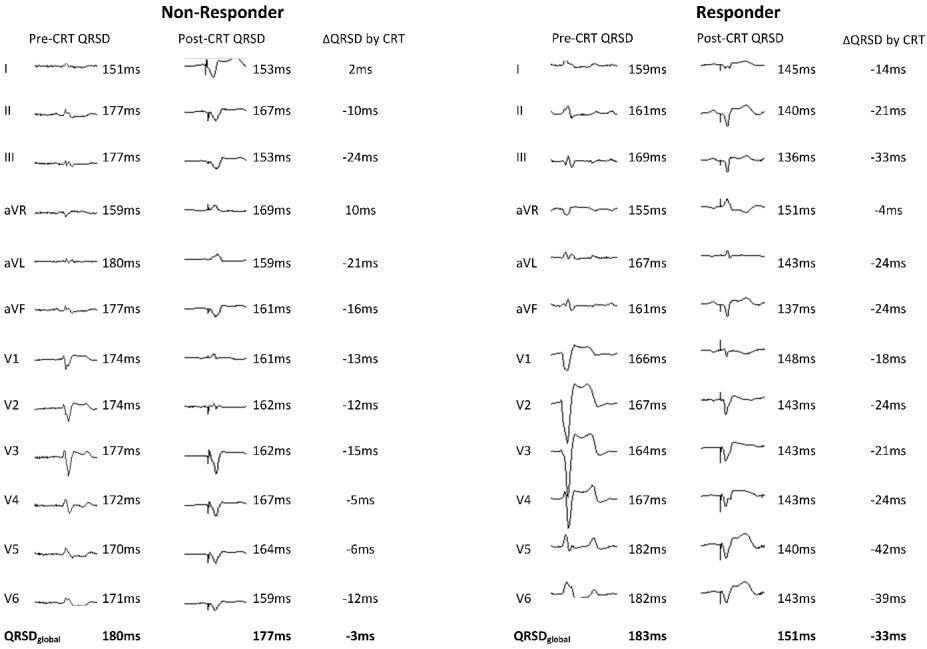


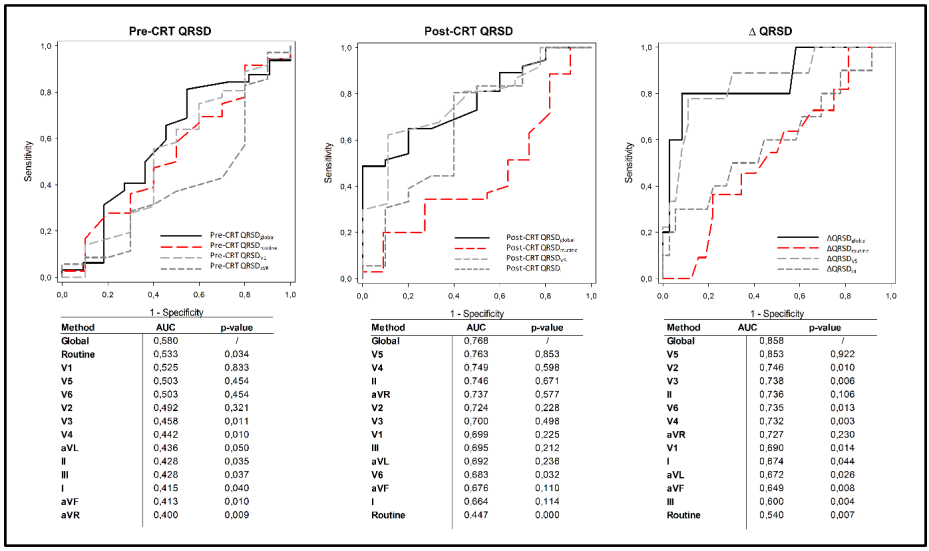
Figure 2.2. *Manual measurements of QRSD in representative examples of a non-responder and responder patient. Nominal values for QRSD, both pre- and post CRT differ according to the method used.*

CRT: Cardiac resynchronization therapy. $QRSD_{global}$: global QRS duration measured by custom made software. $QRSD_{I,II,III}$: lead-specific QRS duration measured by custom made software. $QRSD_{routine}$: QRS duration automatic measured by a routinely used ECG device. ΔQRSD: post-CRT minus pre-CRT QRSD.

3.3. Measurement of post-CRT QRSD and its predictive value for CRT response: impact of the methodology

Post-CRT QRSD for all patients was significantly different depending on the method (median values ranging from 130 to 152ms, $p<0.001$) (Table 2.2). The ECGs in figure 2.2 are representative for these findings (Figure 2.2). Nominal values for post-CRT QRSD vary according to the different methods, both for the responder patient (variation up to 15ms) and

non-responder (variation up to 24ms). Overall, when compared to post-CRT $QRSD_{global}$ (median=143ms), post-CRT $QRSD_{aVL}$ (130ms) and $QRSD_{V1}$ (135ms) were significantly different ($p<0.01$ for both). No significant difference was found when comparing post-CRT $QRSD_{global}$ to each of post-CRT $QRSD_{II,III,\ aVR,\ aVF,\ V2,\ V3,\ V4,\ V5,\ V6}$ and post-CRT $QRSD_{routine}$. Also ROC curves for predicting CRT response based on post-CRT QRSD differed significantly according to the method (AUC values ranging from 0.447 to 0.768, $p< 0.05$). (Figure 2.3) Significant difference in predictive value for CRT response based on post-CRT QRSD was observed between post-CRT $QRSD_{global}$ (AUC=0.768) each of post-CRT $QRSD_{V6}$ (AUC=0.683, p=0.032) and $QRSD_{routine}$ (AUC=0.447, $p< 0.001$). In contrast there was no significant difference observed in AUC when comparing post-CRT $QRSD_{global}$ to each of $QRSD_{I,II,III,aVR,aVL,aVF,V1,V2,V3,V4,V5}$.



Method	AUC	p-value
Global	0,580	/
Routine	0,533	0,034
V1	0,525	0,833
V5	0,503	0,454
V6	0,503	0,454
V2	0,492	0,321
V3	0,458	0,011
V4	0,442	0,010
aVL	0,436	0,050
II	0,428	0,035
III	0,428	0,037
I	0,415	0,040
aVF	0,413	0,010
aVR	0,400	0,009

Method	AUC	p-value
Global	0,768	/
V5	0,763	0,853
V4	0,749	0,598
II	0,746	0,671
aVR	0,737	0,577
V2	0,724	0,228
V3	0,700	0,498
V1	0,699	0,225
III	0,695	0,212
aVL	0,692	0,238
V6	0,683	0,032
aVF	0,676	0,110
I	0,664	0,114
Routine	0,447	0,000

Method	AUC	p-value
Global	0,858	/
V5	0,853	0,922
V2	0,746	0,010
V3	0,738	0,006
II	0,736	0,106
V6	0,735	0,013
V4	0,732	0,003
aVR	0,727	0,230
V1	0,690	0,014
I	0,674	0,044
aVL	0,672	0,026
aVF	0,649	0,008
III	0,600	0,004
Routine	0,540	0,007

Figure 2.3.

Upper panel: ROC curves for predicting CRT response by pre-CRT QRSD, post-CRT QRSD and ΔQRSD measured by different methods. ROC curves for $QRSD_{global}$, $QRSD_{routine}$ and the individual leads

with the highest and lowest AUC are presented. Lower panel: AUCs of ROC curves for all methods. p-values for the comparison of each method to $QRSD_{global}$ are presented. CRT: Cardiac resynchronization therapy. ΔQRSD = post-CRT minus pre-CRT QRSD. AUC: Area under the curve. $QRSD_{global}$: global QRS duration measured by custom made software. $QRSD_{I,II,III,...}$: lead-specific QRS duration measured by custom made software. $QRSD_{routine}$: QRS duration measured automatic by a routinely used ECG device.

3.4. Measurement of ΔQRSD and its predictive value for CRT response: impact of the methodology

ΔQRSD for all patients was significantly different depending on the method (median values ranging from -27 to 0ms, $p<0.001$) (Table 2.2). In figure 2.2 nominal values for $\Delta QRSD_{global}$ differ strongly according to the method used to measure the QRSD (Figure 2.2). In the responder patient ΔQRSD varies from -4ms up to -33ms. In the non-responder patient ΔQRSD varies from 10ms up to -24ms. Overall, when compared to $\Delta QRSD_{global}$ (-27ms), $\Delta QRSD_{II}$ (-16ms, $p=0.016$), $\Delta QRSD_{aVR}$ (-14ms, $p=0.018$) and $\Delta QRSD_{routine}$ (0ms, $p<0.001$), were significantly different. No significant difference was found when comparing $\Delta QRSD_{global}$ to $\Delta QRSD_{I, III, aVL, aVF, V1, V2, V3, V4, V5, V6}$.

Also ROC curves for predicting CRT response based on ΔQRSD differed according to the method (AUC values widely ranging from 0.540 to 0.858, $p< 0.05$). (Figure 2.3) Significant difference in predictive value for CRT response based on ΔQRSD was observed between $\Delta QRSD_{global}$ (AUC=0.858) and each of $\Delta QRSD_{V2}$ (AUC=0.746, $p=0.010$), $QRSD_{V3}$ (AUC=0.738, $p=0.006$), $QRSD_{V6}$ (AUC=0.735, $p=0.013$), $QRSD_{V4}$ (AUC=0.732, $p=0.003$), $QRSD_{V1}$ (AUC=0.690, $p=0.014$), $QRSD_{I}$ (AUC=0.674, $p=0.044$), $QRSD_{aVL}$ (AUC=0.672, $p=0.026$), $QRSD_{aVF}$ (AUC=0.649, $p=0.008$), $QRSD_{III}$ (AUC=0.600, $p=0.004$), $QRSD_{routine}$ (AUC=0.540, $p<0.001$). In contrast there was no significant difference observed in AUC when comparing $\Delta QRSD_{global}$ to each of $\Delta QRSD_{II,aVR,V5}$.

Table 2.2: Pre-CRT QRSD, post-CRT QRSD and ΔQRSD by CRT according to different methods in responders versus non-responders.

		$QRSD_{global}$	$QRSD_{I}$	$QRSD_{II}$	$QRSD_{III}$	$QRSD_{aVR}$	$QRSD_{aVL}$	$QRSD_{aVF}$	$QRSD_{V1}$	$QRSD_{V2}$	$QRSD_{V3}$	$QRSD_{V4}$	$QRSD_{V5}$	$QRSD_{V6}$	$QRSD_{routine}$	
Pre-CRT QRSD[ms]																
	All	172 [153;191]	152 [137;175]	161 [135;178]	159 [134;177]	153 [135;171]	155 [136;173]	158 [140;177]	161 [140;178]	161 [142;177]	160 [144;178]	160 [145;178]	167 [150;181]	161 [145;178]	158 [130;172]	†p<0.001
	NR	169 [150;184]	159 [144;183]	172 [140;178]	164 [141;176]	158 [147;178]	158 [138;182]	163 [144;181]	151 [132;185]	165 [142;178]	160 [143;186]	167 [146;186]	165 [146;182]	163 [146;179]	148 [128;170]	
	R	172 [154;191]	150 [136;173]	159 [135;177]	152 [133;179]	153 [134;169]	155 [133;171]	156 [139;174]	161 [141;177]	160 [141;177]	160 [142;176]	159 [144;177]	167 [147;180]	161 [144;181]	159 [133;174]	
Post-CRT QRSD[ms]																
	All	143 [127;159]	138 [121;154]	140 [121;159]	138 [111;153]	140 [122;159]	130 [111;153]	137 [116;153]	135 [122;148]	139 [111;153]	137 [116;150]	142 [124;153]	140 [123;154]	141 [119;153]	152 [132;176]	†p<0.001
	NR	**154 [145;190]**	154 [129;188]	**155 [138;190]**	151 [134;180]	**155 [140;183]**	149 [125;175]	148 [127;180]	142 [136;181]	**151 [137;178]**	152 [137;176]	**153 [140;181]**	**153 [144;192]**	148 [133;194]	146 [130;172]	
	R	**141 [122;153]**	138 [115;147]	**137 [112;148]**	135 [110;150]	**132 [119:153]**	130 [11;146]	135 [110;151]	132 [111;146]	**135 [111;153]**	132 [116;145]	**138 [116;147]**	**135 [116;148]**	138 [115;148]	154 [132;176]	
ΔQRSD by CRT[ms]																
	All	-27 [-14;-45]	-16 [4;-32]	-16 [0;-35]	-17 [-2;-35]	-14 [0;-27]	-19 [-5;-37]	-21 [1;-37]	-27 [-5;-37]	-26 [1;-44]	-24 [-1;-47]	-21 [-6;-43]	-25 [-7;-40]	-17 [-4;-41]	0 [18;-21]	†p<0.001
	NR	**-5 [21;-21]**	4 [20;-25]	**5 [29;-25]**	-10 [21;-34]	**4 [21;-20]**	-12 [7;-24]	-8 [7;-28]	-3 [20;-37]	**-4 [30;-22]**	**8 [23;-36]**	**-6 [20;-27]**	**-3 [29;-12]**	**-2 [29;-33]**	2 [20;-21]	
	R	**-29 [-22;-48]**	-21 [0;-32]	**-16 [-2;-44]**	-19 [-4;-36]	**-16 [0;-28]**	-20 [-6;-41]	-23 [-1;-39]	-29 [-11;-39]	**-26 [-3;-45]**	**-29 [-8;-48]**	**-24 [-12;-44]**	**-28 [-14;-42]**	**-24 [-9;-45]**	-2 [16;-22]	

Values are expressed as median [inter quartile range]. **†:** p-value comparing all measuring methods for all patients. CRT: Cardiac resynchronization therapy. All: All patients NR: Non-responding group R: Responding group $QRSD_{global}$: global QRS duration measured by custom made software. $QRSD_{I,II,III,...}$: lead-specific QRS duration measured by custom made software. $QRSD_{routine}$: QRS duration measured by a routinely used ECG device. ΔQRSD = post-CRT minus pre-CRT QRSD.

3.5. Inter- and intra-observer variability of QRSD measurements

$QRSD_{global}$ measurements revealed better inter-observer variability (ICC=0.92) compared to lead-specific QRSD (ICC=0.61). The mean variation in QRSD measurements among observers was lower for the $QRSD_{global}$ compared to lead-specific QRSD (11±4 vs. 35±12, p=0,015)

$QRSD_{global}$ measurements revealed better intra-observer variability (ICC 0.91±0.03) compared to lead-specific QRSD (ICC 0.79±0.18). The variation in QRSD between the initial and the repeated measurement of each observer was lower for the $QRSD_{global}$ compared to lead-specific QRSD (4±1 vs. 11±6ms, p=0.042)

3.6. Predictive value of various QRSD measurements on CRT response

Of all methods to measure pre-CRT QRSD, $QRSD_{global}$ revealed the highest AUC (0.580). AUC values for pre-CRT QRSD in single leads varied from 0.413 (aVR) to 0.525 (V1). Pre-CRT $QRSD_{routine}$ revealed an AUC of 0.533. Of interest, a cut off of 150ms when measuring pre-CRT QRSD using $QRSD_{global,V1,V2\ or\ routine}$ was associated with a trend to better response rate when QRSD ≥ 150ms compared to <150ms (resp. 79 vs. 71%, 81% vs. 74%, 80 vs; 73% and 80 vs. 66%, p=NS). In contrast, this trend was not observed measuring pre-CRT QRSD in the other leads.

ROC curves for post-CRT QRSD measured by $QRSD_{global}$ revealed the highest AUC (0.768) of all methods to differentiate responders from non-responders based on post-CRT-QRSD. At an optimal cutoff of 146ms, post-CRT $QRSD_{global}$ yielded a sensitivity of 75% and a specificity of 67% for CRT response. ROC curves for predicting CRT response based on lead-specific post-CRT QRSD revealed AUC-values ranging from 0.664 ($QRSD_I$) to 0.763 ($QRSD_{V5}$). Post-CRT $QRSD_{routine}$ revealed the lowest AUC (0.447) of all methods.

Of all methods $\Delta QRSD_{global}$ revealed the highest AUC (0.858) to differentiate responders from non-responders based on ΔQRSD. At an optimal cutoff of 14ms shortening, $QRSD_{global}$ yielded

a sensitivity of 96 % and a specificity of 86 % for CRT response. ROC curves for predicting CRT response based on lead-specific ΔQRSD revealed AUC values ranging from 0.600 ($\Delta QRSD_{III}$) to 0.853 ($\Delta QRSD_{V5}$). $\Delta QRSD_{routine}$ revealed the lowest AUC (0.540) of all methods.

4. Discussion

4.1. Main findings

Different methods to measure QRSD show divergent nominal values. The predictive value of QRSD measurements on CRT response is sensitive to the method by which QRSD is measured. Compared to single lead measurements $QRSD_{global}$ has the lowest inter- and intra-observer variability.

4.2. Measurement of QRS duration: QRSD global versus lead-specific QRSD

QRSD is key parameter in managing patients with heart failure and CRT. QRSD can be measured using individual leads or by using a global method, taking into account all twelve leads simultaneously.

Theoretically, measurements of QRSD in individual leads might underestimate the QRSD because isoelectric segments may occur due to a perpendicular projection of the lead orientation to the starting or ending QRS vector. Moreover, the beginning and end of the QRS complex can be hard to define in an individual lead which might lead to a substantial inter-and intra-observer variability. Prior studies reported marked inter-and intra-observer variability of QRSD measurements using individual leads. Tomlinson et al. reported a median intra-observer variability up to 25ms (range 10-50ms) and a median inter-observer variability of 35ms (range 20-50ms) when measuring the QRSD in an individual lead of the standard twelve lead ECG of a general patient group.[10] Using precordial leads only (at 50 mm/s), intra-observer variability was reduced to 12,5ms (range 10-35ms) and inter-observer variability to 12.5ms (range 0-

30ms). Likewise in the CRT population, De Guillebon et al. found significant inter-observer variability (absolute variation up to 50ms) and intra-observer variability (absolute variation up to 40ms) when measuring the QRSD manually in the individual lead showing the widest QRS complex.[9] This large inter- and intra-observer variability by using individual leads was confirmed in our study.

Measurements of global QRSD ($QRSD_{global}$) is based upon measuring the QRSD between the earliest onset of the QRS waveform in any lead till the latest offset in any lead.[11] This method has been recommended by the AHA/ACC/HRS guidelines on general ECG interpretation. In case of paced QRS complexes showing latency between the pacing spike and the QRS waveform, the onset of the QRS waveform is taken as start of the QRSD measurement.

In the CRT population measurements of QRSD are not standardized and no preferred technique is specified.[8-10] We introduced and validated a custom-made algorithm to measure global QRSD ($QRSD_{global}$). This method showed lower inter- and intra-observer variability compared to the use of lead-specific QRSD. This might be explained by a better identification of the beginning and end of the QRS complex when using all leads simultaneously.

4.3. Critical appraisal of prior studies.

ESC guidelines on CRT consider baseline QRSD as a key parameter in setting the indication for CRT. A QRSD threshold > 120ms is often recommended to select candidates eligible for CRT[8], whereas guidelines on heart failure recommend a QRSD threshold > 150ms in patients without left bundle branch block[14].

In the REVERSE trial pre-CRT QRSD was found to be a good predictor of CRT response, when using the mean of the QRSD in leads II, V1 and V6.[15] A recent meta-analysis confirmed that patients with QRS duration ≥150ms have more benefit of CRT than patients with QRSD <150ms.[16] Our study was not set up to verify the results of these large studies. Of interest, in

our study a trend to better response was observed when comparing patients with pre-CRT-$QRSD_{global}$ ≥150ms versus those with pre-CRT $QRSD_{global}$ <150ms. No statistical significance was reached, most likely due to low sample size. The same was true for pre-CRT $QRSD_{V1,V2}$ and routine. On the other hand, this study demonstrated that the predictive value of pre-CRT QRSD in a small sample size varies significantly according to the method used. Our study might explain the results of other studies which are in contrast with the REVERSE trial. First, most of these studies have small sample size and secondly, these studies used QRSD measurements in single leads that differ from the method used in the REVERSE trial (mean of QRSD in leads II, V1 and V6). Indeed Molhoek et al. demonstrated the pre-CRT QRSD not to be significantly different between responders and non-responders.[17] The QRSD was measured as the maximum value in lead II, V1 or V6. Likewise, Mollo et al. found no significant difference in pre-CRT QRSD, measured in lead V1 and V6, between responders and non-responders.[12] Del-Carpio et al. measured the pre-CRT QRSD in leads I, aVL, V1, V2, V5 and V6, but QRSD measured in these leads neither predicted CRT response.[18] Dupont et al. found pre-CRT QRSD inferior to QRS morphology to predict CRT response (using an automatically calculated QRSD by ECG analysis software).[19] Lecoq et al found pre-CRT QRSD not predictive of CRT response, although the method to measure the QRSD was not specified in their study.[20]

The REVERSE trial observed CRT-induced shortening in QRSD not to be predictive by using the mean of QRSD in leads II, V1 and V6.[15] Our study was underpowered to assess the predictive value of CRT induced shortening in QRSD. On the other hand, as we measured the shortening of QRSD by different methods, we demonstrated that the predictive value of QRSD shortening in a small sample size varies according to the method used. This may explain the findings of the REVERSE trial (using the mean of leads II, V1 and V6) who are in contrast with smaller prior studies using maximums of single leads. Indeed, in contrast with the REVERSE

trial, Molhoek et al. found the shortening in QRSD after biventricular pacing predictive for CRT response using the maximum QRSD of leads II, V1 or V6.[17] They identified an optimal cutoff value of 30 ms shortening, but yielded a low sensitivity (58%) and low specificity (56%) in predicting CRT response. Lecoq et al found that shortening in QRSD was the single best predictor of response to CRT in multivariable analysis, although, they did not define a reliable cutoff for QRSD shortening and the method to measure QRSD was not specified.[20] Conversely Rickard et al. found that the widening in QRSD after CRT is associated with deteroriation in left ventricular function.[21] Their results are based on QRSD measurement by computer analysis (confirmed by visual inspection).

In our study $\Delta QRSD_{global}$ reveals higher AUC than single lead measurements, which suggests a better diagnostic accuracy of QRSD shortening using the $QRSD_{global}$ as compared to the use of lead-specific QRSD. Given this strong AUC of $\Delta QRSD_{global}$, it would be of interest to reassess the results of the REVERSE trial using this method.

4.4. Automated QRSD measurements with commercially available ECG recording devices

Current ECG recording devices provide automatic measurements of QRSD. Although no specific descriptions are available, the commercial ECG device used in our study is based upon assessment of the QRSD by taking into account the first detected Q wave as the onset and the latest S wave as ending of the QRS complex. Pacing spikes are not taken into account as onset of the QRS complex. In the present study the commercial QRSD measurements ($QRSD_{routine}$) yielded QRSD values significantly different from digitally assisted measurements. Prior studies also reported on low concordance between commercially available automated QRSD measurements and manual measurements, both for paced and unpaced ECGs.[9] Moreover, in the present study, QRSD measured by a routinely used ECG device revealed low predictive value of CRT response both for pre-$CRT_{routine}$, post-$CRT_{routine}$ and $\Delta QRSD_{routine}$.

4.5. Clinical implications

Clinicians and researchers should be aware that both nominal values and the predictive value for CRT response based on QRSD measurements are sensitive to the method by which QRSD is measured. This makes studies on QRSD in CRT patients difficult to compare and may explain conflicting results. Moreover as QRSD has a key role in setting the indication for CRT, consistent measurements of the QRSD may improve identification of eligible candidates for CRT.

Methods to measure QRSD in CRT patients are not standardized and automatic computer-calculated QRSD measurements by a routinely used ECG device may not be reliable. QRSD measurements based on such an algorithm revealed poor predictive value for CRT response in our study. This however was done using only one commercial system, as such, we are not able to report the performance of the algorithms in other commercial systems.

Measurements in a single lead, such as V5, may be fairly well in approximating the nominal value of the global QRSD and in predicting CRT response. $QRSD_{global}$ however, showed a lower inter- and intra-observer variability as compared to single lead measurements. Using a global method for measuring QRSD could be of value in standardizing QRSD measurements in clinical practice and future studies.

When tailoring CRT to individual patients clinicians should understand how the method of QRSD measurements may influence the shortening in QRSD after biventricular pacing. Shortening in $QRSD_{global}$ of at least 14ms can predict CRT response with a sensitivity of 96% and a specificity of 86%. As such, aiming for the largest shortening in $QRSD_{global}$, by selecting the most appropriate LV-pacing site during CRT implant and by optimizing AV and VV delays, may enhance response to therapy.

5. Limitations

No standardized definition of response to CRT is used in literature. We used a combination of both echocardiographic improvement (increase in LVEF > 7.5%) and an improvement in clinical performance status (improvement of at least one class in NYHA Classification). Increases in LVEF varying between 5 and 10% have been used to determine response to CRT, whether or not with evaluating clinical performance status.

Inter- and intra-observer variability were evaluated in a limited number of patients. We did not evaluate the accuracy of the QRSD measurements using other commercially ECG-recording devices. Further validation of the accuracy of $QRSD_{global}$ requires comparison with intracardiac mapping (as gold standard).

6. References

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CHAPTER 3

Biventricular paced QRS area predicts acute hemodynamic CRT response better than QRS duration or QRS amplitudes

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Abstract:

Introduction *Vectorcardiographic (VCG) QRS area of left bundle branch block (LBBB) predicts acute hemodynamic response in cardiac resynchronization therapy (CRT) patients. We hypothesized that changes in QRS area occurring with biventricular pacing (BV) might predict acute hemodynamic CRT response (AHR).*

Methods and results: *VCGs of 624 BV paced electrocardiograms (25 LBBB patients with 35 different pacing configurations) were calculated according to Frank's orthogonal lead system. Maximum QRS vector amplitudes (X_{Ampl}, Y_{Ampl}, Z_{Ampl} and $3D_{Amp}$) and QRS areas (X_{Area}, Y_{Area}, Z_{Area} and $3D_{Area}$) in the orthogonal leads (X, Y and Z) and in 3D projection (3D) were measured. Volume of the 3D vector loop and global QRS duration (QRSD) on the surface ECG were assessed. Differences (Δ) in VCG parameters between BV paced and LBBB QRS complexes were calculated. An increase of 10% in dP/dt max was considered as AHR. LBBB conduction is characterized by a large Z_{Area} (109μVs, inter quartile range (IQR):75;135), significantly larger than X_{Area} (22μVs, IQR:10;57) and Y_{Area} (44μVs, IQR:32;62, $p<0.001$). Overall QRS duration, amplitudes and areas decrease significantly with biventricular pacing ($p<0.001$). Of all vectorcardiographic parameters $3D_{Ampl}$, $\Delta 3D_{Ampl}$, $Z_{Area,}$ ΔZ_{Area}, $\Delta 3D_{Area}$ and ΔQRSD differentiate AHR response from non-response ($p<0.05$). ΔZ_{Area} predicted best positive AHR (Area under the curve, AUC=0.813) and outperformed any other VCG parameter or QRSD measurement.*

Conclusion: *Of all VCG parameters, reduction in QRS area, calculated in Frank's Z lead predicts acute hemodynamic response best. This method might be an easy, non-invasive tool to guide CRT implantation and optimization.*

1. Introduction

Cardiac resynchronization therapy (CRT) improves morbidity and mortality in patients with left bundle branch block (LBBB) and systolic heart failure.[1] Biventricular (BV) pacing of the right (RV) and left ventricle (LV) aims to resynchronize the abnormal conduction in these patients. In current clinical practice, electrocardiographic (ECG) parameters, such as QRS duration (QRSD) and QRS morphology, are the most widely accepted methods to select patients for CRT.[2-4] Recently, the area of the QRS complex (QRS area) obtained by vectorcardiography (VCG) has been proposed as a new parameter to select patients eligible for CRT.[5, 6] The QRS area of the intrinsic LBBB, which combines both QRSD and QRS morphology, has shown to predict CRT response and regions of delayed left ventricular activation better than QRSD or current LBBB definitions. We hypothesized that changes in VCG parameters, such as QRS area, occurring with biventricular pacing (BV), might function as a non-invasive tool to predict acute CRT response.

2. Methods

2.1. Study design and subjects

Patients were enrolled in a prospective, multicenter, non-randomized CRT study (iSPOT) evaluating LV contractility using positive LV dP/dt max (mmHg/s), between various BV and multisite pacing protocols.[7] The study was conducted at 7 hospitals in Europe and the Middle East. All patients had an indication for CRT according to ESC and ACCF/AHA guidelines.[8, 9] All subjects had LBBB conduction pattern and stable sinus rhythm at the time of implant. The study was approved by local ethics committees and all patients gave written informed consent.

2.2. CRT-implant, pacing protocol and response definition

BV pacing was performed by pacing the RV apex and seven different LV pacing configurations (Figure 3.1). A venogram was obtained to identify the target vessels for left ventricle (LV) stimulation. A posterolateral vein was targeted with a multipolar lead to achieve three LV pacing configurations (BV_1:distal, BV_2: mid or BV_3: proximal electrode of multipolar LV lead) and one multispot (MS) pacing configuration (LV pacing on all three electrodes of the multipolar lead). Subsequently an anterior and posterior coronary vein were cannulated with a standard bipolar LV lead to perform BV pacing with respectively an anterior LV lead (BV_4) and a posterior LV lead (BV_5). The seventh LV configuration included multivein (MV) pacing by using both LV leads in the anterior and posterior vein. LV lead positions were determined by fluoroscopy.

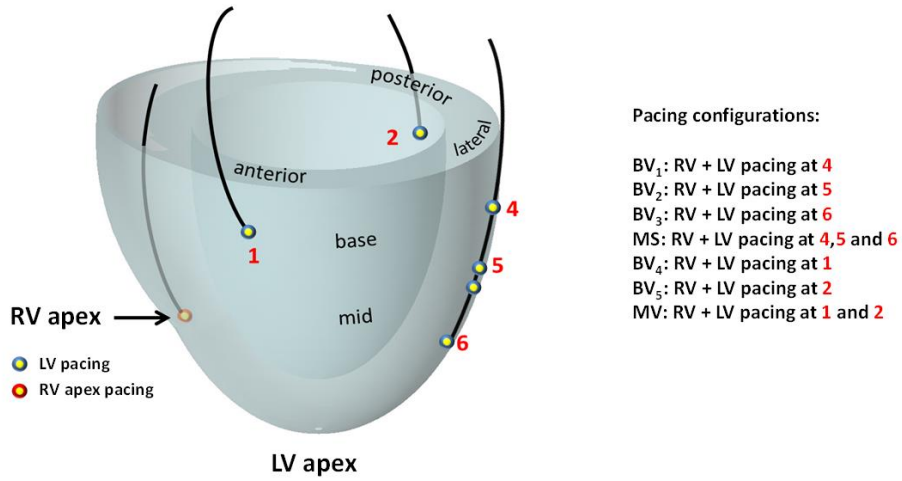

Figure 3.1 *Overview of the different LV lead positions to achieve seven different biventricular (BV) pacing configurations. LV: left ventricle, MS: multispot pacing. MV: multivein pacing, RV: right ventricle*

The heart rate was kept constant by atrial pacing at a rate of 100 bpm, identical for baseline AAI and BV, MS and MV pacing. For each configuration, measurements were performed at 5 different sensed atrioventricular (AV) delays (i.e. patient specific optimal AV delay determined by the CardioSync algorithm[10], optimal AV delay +/- 20 and +/- 40ms). All configurations used an interventricular (VV) pacing delay of 0ms. At each pacing configuration and AV-delay the heart was paced during 20 beats interspersed with baseline pacing (AAI; 20 beats). Each setting was repeated four times and mean measurements were used. Pacing was performed using four individual cardiac stimulators (5388 DDD, Medtronic plc, Maastricht, The Netherlands) synchronized by a Model 2090 programmer for simultaneous, independent, multisite ventricular stimulation. During implantation customized 9 leads ECGs were applied (Figure 3.2, left panel) which enabled the construction of an accurate and reliable spatial vectorcardiography.[11] All ECGs were recorded at sampling rates of 1000Hz and stored digitally for off line analysis.

At each pacing configuration, the maximum LV pressures (dP/dt max) were measured (Micro-CathTM, Millar, TX). The mean change in dP/dt max from baseline AAI pacing was used to define acute hemodynamic response. An increase of 10% in dP/dt max was considered as positive acute hemodynamic response (AHR), as previously defined.[12]

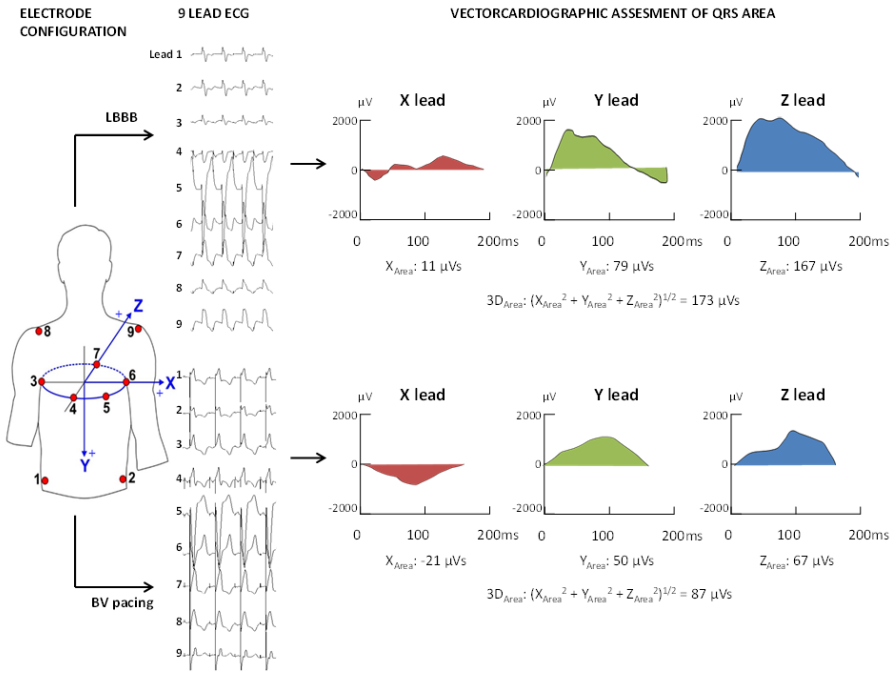

Figure 3.2 Left: *Model of the customized 9 lead electrocardiogram (ECG) with position of the electrodes on the patient. The three orthogonal (X, Y and Z) leads according to Frank's orthogonal leads system are shown* ***Middle:*** *Nine lead ECG of left bundle branch block (LBBB) configuration (top panel) and during biventricular (BV) pacing (lowe panel, patient 14, RV apex and LV pacing in the mid posterolateral vein, AV delay -40ms)* ***Right:*** *Conversion of 9-lead ECG to vectorcardiography with determination of QRS area in the X, Y and Z lead (Respectively X_{Area}, Y_{Area} and Z_{Area}). QRS area in the 3D vector loop ($3D_{Area}$) is calculated based on X_{Area}, Y_{Area} and Z_{Area}. With LBBB Z_{Area} is larger compared to the X_{Area} and Y_{Area}. With BV pacing, reduction in Z_{Area} is most distinct*

2.3. Vectorcardiographic parameters and global QRS duration

Custom made software (Matlab software, Mathworks, MA, US) was used to convert digital ECGs to VCGs according to Frank's orthogonal lead system (Figure 3.2, right panel).[11] Each VCG was plotted against the three orthogonal leads (X, Y, and Z) allowing to form a 3D vector. The magnitude of the maximum QRS vector was calculated as QRS vector amplitude in the

three VCG leads (X_{Ampl}, Y_{Ampl}, Z_{Ampl}) and in the 3D loop ($3D_{Ampl}$). QRS area was calculated as the integral between the ventricular deflection curve and the baseline from the beginning to the end of the QRS complex in leads X, Y and Z (X_{Area}, Y_{Area}, Z_{Area}). QRS area in the 3D vector loop ($3D_{Area}$) was calculated as $(X_{Area}^2 + Y_{Area}^2 + Z_{Area}^2)^{1/2}$, as previously reported.[6] The volume of the 3D vector loop ($3D_{Vol}$) was estimated by a convex hull method using Qhull algorithm (Matlab software, Mathworks, MA, US).[13]

QRSD was measured on the surface ECG using global QRS duration, defined as the interval between the earliest onset of the QRS waveform among any lead till the latest offset in any lead.[14, 15] With ventricular paced QRS complexes the onset of the QRS complex and not the pacing spike was considered as the beginning of the QRS complex.

QRSD and VCG parameters were calculated during AAI pacing (LBBB) and for each BV configuration (5BV, 1MS and 1 MV) at five different AV delays. Differences between ventricular paced QRS complexes and intrinsic LBBB were calculated for every VCG parameter (Δ= paced VCG - LBBB VCG, respectively ΔQRSD, ΔX_{Ampl}, ΔY_{Ampl}, ΔZ_{Ampl}, $\Delta 3D_{Ampl}$, ΔX_{Area}, ΔY_{Area}, ΔZ_{Area}, $\Delta 3D_{Area}$, $\Delta 3D_{Vol}$). QRSD and VCG parameters were compared to changes in left ventricular pressure, expressed as dP/dt max.

2.4. Statistical Analysis

Continuous variables are expressed as mean ± standard deviation or median; interquartile range (IQR) if data were non-Gaussian distributed. Categorical variables are expressed as absolute number with percentage (%). Linear mixed-effects models were used to account for different pacing configurations and multiple VCG measurements originating from the same patient. Comparison among groups is done by Mann-Whitney U test or Wilcoxon Signed Rank for paired analysis. Receiver operating characteristic (ROC) curves are constructed to determine the diagnostic performance of different VCG parameters in identifying acute hemodynamic

CRT response. Statistical significance is set at a 2-tailed probability level of <0.05. All statistical analysis is performed using SPSS software (Version 22.0, IBM, Armonk, NY, US).

3. Results

3.1. Study population and hemodynamic response

Patients clinical characteristics are summarized in Table 3.1. All patients (n=25) had LBBB and QRSD ≥ 120ms. VCGs of baseline QRS complexes (LBBB) were acquired during AAI-pacing in all patients. Out of 875 predefined pacing configurations (25 patients, 35 pacing configurations), 188 (21.5%) pacing configurations were excluded due to the inability to cannulate the target vein or due to unstable capture. Sixty-three (7.2%) ventricular paced electrograms were excluded as the pacing stimulus caused distortion at the onset of the QRS complex, which impeded further accurate VCG analysis. VCG conversion was successfully analyzed in 624 (71.3%) BV, MS or MV paced configurations.

With AAI pacing, baseline dP/dt max was 721±186 mmHg/s and increased to 854±213 mmHg/s with ventricular pacing (p=0.04, all configurations). According to different LV pacing configurations, dP/dt max measured in BV_1: 869±234 mmHg/s, BV_2: 862±203 mmHg/s, BV_3: 852±231 mmHg/s, BV_4: 836±196 mmHg/s, BV_5: 838±208 mmHg/s, MS: 874±228 mmHg/s, MV: 847±202 mmHg/s. Overall, differences among all LV lead pacing configurations were non-significant (Kruskal Wallis, p=0.904). When comparing individual configurations pairwise, BV_2 revealed higher dP/dt max measurements compared to BV_4 (p=0.02). MS and MV pacing configurations did not reveal significant better dP/dt max compared to BV_1, BV_2 or BV_3 pacing. Out of 624 electrograms, 535 electrograms (86%) were characterized by positive AHR (i.e. increase of >10% in dP/dt max compared to baseline).

Table 3.1: Patient characteristics

Patient characteristics	
Male (n,%)	21 (84%)
Age (years)	61 ± 13
LVEF (%)	24 ± 6
NYHA (n,%)	
Class II	10 (40%)
Class III	15 (60%)
Cardiomyopathy	
Non-ischemic (n,%)	11 (44%)
Ischemic (n,%)	14 (56%)
LBBB	25 (100%)
QRS duration (ms)	180 ± 25

Table 3.1: *Patient characteristics of the study population. LBBB: Left Bundle Branch Block; LVEF: Left Ventricular Ejection Fraction; NYHA: New York Heart Association Classification*

3.2. VCG parameters during LBBB conduction

VCG parameters during LBBB conduction are summarized in Table 3.2. Z_{Ampl} (Median: 1.57mV) and $3D_{Ampl}$ (1.78mV) were significantly greater compared to X_{Ampl} (0.39mV) and Y_{Ampl} (0.71mV) ($p<0.001$). Likewise, Z_{Area} (109μVs) and $3D_{Area}$ (145μVs) were significantly larger compared to X_{Area} (22μVs) and Y_{Area} (44μVs) ($p<0.001$). A representative example of a LBBB VCG loop, projected in the frontal (X-Y), horizontal (Y-Z) and left sagittal plane (Y-Z plane), is illustrated in figure 3.3. During LBBB conduction, a dominantly leftward and posterior orientated ventricular activation front can be appreciated in these planes.

Table 3.2: VCG parameters during LBBB and ventricular pacing

	LBBB	Ventricular pacing	Difference (Δ)		p-value*
QRSD (ms)	180 [164;194]	151 [140;164]	**ΔQRSD**	-31 [-45;-11]	p<0.001
X_{Ampl} (mV)	0.39 [0.34;0.86]	-0.68 [-0.97;-0.30]	**ΔX_{Ampl} (mV)**	-1.01 [-1.48;-0.52]	p<0.001
Y_{Ampl} (mV)	0.71 [0.60;1.04]	0.43 [0.11;0.70]	**ΔY_{Ampl} (mV)**	-0.27 [-0.61;-0.040]	p<0.001
Z_{Ampl} (mV)	1.57 [1.26;1.96]	0.76 [0.25;1.12]	**ΔZ_{Ampl} (mV)**	-0.79 [-1.20;-0.44]	p<0.001
$3D_{Ampl}$ (mV)	1.78 [1.50;2.33]	1.20 [0.91;1.59]	**$\Delta 3D_{Ampl}$ (mV)**	-0.57 [-0.98;-0.22]	p<0.001
X_{Area} (µVs)	22 [10;57]	-34 [-59;-7]	**ΔX_{Area} (µVs)**	-56 [-92;-34]	p<0.001
Y_{Area} (µVs)	44 [32;62]	24 [5;44]	**ΔY_{Area} (µVs)**	-21 [-40;-4]	p<0.001
Z_{Area} (µVs)	109 [75;135]	38 [4;62]	**ΔZ_{Area} (µVs)**	-68 [-101;-40]	p<0.001
$3D_{Area}$ (µVs)	145 [118;199]	90 [62;122]	**$\Delta 3D_{Area}$ (µVs)**	-62 [-101;-27]	p<0.001
$3D_{Vol}$ (μV^3)	36 [14;61]	19 [8;44]	**$\Delta 3D_{Vol}$ (μV^3)**	-5 [-28;10]	NS

Table 3.2: *VCG parameters during LBBB, ventricular pacing (median of biventricular, multivein and multispot pacing) and differences between LBBB and ventricular pacing (Δ). *p-Value indicates significance between LBBB and ventricular paced VCG parameter (linear mixed-effects model). LBBB: Left Bundle Branch Block*

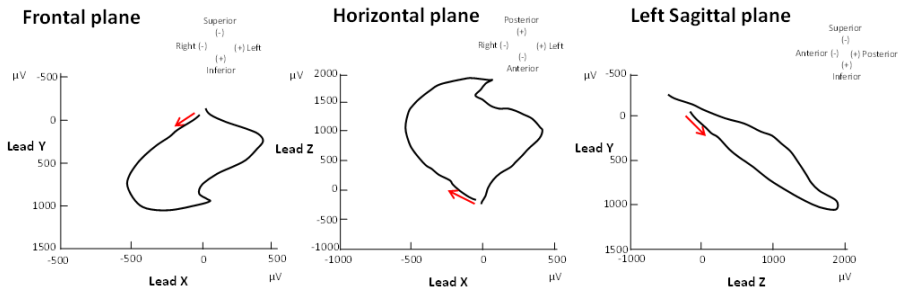

Figure 3.3 *Vectorcardiography of left bundle branch block (LBBB) (patient 14) projected in the three classical planes: frontal (XY), horizontal (XZ) and left sagittal plane (YZ). A dominant posterior and leftward orientated ventricular wave front is seen in typical LBBB. Red arrow indicates start and direction of the ventricular activation wave front*

3.3. Changes in VCG parameters with BV, MS and MV pacing

With ventricular pacing (BV, MS and MV) VCG parameters and QRSD decreased significantly ($p<0.001$) compared to LBBB, except for the volume of the 3D vector loop (Table 3.2). Decreases in ΔY_{Ampl} (-0,27 mV) were smaller compared to ΔX_{Amp} (-1.01mV), ΔZ_{Ampl} (-0.79mV) and $\Delta 3D_{Ampl}$ (-0.57mv) ($p<0.01$). Decreases in ΔY_{Area} (-21μVs) were smaller compared to ΔZ_{Area} (-68μVs), 3DArea (-62μVs) and ΔX_{Area} (-56μVs) ($p<0.01$). A representative example of the changes in QRS area during BV pacing is shown in Figure 3.2, right panel.

Taking into account different pacing locations of the LV lead, QRSD with MS (143±15ms) and BV_2 (144±18ms) revealed the smallest QRSD, whereas QRSD was widest for BV_3 (164±24ms, $p<0.001$). BV_4 revealed the smallest decreases for ΔY_{Ampl}, ΔZ_{Ampl}, ΔY_{Area} and ΔZ_{Area} compared to BV_{1-3}, BV_5, MS and MV configurations ($p<0.05$) (data not shown).

3.4. Prediction of acute hemodynamic response

During ventricular pacing, only $3D_{Ampl}$ and Z_{Area} of the paced QRS differentiated response from non-response (1.14mV vs 1.46mV, p=0.01 and 30μVs vs 57μVs, p=0.003 respectively, p values by linear mixed-effects regression analysis). Areas under the curve (AUC) were higher for Z_{Area} (AUC=0.727) than $3D_{Ampl}$ (AUC= 0.633).

Accounting for the differences between paced and LBBB VCGs; $\Delta 3D_{Ampl}$, ΔZ_{Area}, $\Delta 3D_{Area}$ and ΔQRSD differentiated response from non-response respectively $\Delta 3D_{Ampl}$: -0.66 vs. -0.35mV, $p<0.001$; ΔZ_{Area}: -74 vs. -19μVs, p=0.013; $\Delta 3D_{Area}$: -70 vs. -32μVs, p=0.011; ΔQRSD: -32 vs. -11ms, p=0.02 (p-values by linear mixed-effects regression analysis). The diagnostic accuracy to predict acute response was highest for ΔZ_{Area} (AUC=0.813) and significantly different from Z_{Area} (0.727, p=0.02), $\Delta 3D_{Area}$ (0.716, p=0.01), ΔQRSD (0.694, p=0.002) and $\Delta 3D_{Ampl}$ (0.592,

p<0.001) (Figure 3.4). ΔZ_{Area} revealed an optimal cutoff to predict positive AHR at -57μVs, with a sensitivity of 81% and specificity of 72%. In individual patients AUC of ΔZ_{Area} measured 0.840 ± 0.120. For positive AHR at cutoffs of 15, 20 and 25% increase in dP/dt max, ΔZ_{Area} remained the best predictor (AUC 0.766 ± 0.046).

No significant differences in predictive value (AUCs) for the discriminating VCG parameters were documented based on etiology (ischemic versus non-ischemic). In both ischemic and non ischemic patients, ΔZ_{Area} was also the best predictor (AUCs 0.776 versus 0.825, p=NS). Categorizing the patients according to baseline QRSD (<150ms or ≥ 150ms), ΔZ_{Area} showed higher predictive value in patients with wide QRSD compared to narrow QRSD (AUCs 0.869 versus 0.764, p=0.015). However in patients with narrow QRSD, ΔZ_{Area} still remained the best predictor of acute CRT response.

Of all VCG parameters, differentiating response from non-response, ΔZ_{Area} revealed the highest correlation to dP/dt (r_s: -0.66, p<0.001). Correlation coefficients for the other differentiating VCG parameters were Z_{Area} (r_s: -0.48), $\Delta 3D_{Area}$(r_s: -0.35), ΔQRSD (r_s: -0.32), $3D_{Ampl}$ (r_s:-0.239) and $\Delta 3D_{Ampl}$ (r_s: -0.26, p<0.001 for all) (Supplemental Figure 3.1).

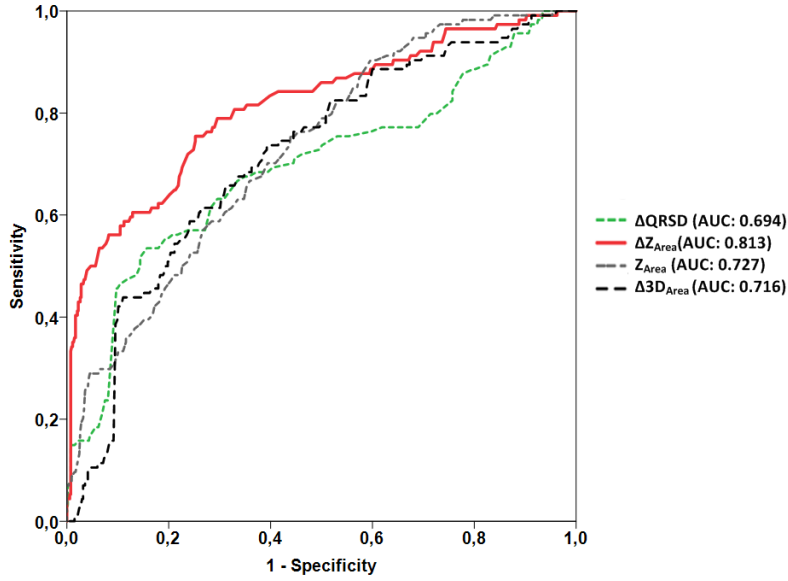

Figure 3.4 *ROC curves of VCG-parameters with an area under the curve (AUC) > 0.650 to predict acute hemodynamic response.*

3.5. Prediction of optimal AV delay and best LV lead position

No significant differences in positive AHR were found for each 20ms stepwise increase in AV delay, although the highest AHR was noticed at the optimal AV delay (Figure 3.5). Likewise, differences among VCG parameters were not significant with 20ms changes in AV delay. However, the smallest Z_{Area} and largest changes in ΔZ_{Area} can be observed at the optimal AV delay. Both the lowest Z_{Area} and ΔZ_{Area} identified the optimal AV delay with a median accuracy of 20ms [IQR: -20;0]. Positive AHR between different pacing configurations was not significantly different except for BV_4 compared to BV_2 (increase in dP/dt max 17mmHg/s, IQR=17:33 vs. 27 mmHg/s, IQR=12:28, p=0.024). This less favorable response was identified by lower decreases in ΔZ_{Area} occurring with the BV_4 compared to BV_2 (-45µVs, IQR=-72:-19 vs. -81µVs, IQR=-101:60, p<0.001) (Figure 3.6).

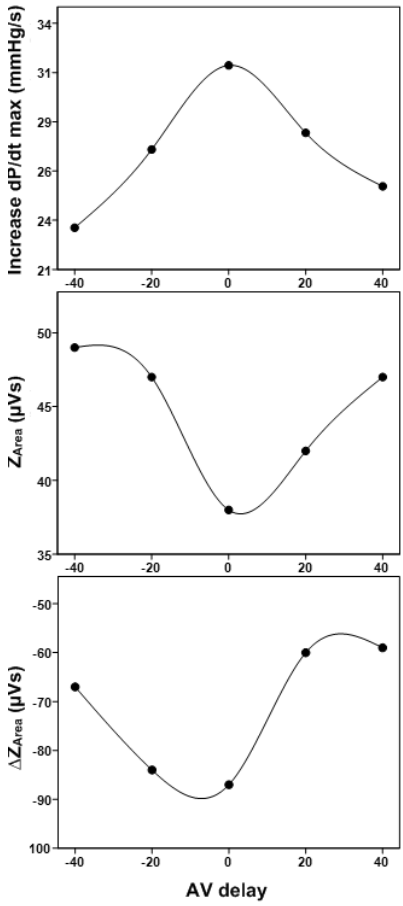

Figure 3.5 *Optimal AV delay predicted by the CardioSync algorithm. Median values of all patients (n=25) for the BV_2 configuration (LV lead in a mid posterolateral branch) are shown* ***Upper Panel:*** *Optimal AV delay corresponding with the highest dP/dt max* ***Middle panel****: The smallest ventricular paced Z_{Area} coincides with the optimal AV delay.* ***Left panel:*** *The minimum value of ΔZ_{Area} coincides with the optimal AV delay*

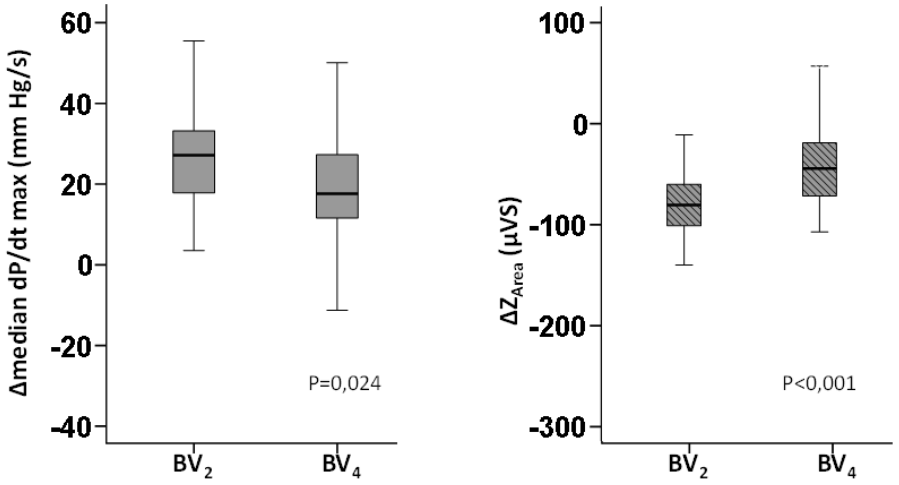

Figure 3.6 *The BV_4 configuration (LV lead in an anterior vein) showed less favorable acute hemodynamic response compared to BV_2 pacing LV lead in a mid posterolateral vein). This less favorable response is reflected in smaller ΔZ_{Area} values for BV_2 versus BV_4*

3.6. Optimizing CRT therapy to ΔZArea : comparison with clinical predictors

Differences in acute hemodynamic CRT response predicted by clinical parameters was low: non ischemic etiology showed 10% increase in dP/dt max compared to ischemic, QRSD of ≥ 150ms to narrow QRSD :12% increase in dP/dt max and posterior versus anterior LV lead position: 10% increase in dP/dt max. However when optimizing CRT therapy using ΔZ_{Area} (optimal cutoff at -57 μVs), configurations with large ΔZ_{Area} revealed 23% increase in dP/dt max compared to configurations with low ΔZ_{Area}

4. Discussion

4.1. Paced QRS area and prediction of CRT response

In this study we analyzed different VCG parameters to predict acute hemodynamic response in a wide range of BV, MS and MV pacing configurations at different AV delays. With ventricular

pacing both QRS amplitudes and QRS areas in all three orthogonal Frank leads and in the 3D vector loop decreased significant compared with LBBB conduction. Interestingly this was not the case for the volume of the 3D vector loop, calculated by the convex hull method. Presumably this method is not accurate enough to estimate the real 3D volume of the vector loop.

Of all paced QRS areas only the paced Z_{Area} predicted positive AHR. Paced $3D_{Area}$ did not differentiate between response and non-response. This is in contrast with the study of van Deursen et al., who found $3D_{Area}$ useful to define optimal AV and VV delays. However, in their study, QRS areas limited to one lead were not investigated separately. Our findings suggest that a potential predictive value of $3D_{Area}$ is mainly driven by the share of Z_{Area}. Predictive value of paced Z_{Area} and $3D_{Area}$ could be increased when accounting for the difference compared to LBBB (i.e. ΔZ_{Area} and $\Delta 3D_{Area}$). Of all parameters, ΔZ_{Area} predicted best positive AHR, which makes sense as the concept of CRT is to resynchronize delayed posterior LV activation in LBBB conduction and therefore reducing the Z_{Area}. This is in line with the findings of van Deursen et al. describing the largest changes in maximum amplitude to occur in a posterior orientation with effective BV pacing.[16] Data concerning QRS morphology with BV pacing to predict CRT response are limited. An R-wave in lead V1 is generally considered proof of posterolateral LV capture during BV pacing and may predict CRT response [17-19]. However some authors report that up to 30% of CRT patients do not show an R-wave in lead V1 during BV pacing, which may limit the use of this method [20] and may favor the use of QRS area measurements. Moreover, our study demonstrates that change in Z_{Area} outperforms well-known clinical predictors of acute CRT response such as non ischemic etiology, wide baseline QRSD and posterior LV lead locations.

As our study was not set up, neither by concept nor by design, this study cannot conclude that reduction in QRS area predicts chronic CRT response. However recent literature provide some

indirect arguments why reduction in paced QRS area might be promising to predict long-term CRT response. It has been shown that baseline QRS area during LBBB predicts chronic CRT response [6]. Van Deursen et al. showed that the larger the QRS area at baseline, the more likely the patient will have a positive CRT response at six months. This is in line with our findings. Additionally it has been shown in literature that shortening in QRS duration with biventricular pacing is a marker to predict chronic CRT response [14, 21, 22]. As QRS area is the result of both QRS duration and amplitude, reducing paced QRS duration certainly reduces also the paced QRS area. As our study demonstrated that reduction in QRS area is more predictive than shortening in QRS duration for acute CRT response, this reduction in paced QRS area seems promising to predict chronic CRT response. Another intriguing question is whether reduction in paced QRS area (electrical changes after pacing) relate to resolving of dyssynchrony (functional changes after pacing). Although baseline QRS area identifies delayed left ventricular wall activation, causing dyssynchrony, it is currently unclear whether reduction in QRS area by BV pacing relates to the abolition of dyssynchrony [5]. The value of BV paced QRS area to predict both long-term clinical follow up and to resolve dyssynchrony should be determined in a larger, more heterogeneous population.

4.2. Paced QRS duration and prediction of CRT response

Reduction in Z_{Area} predicts better CRT response than shortening of QRSD, which may be explained as QRS area combines both QRSD and QRS morphology. Whether shortening in QRSD predicts CRT response has been a matter of debate since the introduction of CRT. [3, 22, 23] Other authors reported QRS widening after CRT implant to be associated with deterioration of left ventricular function.[24] Part of this heterogeneity in literature may be explained by different methods used to measure the QRSD. [25] In this study, global QRSD was measured on

the surface ECG, as recommended by guidelines.[15] This method has low inter- and intra-observer variability compared to single lead QRSD measurements, when measuring QRSD in LBBB and paced QRS complexes. [25] Although paced QRSD solely does not predict CRT response, shortening in global QRSD does predict CRT response, but its predictive value is moderate compared to Z_{Area}. Additionally, previous work of the group of Prinzen has shown that VCG measurements such as QRS area are highly reliable in terms of reproducibility.[16, 25] A representative example of the robustness of QRS area compared to QRSD measurements is shown in Supplemental figure 3.2.

4.3. QRS area in LBBB patients

Values for $3D_{Area}$ in our LBBB population was within the same range as previously reported and is approximately three times larger compared to healthy adult patients without LBBB. [6, 26] Our data show that the extent of $3D_{Area}$ was mainly attributed to a large Z_{Area} which has a QRS area twice that of Y_{Area} and even fivefold that of X_{Area}. Previous studies investigated the QRS area during LBBB solely in the 3D vector loop, but reported data revealed large maximum amplitudes in the Z lead, which may indicate that also in these studies the large $3D_{Area}$ is mainly driven by a large Z_{Area}. This large Z_{Area} in LBBB patients, with the Z lead representing an anteroposterior axis, can be explained by strong unopposed electrical forces generated by the delayed activation of the posterior and basal parts of the LV, as typically seen in LBBB.[27]

van Deursen et al. reported that a QRS area of the 3D vector loop of > 98μVs is a good predictor for chronic CRT response and even outperforms most LBBB definitions.[6] Mafi et al. showed a clear correlation between QRS area of the 3D vector loop and delayed left ventricular activation, when using a cut off > 69μVs.[5] The median $3D_{Area}$ in our study was higher than those cut offs, which may be linked to the high response rate in this study (86% of the configurations showed positive AHR).

4.4. Optimal AV-delay and LV lead position prediction by QRS area

Within the tested range of AV delays, changes in both dP/dt, Z_{Area} and ΔZ_{Area} were small, although trends to larger reductions in Z_{Area} corresponding with a trend to better dP/dt at the optimal AV delay could be observed. As Z_{Area} had an accuracy of 20ms to predict optimal AV delay, Z_{Area} might serve to the clinician as a tool for AV optimization.

Hemodynamic differences among different LV lead configurations were not significant, except for pacing from an anterior versus a posterolateral branch. MS and MV pacing did not increase AHR compared to biventricular pacing using a posterolateral branch. Hemodynamic response according to the different LV lead configurations was discussed in extent by Sterlinkski et al. [7] Interestingly, the LV lead locations with better AHR were characterized as having a lower ΔZ_{Area} compared to pacing configurations with less favorable hemodynamic response, demonstrating that reduction in Z_{Area} can identify favorable LV lead configurations. Our findings suggest that Z_{Area} may be used during implantation or at clinical follow up to select respectively the appropriate vein or best pacing bipoles on a multipolar LV lead.

4.5. Clinical Implication

Predicting and optimizing response to biventricular pacing is challenging and current existent tools like echo optimization are time consuming and operator dependent. QRS area assessment requires an ECG device, able to calculate VCG leads. Current ECG-devices can already calculate Franks VCG leads, using an inverse Dower and Kors matrix. Calculating QRS area then only requires a mathematical formula (integrating the QRS waveform). This can be incorporated in the ECG device or offered as an on-line program at the electrophysiologic lab or outpatient clinic. As such assessment of QRS area has some unique advantages: easily

obtainable, cheap investment, operator-independent, automated measurements possible, little time consuming, non-invasively. One could even think of a far field electrogram of the CRT device itself measuring QRS area and automate CRT optimization.

5. Limitations

Although the number of VCGs was high, the number of patients in this study was limited. As all patients had LBBB conduction, caution is needed to extrapolate the results to non-LBBB patients. Moreover response rate was higher than generally reported, consistent with the exclusively LBBB nature of our cohort. This study used changes in dP/dt max to predict positive AHR, but whether dP/dt max predicts chronic response is uncertain. Further investigations evaluating the decrease in Z_{Area} to predict chronic response are needed. The assessment of paced QRS area requires an invasive approach, by at least placing a pacing lead or implanting a CRT device. As such this method might be less useful to select appropriate CRT candidates. A major limitation of this study is that all pacing configurations were programmed as simultaneous biventricular pacing (VV delay 0ms). From an anatomical point of view, one may consider the different LV lead locations (with BV pacing) used in this study to act as different VV delays. Although it seems likely that electrical VV interval adjustment may reduce QRS area and further improve hemodynamics, this was not investigated as such. Reliable VCG analysis may not be possible when the onset of the QRS complex becomes disturbed by the pacing stimulus artefact (7% of the VCGs excluded due to this reason). Comparison to parameters of the standard twelve lead ECG (such as R wave amplitude in V1) could not be performed as customized nine lead ECGs, suited for VCG construction, were used.

6. Conclusion

This study analyzed nine different VCG parameters and a standardized method of QRSD in a wide range of BV, MS and MV pacing configurations. Reduction in QRS areas, calculated in the Z lead (i.e. ΔZ_{Area}), predicts acute hemodynamic response better than QRS duration or any other VCG parameter. QRS area is a non-invasive parameter which might easily be calculated out of a surface ECG. These results demonstrated that QRS area measurements have the potential to identify appropriate locations for LV lead, best bipoles of a multipolar LV lead and to optimize AV-delays.

Conflict of interest: Funding for the original multicenter trial was provided by Medtronic, Inc., Bakken Research Center (BRC), Maastricht, The Netherlands, USA. Richard Cornelussen, Hernandez Alfonso Aranda, and Berthold Stegemann are Medtronic full time employees. Dr. Sterlinski receives consulting fees from Biotronik, Medtronic, St. Jude Medical, and Zoll Medical Corporation. Dr. Sokal receives consulting fees from Biotronik, Medtronic, and St. Jude Medical. Dr. Rinaldi receives support from Medtronic. Dr Francis receives consulting fee from CVRx. Other authors: No disclosures.

Participating Centers: Aalst, OLV, Belgium. Ghent, UZ, Belgium. Ashkelon, Israel. Warsaw, Poland. Katowice, Poland. London, Healthcare NHS Trust, UK . London, St Thomas Hospital, UK.

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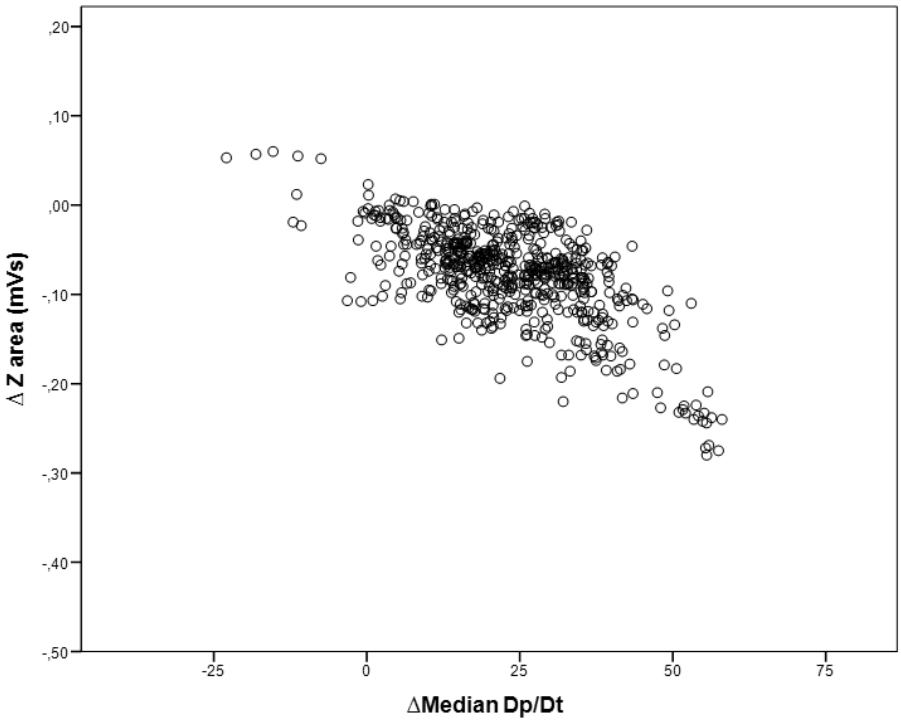
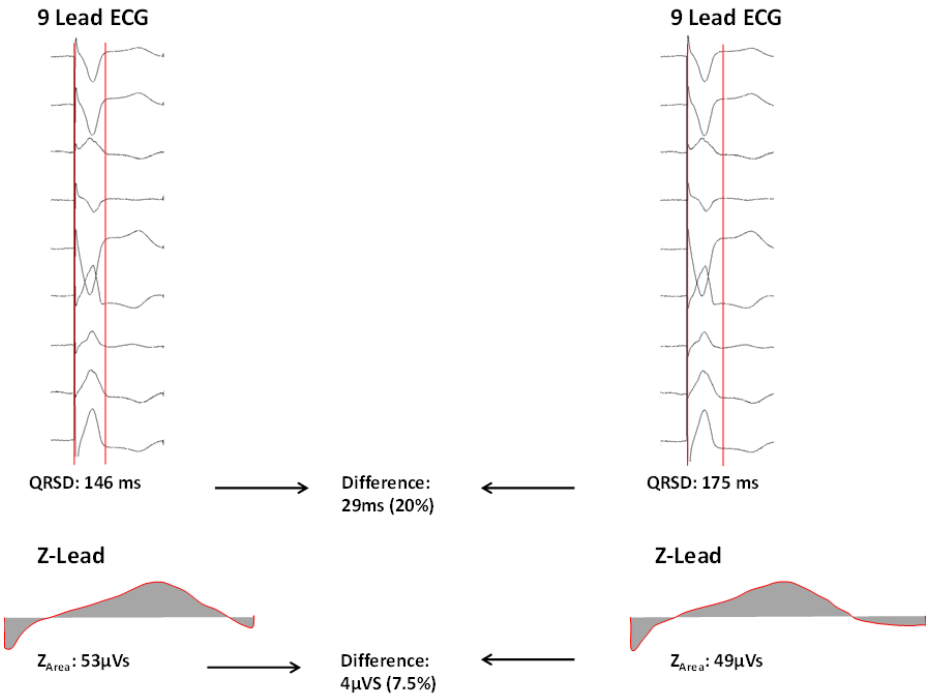
8. Supplemental figures



Supplemental figure 3.1: *Scatterplot with change in Z-area vs change in dP/dt max, Spearman's correlation coefficient (r_s) -0.66, $p<0.001$).*



Supplemental figure 3.2 *Illustration of robustness of QRS Area (Z_{Area}) compared to QRS duration (QRSD). Although QRSD differed by 29ms (20%) between two (hypothetically) measurements, Z_{Area} varies much less (difference 4µVs, 7.5%)*

CHAPTER 4

The electrocardiographic characteristics of septal flash in patients with left bundle branch block

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*Ben Corteville and Jan De Pooter equally contributed to the manuscript

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Abstract

Aim: *In patients with systolic heart failure and left bundle branch block (LBBB), septal flash (SF) movement has been described by echocardiography. We evaluated the prevalence of SF in LBBB patients and non-LBBB patients, and evaluated whether specific electrocardiographic (ECG) characteristics within LBBB are associated with the presence of SF on echocardiography.*

Methods: *One hundred and four patients with probable LBBB on standard 12-lead ECG were selected, 40 patients with non-LBBB, served as controls. LBBB and non-LBBB were defined according to most recent guidelines. The presence of SF was assessed by echocardiography.*

Results: *Strict LBBB criteria were met in 93.3% of patients. SF was present in 45.2% of LBBB patients, and was not present in non-LBBB patients. SF was more prevalent in patients without anterior ischemic cardiomyopathy compared to patients with anterior ischemic cardiomyopathy ($p=0.008$). QRS duration was longer in SF patients compared to non-SF patients ($p < 0.05$). The presence of a mid-QRS-notching in >2 consecutive leads is associated with the presence of SF ($p=0.01$), and when combined with an absent R-wave in lead V1, the presence of SF is likely ($p=0.001$).*

Conclusion: *Our data show that SF is present in 45,2 % of LBBB patients, whereas it was absent in patients with non-LBBB. Patients with SF fulfilled more LBBB criteria compared to LBBB patients without SF. Our findings raise the provocative question whether the presence of SF identifies patients with 'true LBBB' and whether this echocardiographic finding might be considered as a selection parameter in CRT.*

1. Introduction

Left bundle branch block (LBBB) can be associated with a dyssynchronous contraction of the left ventricle (LV), and these hemodynamic changes negatively affect outcome in heart failure (HF).[1,2] The main purpose of cardiac resynchronization therapy (CRT) is to restore LBBB-induced dyssynchrony. Randomized trials have consistently shown significant improvements of morbidity and mortality in patients treated with CRT.[3] Therefore, correct diagnosis of LBBB is crucial for selecting patients who most likely benefit from CRT. In 2009, the American Heart Association together with the American College of Cardiology Foundation and the Heart Rhythm Society published the recommendations for the standardization and interpretation of the electrocardiogram. In this document, several ECG criteria are proposed to identify left bundle branch block (LBBB).[1]

Echocardiographic manifestations of LBBB have been described for over 40 years. In experimental LBBB (ablation of the proximal left bundle branch in canine models)[2] and in humans with LBBB, a typical septal motion called septal beaking or septal flash (SF) has been described by echocardiography.[3] This myocardial dyssynchronous movement can be identified by echocardiography using visual 'eyeballing', anatomical M-mode or strain imaging. In SF, the early septal contraction (right to left motion) occurs before aortic valve opening and is followed by late contraction of the lateral wall of the left ventricle, that in its turn causes a left to right motion of the septum. This dyssynchrony creates a highly inefficient LV pump function, as the brief septal contraction does not contribute to the ejection of blood.[2] The SF movement is very amenable for CRT therapy as recent studies have shown that the presence of SF is highly predictive of CRT response in heart failure patients with LBBB.[3, 4] Nevertheless, this septal motion appears not to be always present in LBBB HF patients, and this might be one of the reasons of non-response in CRT patients, despite LBBB.[3]

We therefore examined the prevalence of SF in patients with typical LBBB, left anterior hemiblock (LAHB), left posterior hemiblock (LPHB) and right bundle branch block (RBBB). Furthermore, we investigated whether the presence of SF was associated with a specific ECG-pattern within LBBB.

2. Methods

2.1. Patient selection

The study patients were consecutively selected from a clinical, digitally stored ECG database at the department of cardiology and consisted of 125 randomly chosen subjects, with diagnosis of LBBB, judged by the treating physician. A different dataset of 40 non-LBBB patients (LAHB, LPHB or RBBB) was used as a control group.

Exclusion criteria were the unavailability of echocardiography at the moment of LBBB diagnosis, continuous right ventricular pacing during echocardiography or poor quality ECG. In case of device therapy (pacing/CRT), ECGs were obtained from the episode prior to CRT-implantation or, in presence of a pacemaker, ECGs were recorded in non-pacing mode.

Patients were classified as ischemic cardiomyopathy (ICMP) if either they had a history of myocardial infarction, revascularisation or showed angiographic evidence of single-vessel coronary disease.

All patients gave written informed consent. This retrospective study was approved by the Ethical Committee of the Ghent University Hospital.

2.2. ECG parameters and analysis

Baseline standard supine 12-lead electrocardiograms were recorded at a paper speed of 25mm/s and a calibration of 10mm/mV, with a standard General Electric Healthcare device type MACC 5500 or with a Schiller Cardiopulmonary Diagnostics AT 104 device. All measurements of PR-

interval, QRS-width and QTc-duration were taken from the automated report of the ECG device (GE software version 2.37 or Schiller AT 104 version 2.13 or Schiller AT 104 version 2.51).
LBBB was defined according to the standard AHA/ACCF/HRS-criteria[1]: i) QRS duration > 120 ms in adults, with the presence of ii) a broad notched and/or slurred R-wave in the lateral leads, iii) deep S-wave in the anteroseptal leads, and iv) the absence of Q-waves in the leads V5, V6 and lead I; v) T-waves are opposite in direction to the QRS or have positive concordance.

2.3. Echocardiography

Patients were imaged in left lateral decubitus with a commercially available system (GE Healthcare Ultrasound Vivid 7, Vingmed, Horton, Norway; GE Healthcare Ultrasound Vivid E9, Vingmed, Horton, Norway; Philips Ultrasound iE 33, Best, Netherlands) in conventional parasternal and apical views. Standard 2-dimensional cine-loops were recorded in all patients and analysis was performed off-line, using EchoPAC version 7.1.13 in the GE scanning system and Xcelera viewer R3 version 3.3.1 2013 was used in Philips scanning system. The left ventricular ejection fraction (EF) was judged as normal (55% or more), mildly reduced (45%-54%), moderately reduced (30%-44%) and severely reduced (< 30%).
The echocardiographic examinations were performed during the pacing-off modus or prior to PM/CRT implantation.

2.4. Assessment of septal flash

To determine the presence and extent of SF, one independent echocardiography expert (FT), blinded to the ECGs, reviewed all echocardiography images. The presence of SF was defined as reported previously and assessed based on: i) visual ‘eyeballing’ on parasternal short axis (PSSAX), parasternal long axis (PSLAX) or apical views (AP); ii) 2-dimensional anatomic M-

Mode in the PSLAX or PSSAX, or using the off-line automated M-mode to allow adjustments/perpendicularity of the cursor; and iii) using speckle tracking strain analysis (off-line, using EchoPAC version 7.1.13) in the AP views.[3, 5, 6] SF was scored as absent, moderate or manifest based on septal excursion amplitude. The degree of the inward SF excursion was assessed by eyeballing, using the M-mode and by assessing the extent of the early negative peak strain.

As a control group, the presence of SF was evaluated in 40 non-LBBB patients (LAHB, LPHB and RBBB). The diagnosis of LAHB, LPHB and RBBB was based on the surface ECG according to the AHA/ACCF/HRS-criteria.[1]

2.5. Interobserver variability

The interobserver variability for ECG characteristics was evaluated in 40 consecutive patients with LBBB by two independent observers (except for the QRSd and QTc as these parameters were measured automatically). The ECG analysis was performed by two cardiologists familiar with ECG reading and scoring (BC and JDP). The interobserver variability for echocardiographic assessment of SF was evaluated in this same population of 40 LBBB patients by two independent echocardiography experts (TDB and FT).

2.6. Statistical analysis

Statistical analysis was performed using SPSS software package Version 21 (IBM, Chicago, IL USA). Continuous variables were presented as mean ± standard deviation (SD). Where appropriate, continuous variables were assessed with a student's t-test. To compare means of two variables we used the Student t test and the Mann Whitney U-test. Categorical variables were expressed as total number (percentages) and compared between groups using the Fisher exact test. Kruskal-Wallis test was used for comparing categorical variables to continuous

variables. Multivariate analysis was used to test whether several combinations of ECG characteristics predicted SF. Binary logistic regression tests were used to assess whether some selected combinations of ECG characteristics predicted SF independent of contributing constituents of the combinations and other selected ECG characteristics. Interobserver variability was assessed using intraclass correlation coefficients (ICC). P values of < 0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

Of 125 patients, 14 patients were excluded because of unavailable echo images. Another 4 patients had continuous right ventricular or biventricular pacing during echocardiography, and were excluded. In 2 patients, ECG tracings were inappropriate and one patient refused to participate. Of the included patients 66.3% were males and 42.3% had ICMP. Mean age at the time of the ECG was 70.4yrs (± 12.7yrs). Of all patients, 10 (9.6%) had atrial fibrillation. Overall, 31.7% of patients had a pacing device at the time of ECG recording: 8 (24.2%) CRT (P or D) device, 25 (75.8%) pacemaker or ICD (Table 4.1).

One hundred and fifty patients were initially considered as negative controls, but 40 patients were finally selected based on the presence of true isolated LAHB (n=14), LPHB (n=6) or RBBB (n=20).

Table 4.1: Baseline characteristics of the patient population

Variables	Total (n = 104)	SF (n = 47)	No SF (n = 57)	p value
Age (years)	70 ± 13	69 ± 12	72 ± 13	0.258
Male	69 (66%)	27 (57%)	42 (74%)	0.502
LBBB	97 (93%)	47 (100%)	50 (88%)	0.502
Ischemic cardiomyopathy	44 (42%)	15 (32%)	26 (46%)	0.072
QRS width (ms)	146 ± 16	149 ± 15	143 ± 16	0.028*
EF (%)	49 ± 12	49 ± 12	49 ± 13	0.655
EF<45%	47 (45%)	23 (49%)	24 (42%)	0.486
NYHA	2 ± 1	2 ± 1	2 ± 1	0.828
NYHA II-IV	67 (64%)	30 (64%)	37 (65%)	0.909
Device therapy	33 (32 %)	13 (28%)	20 (35%)	0.231
CRT (Pacemaker-Defibrillator)	8 (24 %)	5 (11%)	3 (5%)	0.225

* *indicates statistically significant correlation*

3.2. LBBB and SF

According to the criteria of the AHA/ACCF/HRS-guidelines, 97 (93.3%) of the 104 patients were identified as having LBBB. Seven patients were initially misclassified as LBBB, but none of these patients revealed SF on echocardiography. Of all 104 patients, SF was detected in 47 (45.2%) patients. By eyeballing 97.9% of the SF patients were detected, anatomic M-Mode and Speckle tracking strain analyses identified 25 (53.2%) and 33 (70.2%) patients with SF, respectively (Table 4.2). The intraclass correlation coefficient showed a good agreement between the three echocardiographic methods to detect SF (Crohnbach's Alpha coefficient =0.94).

There were no significant gender or age differences in the LBBB population between subpopulations as shown in Table 4.1. SF was less likely to be present in patients with ICMP with LBBB (15 (31.9%)), whereas SF was present in 26 patients (68.1%) of NICMP patients

with LBBB (p=0.064) (Table 4.3). When categorizing for location of ischemia, 42 out of 47 (89.4%) SF patients did not have ischemia in the anterior region (no left main or left anterior descending artery infarction or stenosis). Compared to the SF negative patients (50), there were 34% with anterior ischemia or stenosis (p=0.008).

3.3. SF and RBBB, LPHB or LAHB

No SF was detected, with either detection method (eyeballing, M-mode, strain analysis) in 40 patients with true, isolated LAHB, LPHB, or RBBB. Eyeballing and M-mode could be assessed in all 40 patients, whereas strain analysis was feasible in 82.5% of patients.

Table 4.2: Assessment of septal flash on echocardiography in general population and in LBBB patients.

		None	Moderate	Manifest	Missing	SF detected	% of total	% of SF detected by TTE
Septal Flash	**Eyeballing**	58	23	23	0	46	44%	98%
	M-mode	55	12	13	24	25	24%	53%
	Speckle Tracking	58	19	14	13	33	32%	70%
	Total	57	19	28	0	47	45%	100%
LBBB and Septal Flash	**Eyeballing**	51	23	23	0	46	47%	98%
	M-mode	49	12	13	23	25	26%	53%
	Speckle Tracking	51	19	14	13	33	34%	70%
	Total	50	19	28	0	47	48%	100%

Upper part is SF diagnosis for the entire population (N=104), subcategorized by the three diagnostic methods and scored for extend of SF (none, moderate or manifest). The column 'missing' indicates patients in whom diagnostic echocardiography method was not applicable.

Bottom part are the diagnostic echocardiographic methods in population with LBBB according to AHA/ACCF/HRS criteria (N=97).[1]

Table 4.3: Baseline characteristics in LBBB population

LBBB and Septal Flash (SF)		SF (n = 47)	No SF (n = 50)	Total (n = 97)	p value
	Female	20	12	32	0.083
	Ischemic Cardiomyopathy	15	26	41	0.064
	Age (years)	69 ± 12	72 ± 13	70 ± 13	0.135
	QRS width (ms)	149 ± 12	142 ± 15	146 ± 16	0.031*
	Ejection fraction (%)	46 ± 12	47 ± 13	46 ± 12	0.894

** indicates statistically significant correlation.*

Ischemic cardiomyopathy when history of myocardial infarction, revascularization or angiographic evidence of multiple- or single-vessel disease.

3.4. SF and QRS-morphology in LBBB-ECG

The SF group had significantly longer QRS-duration[7] with a mean of 149 ms (± 12 ms) compared with 142 ms (± 15 ms) in patients without SF (p=0.031) (Table 4.3). There was no difference between the SF-positive group and SF-negative group considering broad slurred R-wave (p=0.495) (Table 4.4). Absent R-wave[1, 7-10] (or R-wave less than 1mm for a scale of 10mm/mV) in lead V1 was categorized as presence of QS-wave in V1. For the SF population, 36 (76.6%) had a QS in V1 (p=0.056). Notching in R-wave[7, 11, 12] in leads I and aVL was present in 45 (95.7%) SF patients (p=0.093) and a notch in leads V5 and V6 was present in 41 (87.2%) of SF patients and absent in 16 (32%) of non-SF patients (p=0.03). In all LBBBs, Q-waves in leads V5, V6 and I are absent[1, 7]. A Q-wave in aVL did not differ significantly between SF and no SF, (p=0.093). Finally, considering T-wave concordance[1], there was no correlation between T-wave inversions and presence/absence of SF (p=0.181). All considered ECG characteristics are listed in Table 4.4. Of all single measurements, the only significant ECG characteristic between SF and non-SF is the presence of notch in the R-wave of leads V5 and V6 (p=0.03). For some of the other ECG characteristics, only a trend but no statistical significance was reached.

Table 4.4: ECG characteristics, isolated and combined, and correlation with septal flash in LBBB ECG.

ECG characteristics	No SF (%)	SF (%)	p value	% of total LBBB patients
Broad notched or slurred R-wave in ≥ 2 subsequent lateral leads[4]	50 (100%)	47 (100%)	0.495	100%
Presence of rS in lead V1[10]	21 (42%)	11 (23%)	0.056	33%
Presence of QS in lead V1	29 (58%)	36 (77%)	0.056	67%
Small R-wave, large S-wave in lead V5	20 (40%)	13 (27%)	0.284	34%
Dominant R-wave in lead V5	30 (60%)	34 (72%)	0.284	66%
Small R-wave, large S-wave in lead V6	8 (16%)	3 (6%)	0.202	11%
Dominant R-wave in lead V6	42 (84%)	44 (94%)	0.202	89%
Positive axis of QRS complexes in leads V5 and V6	35 (70%)	40 (85%)	0.093	77%
Positive axis of QRS complexes in inferior leads	19 (38%)	23 (49%)	0.31	43%
Absent Q-wave in lead I and aVL[4, 10]	35(70%)	40 (85%)	0.093	77%
Notching R-wave in leads I and aVL[#]	42 (84%)	45 (96%)	0.093	90%
Notching R-wave in leads V5 and V6[#]	34 (68%)	41 (87%)	0.03*	77%
Notching R-wave in inferior leads[#]	35 (70%)	39 (83%)	0.157	76%
Fragmented QRS (S-wave) V1-V4	21 (42%)	29 (62%)	0.068	52%
Notching in R-wave V5,V6, I, aVL and inferior (=all notch)[#]	26 (52%)	37 (79%)	0.01*	65%
All notch and presence of QS in lead V1[#]	16 (32%)	31 (66%)	0.001*	49%
All notch and positive axis RS V5-V6	19 (38%)	31 (66%)	0.008*	52%
All notch and T-wave inversion or biphasic T-wave	16 (32%)	29 (62%)	0.004*	46%
Notching of R-wave in leads V5-V6 and QS in lead V1[#]	21 (42%)	33 (70%)	0.008*	56%
Notching of R-wave in leads I and aVL and QS in lead V1[#]	25 (50%)	36 (77%)	0.011*	63%
Notching of R-wave in inferior leads and QS in lead V1[#]	22 (44%)	33 (70%)	0.014*	57%
Notching of R-wave in leads I, aVL and inferior leads[#]	31 (62%)	39 (83%)	0.025*	72%
Notching of R-wave in leads V5,V6 and inferior leads[#]	29 (58%)	37 (79%)	0.032*	68%
Notching of R-wave in leads V5, V6 and leads I, aVL[#]	31 (62%)	41 (87%)	0.005*	74%
No T-wave inversion[4]	17 (34%)	10 (21%)	0.334	28%
T-wave inversion or biphasic T-wave[4]	33 (66%)	37 (66%)	0.181	72%
Chapman's sign	6 (12%)	10 (21%)	0.278	17%
Cabrera's sign	6 (12%)	9 (19%)	0.405	16%

** indicates statistically significant correlation. 'All notch' defines presence of mid-QRS notch in anterolateral, high lateral and inferior leads. [#] combination of Strauss et al[7]; Risum et al[11]; Pan et al[12]; and the AHA guidelines[1]*

3.5. Combining ECG-characteristics

When combining different ECG patterns in LBBB there are significant differences between the SF group and the group without SF (Table 4.4). Furthermore, combining QRS notching in all lateral leads and inferior leads, SF presence is very likely (p=0.01). When combining the morphology of V1 (QS or rS) and the presence of notching within two subsequent leads (anterolateral V5, V6 or high lateral I, aVL, or inferior II, III, aVF), the likelihood of SF presence is high (p=0.008, p=0.011 and p=0.014 respectively) (Table 4.4). The combination of notching in all lateral and inferior leads with a QS or rS in lead V1 showed the highest likelihood for SF (p=0.001).

Multivariate analysis showed no statistical significance when using several combined ECG characteristics to predict SF.

3.6. Interobserver variability

The interobserver variability for assessing the ECG characteristics revealed an ICC of 0.82 ± 0.12. The interobserver variability of echocardiographic assessment of SF revealed an ICC of 0.79 (eyeballing), 0.79 (M-mode), 0.83 (speckle tracking strain analysis).

4. Discussion

In the European and American guidelines on CRT therapy, critical predictors of response are included in the selection of HF patients that may benefit from CRT, such as QRS-duration, QRS-morphology (LBBB), reduced EF and variable degrees of NYHA classification.[8, 9] The main purpose of CRT is to restore LBBB-induced dyssynchrony and randomized trials have consistently shown significant reductions of morbidity and mortality in patients treated with CRT.[9] On the contrary, HF patients with non-LBBB (RBBB or other intraventricular conduction pathology (IVCD)) do not appear to benefit from CRT to the same extent, do not

benefit at all, and CRT may be harmful in some.[8] The major reason for this observation in non-LBBB HF patients probably relates to the fact that conduction disorders other than LBBB do not induce the typical electrical dyssynchronous SF that is corrected by CRT ("You cannot fix what is not broken"). Furthermore, although LBBB is a major predictor of CRT response, the diagnostic criteria of LBBB vary considerably among the different studies, which probably explains part of the non-response in CRT patients. The heterogeneous LBBB typing by the studies pleads for an international consensus on the correct diagnosis of LBBB (Table 4.5)[1, 7-10, 13] On the other hand, because of previous controversial studies[14], current guidelines do not recommend echocardiographic measures of dyssynchrony to select HF patients for CRT treatment.[8] Recently however, Doltra et al have shown that in LBBB patients, the presence of SF on echocardiography strongly predicts response (reverse remodeling) in CRT HF patients.[6] In this report, we investigated the prevalence of SF in LBBB patients and whether SF may be associated with specific ECG-morphologies within LBBB. We used rigorous criteria to define 'true' LBBB in our cohort. In this regard, in MADIT, a limited number of criteria were used to define LBBB in CRT candidates. For instance, QS in lead V1 was considered a LBBB-criterion in MADIT, whereas QRS-notching was not (Table 4.5).[9] Yet, we found a correlation between the combined presence of QS in V1 and QRS-notching in LBBB and SF patients. Therefore, MADIT-selected LBBB patients might display less SF and hence, lower response rates in terms of reverse remodeling, as suggested by Doltra et al.[3]

Table 4.5: LBBB diagnostic criteria differ between the different guidelines and trials.

ECG parameter for complete LBBB	ESC	AHA	Strauss	MADIT	REVERSE
QRS width (ms) ≥ Female/Male	120	120	130/140	130	120
QS or rS pattern in V1	Yes	Yes	Yes	Yes	Yes
Positive T-wave in V1	Yes	No	No	No	No
Normal ID R-wave in V1-V3	No	Yes	No	No	No
ID R-wave in V5 ≥ 60ms	No	Yes	No	No	No
ID R-wave in V6 ≥ 60ms	Yes	Yes	No	No	No
ID R-wave in I ≥ 60ms	Yes	No	No	No	No
Notched/Slurred R-wave in I- aVL and V5-V6	No	Yes	No	No	No
Mid-QRS notching/slurring in ≥ 2 leads of V1-V2 and V5-V6 or I-aVL	No	No	Yes	No	No
RS pattern allowed in V5-V6	No	Yes	Yes	Yes	Yes
Absent Q-wave in V5-V6	No	Yes	No	Yes	Yes
Absent Q-wave in I	No	Yes	No	No	No
QS with positive T-wave in aVR	Yes	No	No	No	No
Usually discordant T-wave	Yes	Yes	No	No	No

Guidelines from the European Society of Cardiology[8], American Heart Association/American College of Cardiology Foundation/ Heart Rhythm Society[1], and clinical trials of Strauss et al[7], MADIT-CRT[9] and REVERSE[10]. Abbreviation: ID, intrinsicoid deflection, defined as the interval between the start of the QRS complex to the peak of the R-wave, LBBB: Left bundle branch block. (Adapted from Van Deursen et al[13])

SF patients in our cohort met all LBBB criteria as defined by the AHA/ACCF/HRS[1] and the combined ECG characteristics of LBBB better identified SF patients compared to the non-SF group. Importantly, SF was not detected in LAHB, LPHB or RBBB. This raises the provocative question whether SF might be a major criterion for "true LBBB" or even "redefines" true LBBB or identifies a particular "subset" of LBBB patients. Current criteria that define LBBB on the surface ECG are not sensitive enough to characterize either the location or the extent of specific ventricular delays. Interestingly, electrophysiological (EP) studies have been performed in patients with SF, and these data showed a long transseptal activation time (due to slow muscle to muscle conduction within the septum) and functional lines of bock in the left ventricle.[6] These EP characteristics were also described by Auricchio et al., but no echocardiographic data of dyssynchrony (no SF mentioned) were reported in that study.[6, 15] Importantly, in many other

patients with LBBB, no such EP characteristics were present and often, several early breakthrough sites in the septum were revealed and were associated with much shorter transseptal activation times.[15] Therefore, it appears that not all LBBBs are created equally and it is likely that the heterogeneous EP findings in LBBB may relate to the variable anatomy of the left bundle[16], the site and/or the extent of conduction block in the left bundle.[7, 11, 15] Moreover, myocardial substrate modification (e.g. infarction of the septum or left lateral wall) may also impact the presence and extent of SF and hence, its CRT response.[15]

Regarding the site of conduction block in the left bundle, radiofrequency ablation of the proximal part of the left bundle in dogs results in LBBB with typical characteristics of SF. Eventually, these LBBB-induced dog hearts develop LV dysfunction, which was restored with CRT.[2] It has been suggested that a similar pathophysiology of LBBB induced cardiomyopathy may also occur in humans. These patients (mostly with NICMP) are characterized by a so called CRT super-response, i.e. complete recovery of EF fraction and reverse remodeling. In our cohort, a considerable number of LBBB patients did not have ICMP or NICMP and had normal EF. It is possible that these LBBB patients with SF may have worse cardiac outcome compared to the LBBB patients without SF, but this remains to be explored in large longitudinal follow-up studies.

Based on our findings and the aforementioned reports, SF associated with typical LBBB is most likely caused by proximal block of the left bundle branch in humans (with the prerequisite of relatively intact myocardium, particularly the lateral and septal wall).[6] We therefore hypothesize that SF might be highly prevalent in patients undergoing a Transcatheter Aortic Valve Implantation (TAVI), who develop (proximal) LBBB following the procedure, but this remains to be explored. Interestingly, this pure proximal LBBB in TAVI patients may also explain (as an independent risk factor) the worse outcome in these patients because of unfavorable LV hemodynamics associated with SF.[19]

The initial R-wave of ≥ 1mm in lead V1 was suggested to be a sign of persistent left to right ventricular septum activation and considered as an incomplete LBBB in an EP study.[17] However, a septal scar might also have an initial R-wave in the right precordial deflections from unopposed RV free wall activation.[18] Our data showed a trend of association between absent R-wave in V1 (classified as QS in V1) and the presence of a SF. This fits with the hypothesis that in proximal LBBB, activation of the septum occurs via the right bundle and activates the LV endocardium in a myocyte-to-myocyte activation, as mentioned earlier. However, theoretically, the presence of R-wave in V1 in patients with SF may also reflect fast RBB conduction and RV activation which is unopposed by the slower septal depolarization.

In the recent guidelines, LBBB-morphology and QRS-duration are two major criteria to select patients for CRT. Randomized trials showed that patients with LBBB and QRS-duration >150ms have the best CRT response.[3, 8] In line with these findings and considering the current guidelines, we found a correlation with QRS-duration and the presence of SF: patients with manifest SF had longer QRS-durations. Again, this is in line with recent data from Doltra et al., showing best CRT response in patients with SF compared to non SF. One third of patients fail to respond to CRT, which indicates that current established patient selection criteria might be suboptimal. Considering new criteria to define LBBB, several groups claim for the inclusion of mid-QRS notching or slurring to correctly diagnose true LBBB.[7, 11] Mid-QRS notch in the lateral leads (I, aVL, V6) has been shown to be a good predictor of CRT response.[12] In line with these findings, we found a correlation between mid-QRS notch in leads V5-V6 and the presence of SF. When considering >2 subsequent leads with a mid-QRS notch (leads I, II, III, aVF, aVL, V5 or V6) there is even a better correlation with SF. Risum et al[11] concluded that the presence of a mid-QRS notch is necessary to distinguish true LBBB from LV hypertrophy, LV dilatation

and incomplete LBBB. Thus, these findings argue for a better and uniform manner to redefine (true) LBBB.

Recently a scoring method for selecting HF patients for CRT treatment has been proposed.[4] This system is based on both clinical and ECG-baseline characteristics together with SF on echocardiography. It provides a better predictive power than clinical and ECG characteristics alone. LBBB and SF are the predominant factors in this scoring system, again pointing to the fact that LBBB patients with SF movement are the best CRT-targets.[4]

5. Conclusion

In conclusion, based on recent clinical and experimental data and the present study, we suggest to include SF as an easy, fast and specific echocardiographic marker of a particular subset of LBBB that might be helpful in the prediction of CRT response. However, because of the heterogeneity and the complex (dynamic) nature of the electro-mechanical myocardial substrate, and because HF patients may improve with CRT despite absence of septal flash, no holy grail exists to detect potential CRT responders.

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CHAPTER 5

Relation between electrical and mechanical dyssynchrony in patients with left bundle branch block: an electrocardiographic and vectorcardiographic study

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Abstract

Background: *New electro- and vectorcardiographic parameters have been proposed as markers of electrical and mechanical dyssynchrony. This study assesses whether these parameters correlate to septal flash (SF), a specific echocardiographic sign of left bundle branch block (LBBB) induced mechanical dyssynchrony which is highly predictive for response to cardiac resynchronization therapy.*

Methods: *The study included patients with true LBBB (including mid-QRS notching) on standard twelve-lead electrocardiograms. Mechanical dyssynchrony was assessed by the presence of SF on two-dimensional echocardiography. Previously reported electro- and vectorcardiographic markers of dyssynchrony were analyzed: global QRSD ($QRSD_{LBBB}$), left ventricular activation time ($QRSD_{LVAT}$), time to the intrinsicoid deflection ($QRSD_{ID}$) and vectorcardiographic QRS areas in the 3D vector loop ($QRSA_{3D}$).*

Results: *SF is present in 52% of patients presenting with true LBBB (n=545). Patients with SF are more frequent female, have less ischemic heart disease and smaller left ventricular dimensions. In multivariate analysis longer $QRSD_{LBBB}$, $QRSD_{LVAT}$ and larger $QRSA_{3D}$ were independently associated with SF. Of all parameters, $QRSA_{3D}$ has the best accuracy to predict SF, although overall accuracy remains rather moderate (59% sensitivity, 58% specificity). $QRSD_{LBBB}$ and $QRSD_{LVAT}$ are only associated with SF in male patients. The predictive value of $QRSA_{3D}$ remained constant in both sexes, irrespective of ischemic heart disease and even when categorizing for $QRSD_{LBBB}$.*

Conclusion:

In LBBB patients, mechanical dyssynchrony as assessed by SF, correlates better with larger QRS areas compared to wider QRSD intervals. However, the accuracy to predict mechanical dyssynchrony by electrocardiographic dyssynchrony markers, even by using complex vectorcardiographic parameters, remains low.

1. Introduction

Current guidelines on cardiac resynchronization therapy (CRT) select patients mainly on electrocardiographic criteria such as QRS duration (QRSD) and QRS morphology [1, 2]. These criteria refer to the electrical dyssynchrony caused by block of the left bundle branch (LBBB) as the substrate for CRT. However, it has been shown that patients with LBBB morphology and wide QRSD reveal variable ventricular activation patterns. This heterogeneity in mechanical dyssynchrony among patients with LBBB, is taught to be one of the reasons why a significant number of patients fail to respond to CRT [3]. Several new electro- and vectorcardiographic parameters have been proposed as markers of both electrical and mechanical dyssynchrony [4-7]. However these parameters were validated against different dyssynchrony assessments and not compared head to head. Recently, a simple visual assessment of LBBB-induced mechanical dyssynchrony, called septal flash (SF), has been introduced. This SF refers to an early rapid inward motion of the septum on echocardiography and has been shown to be a strong and independent predictor of CRT response [8, 9]. Moreover, visual assessment of SF is an accurate, highly reproducible and easy parameter to diagnose mechanical dyssynchrony. This study aims to assess 1) the prevalence and determinants of SF among patients with true LBBB and 2) assesses whether new electro- and vectorcardiographic parameters of dyssynchrony correlate with the presence of SF.

2. Methods

2.1. Study design and selection of patients

The study enrolled patients with true LBBB morphology on a standard twelve lead electrocardiogram (ECG) at the Cardiologic department of the University Hospital of Ghent between June 2013 and September 2016. True LBBB was defined according to the recent American Heart Association, American College of Cardiology Foundation and Heart Rhythm Society criteria including: QRSD ≥120ms, QS or rS in lead V1 and broad notched or slurred R

waves in two adjacent leads among leads I, aVL, V5 and V6 [10]. The presence of mid-QRS notching and slurring in the left lateral leads was included as this characteristic differentiates true LBBB from QRS prolongation due to left ventricular hypertrophy [11, 12]. All ECGs were recorded with MAC 5500 ECG recording devices (GE Healthcare, Waukesha, WI, USA) and stored digitally (aHL7 ECGs, sampling rates of 500Hz) in a MUSE Cardiology Information system (GE Healthcare). The study was approved by the ethical committee of the University Hospital of Ghent.

2.2. Electrocardiographic parameters to assess dyssynchrony

QRSD intervals were measured automatically using the Marquette^{TM} 12SL algorithm. The LBBB QRSD ($QRSD_{LBBB}$) is measured as a global QRSD, which is calculated from the earliest beginning until the latest ending of the QRS complex in all leads, as recommended by guidelines [10] (Figure 5.1). This automated algorithm was previously validated in LBBB patients by comparing it to manual QRSD measurements using digital calipers [13]. Besides $QRSD_{LBBB}$, two other QRSD intervals, which have been proposed as makers of both electrical and mechanical dyssynchrony, were calculated (Figure 5.1). $QRSD_{LVAT}$ is defined as the interval from the first notch to the end of the QRS complex and represents the delayed activation time of the left ventricle in LBBB patients [6]. $QRSD_{ID}$ represents the time from the earliest onset of the QRS complex to the latest peak or point at which the maximum deflection (intrinsicoid deflection) to baseline occurs. In LBBB patients this $QRSD_{ID}$ is maximal in the left lateral leads and therefore proposed as marker of delayed left ventricular activation and dyssynchrony [4].

2.3. Vectorcardiographic parameters to assess dyssynchrony

Custom-made software (Matlab software, Mathworks, MA, US) was used to convert digital ECGs to vectorcardiograms (VCG) according to Frank's orthogonal lead system as previously reported [14]. Each VCG was plotted against the three orthogonal leads (X, Y, and Z) allowing to form a 3D vector. QRS areas (QRSA) are calculated as the integral between the QRS waveform and baseline in each orthogonal lead ($QRSA_X$, $QRSA_Y$ and $QRSA_Z$) (Figure 5.1). The QRS area of the 3D vector loop ($QRSA_{3D}$) was calculated as $(QRSA_X^2 + QRSA_Y^2 + QRSA_Z^2)^{½}$ and has been previously validated as a marker of ventricular dyssynchrony [7]. We recently showed that LBBB patients are characterized large QRS areas in the Z-lead. Therefore $QRSA_Z$ was evaluated separately [14]. Additionally, as QRS areas in individual leads of the standard twelve lead ECG have not been investigated, we calculated the QRS area in each lead separately ($QRSA_{I, II, II, aVL, aVR, aVF, V1, V2, V3, V4, V5 and V6}$).

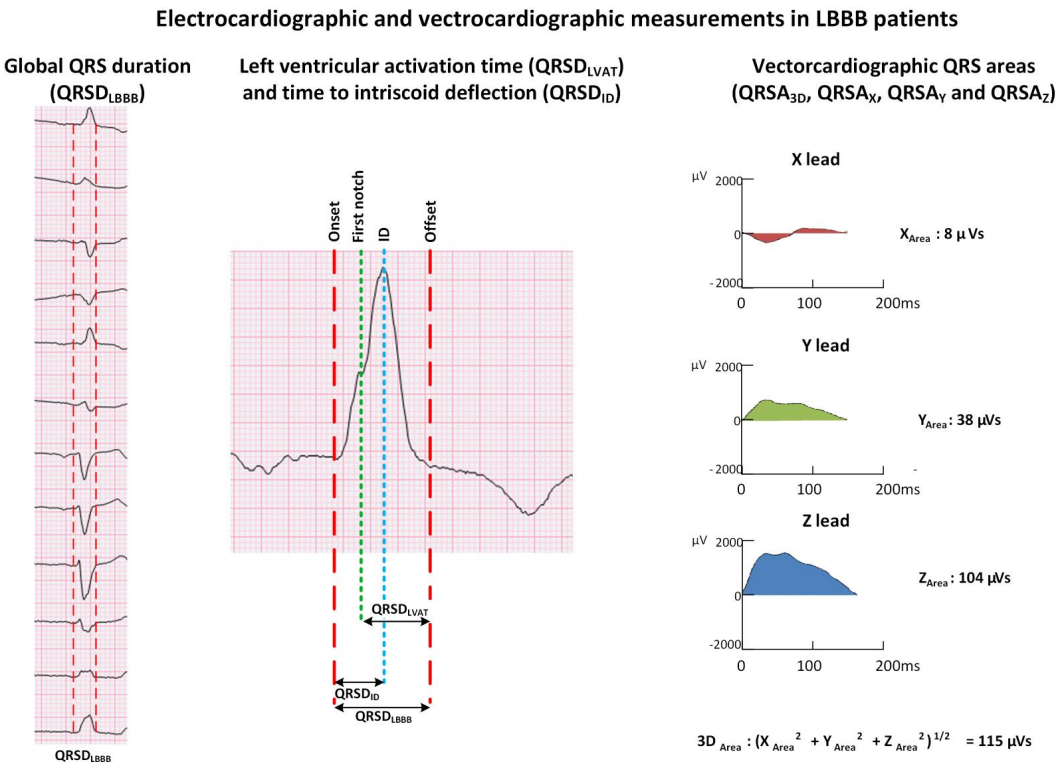

Figure 5.1: *Electrocardiographic and vectorcardiographic measurements in LBBB patients to assess both electrical and mechanical dyssynchrony.*

2.4. Echocardiographic studies and assessment mechanical dyssynchrony

Echocardiographic examinations within 3 months of the ECG recording date were considered for analysis. All echocardiographic examinations were performed using commercially available systems (GE Healthcare Ultrasound Vivid 7 and GE Healthcare Ultrasound Vivid E9, Vingmed, Horton, Norway; Philips Ultrasound iE 33, Best, Netherlands). Two echocardiography experts, blinded to the ECGs, reviewed all echocardiographic studies offline using EchoPAC version 7.1.13 for the GE scanning systems and Xcelera viewer R3 version 3.3.1 2013 for the Philips scanning system.

Left ventricular (LV) dimensions were measured in conventional parasternal views using LV enddiastolic diameter (LV_{EDD}), interventricular septal wall thickness (IVSD) and posterior wall thickness (PWD). LV mass (LV_{MASS}) was calculated as LV_{MASS} (g) =0.8 (1.04 ([LV_{EDD} + IVSD +PWD]^3 - LV_{EDD}^3)) + 0.6 [15]. LV_{EDD} and LV_{MASS} were indexed for body surface area (BSA): LV_{EDDi}, and LV_{MASSi}.

Mechanical dyssynchrony was assessed by the presence of septal flash (SF) on two-dimensional echocardiography. SF refers to a specific echocardiographic pattern in which a rapid, pre-ejection, leftward motion (right to left) of the septum occurs. The presence of SF was assessed visually (parasternal short axis, parasternal long axis or apical views) as validated in prior studies and at our center [8, 9, 16].

2.5. Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median [quartile 1; quartile 3] if data were not Gaussian distributed. Categorical variables are expressed as absolute numbers with percentage (%). Shapiro-Wilk test was used to test for normality. Univariate comparison among groups was done by Mann-Whitney U test and categorical variables were compared by Chi-square tests. Significant determinants of QRSD in univariate analysis were

tested in a multivariate analysis using multiple linear regression. Non-Gaussian distributed variables were log transformed. Multicollinearity was defined as a variance inflation factor >4. Correlations between continuous variables were analyzed using Spearman rank-order correlation coefficients. Receiver operating characteristic (ROC) curves were constructed to compare the ability of electro- and vectorcardiographic parameters in predicting SF. Statistical significance was set at a 2-tailed probability level of <0.05. All statistical analysis was performed using SPSS software (Version 22.0, IBM, Armonk, NY, US).

3. Results

3.1. Patient characteristics and prevalence of septal flash

The study enrolled 605 LBBB patients. In 60 patients, assessment of SF was not possible due to inappropriate image quality. Therefore 545 LBBB patients were considered for further analysis. The cohort compromised 217 (40%) females and mean age was 74±15 years. Ischemic heart disease was prevalent among 230 (42%) of the patients. Patient characteristics are summarized in table 5.1.

3.2. Electro- and vectorcardiographic measurements in LBBB patients

ECG and VCG measurements are summarized in table 5.2. Mean $QRSD_{LBBB}$ was 148 [140;162]ms for all patients. Females had smaller $QSRD_{LBBB}$ (144 [136;153]ms) compared to males (154 [142;168]ms, p<0.001). Similar differences (+/- 10ms) between males and females were found for $QRSD_{LVAT}$ and $QRSD_{ID}$. No differences were found in $QRSD_{LBBB}$, $QRSD_{LVAT}$ and $QRSD_{ID}$ intervals between ischemic and non-ischemic patients (Table 5.2).

Overall mean $QRSA_{3D}$ was 117 [93;147]µVs, with higher $QRSA_{3D}$ in males compared to females (122 [98;156]µVs versus 112 [88;132]µVs, p<0.001). Non-ischemic patients showed

higher $QRSA_{3D}$ compared to ischemic patients (125 [98;156]µVs versus 112 [88:137]µVs, p<0.001). $QRSA_Z$ measurements showed similar trends among these patient groups.

Correlation between $QRSD_{LVAT}$ and $QRSD_{LBBB}$ was higher (r_s 0.80, p<0.001) compared to the correlation between $QSRD_{ID}$ and $QRSD_{LBBB}$ (r_s 0.43 p<0.001). $QRSA_{3D}$ and $QRSA_Z$ had moderate but significant correlation with $QRSD_{LBBB}$ (r_s 0.40, p<0.001 and r_s 0.30, p<0.001 respectively).

3.3. Clinical, echo-, electro- and vectorcardiographic determinants of patients with septal flash

Compared to patients without SF, patients with SF were more frequent female (46% versus 33%, p=0.002), had less ischemic heart disease (35% versus 50%, p=0.001) and had smaller LV dimensions measured by LV_{MASS} (187 [153;241]g versus 205 [164;261]g, p=0.017). $QRSD_{LBBB}$, $QRSD_{LVAT}$, $QRSA_{3D}$ and $QRSA_Z$ were higher in patients with SF (Table 5.3). $QRSD_{LBBB}$, $QRSD_{LVAT}$, $QRSA_{3D}$ and $QRSA_Z$ were independently associated with higher SF prevalence when conducting a multiple regression model including sex, ischemic heart disease and LV_{MASS}. (Table 5.3).

ROC curves to predict the presence of SF by electro- and vectorcardiographic parameters showed areas under the curve (AUC): ranging from 0.519 to 0.674 (Table 5.4). Of all ECG and VCG parameters, $QRSA_{3D}$ (AUC: 0.674) and $QRSA_Z$ (AUC 0.661) revealed the best accuracy to detect SF among LBBB patients and performed significantly better compared to $QRSD_{LBBB}$ (AUC: 0.587, p=0.03 and p=0.04 respectively). The ROC curve for $QRSA_{3D}$ revealed an optimal cut off at 114µVs, showing a sensitivity of 59% with 58% specificity to predict SF by $QRSA_{3D}$. The diagnostic accuracy of $QRSD_{LVAT}$ (AUC 0.621) did not outperform $QRSD_{LBBB}$ (p=0.600) in predicting SF. QRS_{ID} revealed the lowest AUC (0.519) to discriminate LBBB patients with SF from those without SF.

Moreover, the accuracy of $QRSD_{LBBB}$, $QRSD_{LVAT}$ and $QRSD_{ID}$ varied strongly among different patients groups (Table 5.4). In male LBBB patients, QRSD intervals showed higher accuracy to diagnose mechanical dyssynchrony compared to females. On the other hand, the diagnostic accuracy of $QRSA_{3D}$ and $QRSA_Z$ remained constant among different patient groups based on sex or ischemic versus non-ischemic heart disease (range AUCs $QRSA_{3D}$: 0.660 to 0.712 and range AUCs $QRSA_Z$ 0.633 to 0.685, p= not significant for comparison among AUCs). Of interest, even when categorizing for $QRSD_{LBBB}$, $QRSA_{3D}$ and $QRSA_Z$ showed stable AUCs over the entire range of QRSD with AUC ranging from 0.631 to 0.657 (Table 5.4).

3.4. QRS areas in individual leads of the VCG and ECG

$QRSA_{3D}$ correlated strongly with $QRSA_Z$ (r_s 0.875, p<0.001), whereas $QRSA_X$ (r_s 0.115, p< 0.007) and $QRSA_Y$ (rs 0.340, p<0.001) showed poor correlation with $QRSA_{3D}$. Of all leads of the standard twelve lead ECG, lead $QRSA_{V1}$ and $QRSA_{V2}$ showed the best correlation with $QRSA_{3D}$ (r_s -0.744, p<0.001 and r_s -0.827, p<0.001 respectively). As such $QRSA_{V1}$ and $QRSA_{V2}$ revealed the highest accuracy to diagnose SF (AUC 0.665 and 0.637, Figure 5.2). Correlation of left lateral leads with $QRSA_{3D}$ was low (r_s all <0.400 for $QRSA_I$, $QRSA_{aVL}$, $QRSA_{V5}$ and $QRSA_{V6}$).

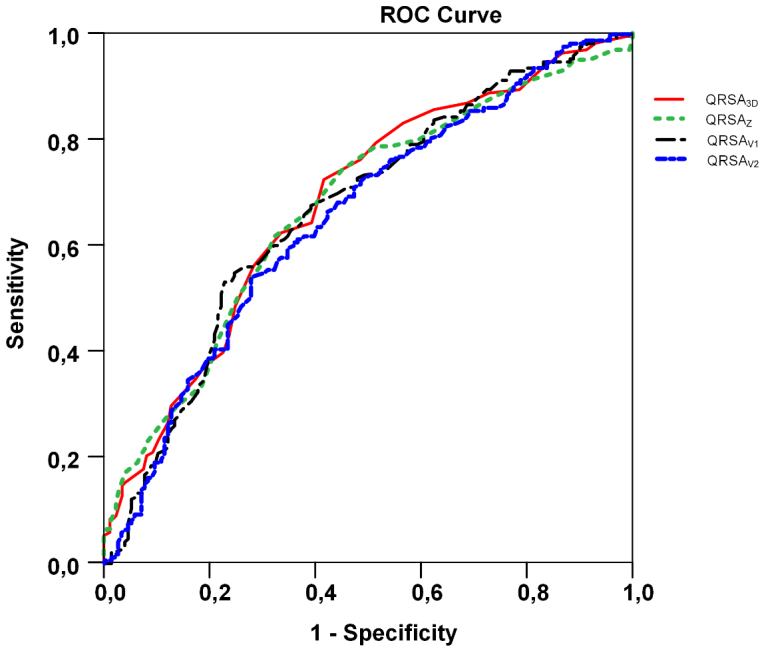

Figure 5.2: *Receiver operating characteristics (ROC) curves to assess the presence of septal flash by electro- and vectorcardiographic parameters. Of all parameters, QRS area in the 3D vector loop ($QRSA_{3D}$) and QRSA area in the Z lead of Franks vectorcardiogram ($QRSA_Z$) revealed the highest accuracy. As the QRS areas calculated in lead V1 ($QRSA_{V1}$) and lead V2 ($QRSA_{V2}$) of the standard twelve lead electrocardiogram correlate highly with $QRSA_{3D}$ and $QRSA_Z$, areas in leads V1 and V2 show similar diagnostic accuracy compared to VCG calculated QRS areas.*

Table 5.1: Patient characteristics

Patient Group	All Patients (n=545)
Prevalence of Septal Flash n(%)	284 (52)
Baseline characteristics	
Age (years)	74±15
Length (cm)	168±10
Weight (kg)	74±16
Body mass index (kg/m²)	26±5.1
Body surface area (BSA) (m²)	1.84±0.22
Blood pressure Systolic (mmHg)	130±36
Blood pressure Diastolic (mmHg)	67±19
Heart rate (beats/min)	71±20
Underlying heart disease n(%)	
Ischemic heart disease	230 (42)
Congenital heart disease	21 (3.9)
Valvular heart disease	132 (24.2)
Atrial fibrillation	48 (8.8)
Echocardiographic measurements	
Enddiastolic diameter (mm)	50±8
Enddiastolic diameter/BSA (mm/m²)	27±5
Left ventricular mass (g)	298±73
Left ventricular mass/BSA (g/m²)	107±36

Table 5.2: ECG and VCG measurements

ECG-VCG parameter	All Patients (n=545)	Females (n=217)	Males (n=328)	p-value	Ischemic (n=230)	Non-ischemic (n=315)	p-value
$QRSD_{LBBB}$ (ms)	148 [140;162]	144 [136;153]	154 [142;168]	p<0.001	150 [140;164]	148 [140;162]	p=0.189
$QRSD_{ID}$ (ms)	68 [56;86]	62 [53;73]	72 [60;92]	p<0.001	68 [58;88]	66 [56;86]	p=0.235
$QRSD_{LVAT}$ (ms)	91 [83;104]	87 [79;95]	96 [84;110]	p<0.001	93 [83;106]	91 [83;104]	p=0.405
$QRSA_{3D}$ (µVs)	117 [93;147]	112 [88;132]	122 [98,156]	p<0.001	112 [88;137]	125 [98;156]	p<0.001
$QRSA_{Z}$ (µVs)	88 [59;122]	83 [59;107]	93 [59;132]	p=0.005	78 [54;112]	98 [63;127]	p=0.001

Table 5.3: Determinants of septal flash, univariate and multivariate analysis.

	Septal flash n=284	No Septal flash n=261	p-value univariate	p-value multivariate
Clinical characteristics				
Age (yrs)	69±14	71±15	p=0.066	
Female n(%)	131(46)	86 (33)	**p=0.002**	**p=0.021**
Length (cm)	167±10	167±10	p=0.406	
Weight (kg)	75±15	76±17	p=0.849	
Body mass index (kg/m²)	27±5	27±5	p=0.826	
Body surface area (BSA) (m²)	1.83±0.21	1.85±0.23	p=0.603	
Heart rate (beats/min)	74±19	75±22	p=0.790	
Underlying heart disease				
Ischemic heart disease n(%)	99 (35)	131 (50)	**p=0.001**	**p=0.004**
Congenital heart disease	12 (4.2)	9 (3.5)	p=0.659	
Echocardiographic measurements				
Enddiastolic diameter (mm)	49 [45;49]	51 [45;56]	p=0.085	
Enddiastoic diameter/BSA (mm/m²)	27 [25;29]	27 [34;30]	p=0.995	
Left ventricular mass (g)	187 [153;241]	205 [164;261]	**p=0.017**	**p=0.011**
Left ventricular mass/BSA (g/m²)	101 [86;127]	114 [89;137]	p=0.060	
ECG and VCG measurements				
$QRSD_{LBBB}$ (ms)	150 [140:164]	146 [136;160]	**p=0.026**	**p=0.007**
$QRSD_{ID}$ (ms)	68 [56;86]	68 [56:84]	p=0.882	
$QRSD_{LVAT}$ (ms)	93 [83;106]	89 [79;102]	**p=0.026**	**p=0.046**
$QRSA_{3D}$ (μVs)	125 [103;156]	107 [85;137]	**p<0.001**	**p<0.001**
$QRSA_{Z}$ (μVs)	98 [68;127]	78 [49;112]	**p<0.001**	**P<0.001**

Table 5.4: Diagnostic value of ECG and VCG parameters in assessing the presence of septal flash

ECG-VCG parameter	Area under the curve (AUC)							
	All (n=545)	Females (n=217)	Males (n=328)	Ischemic (n=230)	Non-ischemic (n=315)	QRSD <130	QRSD 130-149	QRSD >150
$QRSD_{LBBB}$	0.555	0.473	0.644	0.540	0.594	0.535	0.582	0.515
$QRSD_{ID}$	0.519	0.504	0.529	0.550	0.502	0.578	0.495	0.452
$QRSD_{LVAT}$	0.621	0.559	0.653	0.627	0.620	0.638	0.646	0.516
$QRSA_{3D}$	0.674	0.712	0.668	0.660	0.672	0.647	0.644	0.657
$QRSA_{Z}$	0.661	0.685	0.660	0.637	0.684	0.631	0.632	0.653

QRSD are measured in ms, QSRA are measured in µVs.

4. Discussion

4.1. Mechanical dyssynchrony in patients with LBBB

Patients with LBBB benefit more from CRT than patients with non-LBBB [17]. This is explained as patients with LBBB have a desynchronized ventricular contraction caused by delayed activation of the lateral left ventricle, which is most likely to be resynchronized with CRT. However, even when applying current CRT selection criteria, some patients with LBBB and wide QRSD fail to respond to CRT. One of the reasons could be that not all LBBB patients display the same mechanical activation pattern which can be corrected by CRT. For instance, Auricchio et al. showed that among patients with LBBB, heterogeneity in ventricular activation patterns exists [3]. The current study shows that when applying strict criteria for diagnosing LBBB (including mid-QRS notching), SF is merely present in 52% of the patients. This indicates that the presence of electrical dyssynchrony (as defined by wide QRSD and LBBB) does not coincide completely with the presence of LBBB induced mechanical dyssynchrony (as assessed by SF). The presence of SF might therefore identify a particular subset of LBBB patients.

Electrophysiological studies in patients with SF revealed long transseptal activation times, attributed to slow muscle to muscle conduction in the septum [18]. Aurrichio et al. showed that the majority of LBBB patients in his study had long transseptal activation times and revealed a

typical U-shaped activation pattern [3]. However, one third of the patients with LBBB did not show this activation pattern and several early breakthrough sites in the septum occurred leading to shorter transseptal activation times. Although no SF assessments were performed in that study, we hypothesize that those patients with septal breakthroughs are those LBBB patients without SF. In an experimental study by Gjesdal, radiofrequency ablation of the proximal part of the left bundle in dogs results in LBBB with typical characteristics of SF [19]. These LBBB-induced dog hearts eventually developed LV dysfunction, which could be restored with CRT. This suggests that SF associated with typical LBBB, is probably caused by proximal block of the left bundle branch in humans [20].

4.2. Correlation of mechanical dyssynchrony with electro- and vectorcardiographic parameters

In patients with conduction disorders, delayed activation of the ventricle is reflected as wide QRSD on the ECG. In the field of CRT, wide QRSD is used as a marker for electrical dyssynchrony in patients with heart failure. Given the heterogeneity and disparity between QRSD and mechanical dyssynchrony, several new electro- and vectorcardiographic parameters have been developed which claim to reflect both electrical and mechanical dyssynchrony. These parameters use either a well-defined part of the QRS duration interval or calculate the surface of the QRS waveform (QRS area) [4-7]. Although these parameters have shown to better reflect mechanical dyssynchrony and CRT outcome compared to QRSD in different studies, no study compared these parameters head-to-head and against SF. Our study compared these novel ECG and VCG parameters in a well-defined population of patients with true LBBB and using SF as a valid and reproducible measure of mechanical dyssynchrony.

Of all parameters, VCG-calculated QRS areas correlated best with SF. This is in line with a previous study, which showed that large QRS areas are associated with a higher degree of

mechanical dyssynchrony, measured by electro-anatomic mapping [5]. Of interest, the accuracy of QRS areas to assess mechanical dyssynchrony is robust over different patient groups based on gender, presence or absence of ischemic heart disease and ranges of QRSD. Conversely, QRSD parameters seem to be mainly correlated with mechanical dyssynchrony in males. This is most probably explained as though SF is more prevalent in females, it occurs more frequent at narrower QRSD compared to males.

VCG-calculated QRS area combines both the information of the QRS morphology and duration into one single parameter. Patients with LBBB have QRS areas 2-3 times larger compared to patients without conduction delay [7]. These large 3D QRS areas in LBBB patients can be explained by strong unopposed electrical forces generated by delayed activation of the posterior and basal parts of the LV, typically seen in LBBB [21]. The largest QRS areas are therefore detected in antero-posterior oriented leads, such as the Z-lead of the Franks orthogonal system or lead V1 and V2 of the 12 lead ECG. Hence QRS areas in Z, V1 or V2 lead are highly correlated with 3D QRS areas in LBBB patients. Therefore our results show that measuring 3D QRS areas in LBBB patients can be simplified to calculations of QRS areas in lead V1 or V2 of the standard twelve lead ECG.

4.3. Clinical implications

Current CRT guidelines select patients by QRSD cut offs and QRS morphology [1, 2]. However, with current selection criteria, up to one third of the patients do not achieve the expected CRT response [22]. This number of non-responders, despite these patients meet the current selection criteria, might largely be attributed to disparity between electrical and mechanical dyssynchrony. In the last years, emerging evidence exists that the presence of SF in LBBB patients is an important determinant of long term CRT response, with an incremental value over clinical variables and QRSD [8, 9]. The PREDICT-CRT trial, which included 1060 CRT patients,

showed that the presence of SF and its correction with CRT predicts both long term reverse remodeling and all-cause mortality. Additionally, multi-parametric scoring models to select heart failure patients for CRT treatment came to the same conclusion [23, 24]. In these models, the inclusion of simple visual assessments of mechanical dyssynchrony, like SF, identified better CRT responders compared to score models without assessing SF. Likewise, we showed that ECG-derived parameters (even complex VCG-calculated parameters) cannot identify with high accuracy those LBBB patients with SF from those without SF. Even with the best parameter ($QRSA_{3D}$), sensitivity and specificity do not reach 60%. Therefore, SF might be suggested as an additional marker, independently or on top of ECG characteristics, of those LBBB patients who will likely respond to CRT.

5. Limitations

This study was conducted as a retrospective study. Mechanical dyssynchrony was assessed solely by the presence of SF, and therefore no conclusions can be drawn with respect to other markers of inter- or intraventricular dyssynchrony. Patients were selected on LBBB morphology as defined by the American Heart Association, American College of Cardiology Foundation and Heart Rhythm Society. This definition includes the presence of mid-QRS notching. Other LBBB definitions may select other patients with other clinical and echocardiographic characteristics and therefore yield a different prevalence of SF. The majority of patients did not have heart failure or reduced EF. As such, our results should be interpreted with caution, as heart failure patients with LBBB might differ from our population.

6. Conclusion

Mechanical dyssynchrony, as assessed by SF, is present in half of the patients presenting with true LBBB on the ECG. Among these patients mechanical dyssynchrony correlates better with larger QRS areas compared to wider QRSD intervals. However, the accuracy to predict mechanical dyssynchrony by electrocardiographic dyssynchrony markers, even by using complex vectorcardiographic parameters, remains rather low.

7. References

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CHAPTER 6

Gender differences in electro-mechanical characteristics of left bundle branch block: potential implications for selection and response of cardiac resynchronization therapy

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Abstract

Background: *Female patients are underrepresented in cardiac resynchronization therapy (CRT) trials, although they show better CRT response compared to males and at shorter QRS durations. We hypothesized that differences in left bundle branch block (LBBB) characteristics and mechanical dyssynchrony might explain this gender disparity.*

Methods: *Patients presenting with true LBBB-morphology (including mid-QRS notching) on surface electrocardiograms (ECG) were selected. LBBB QRS duration ($QRSD_{LBBB}$) was measured automatically on the ECG. Left ventricular dimensions were assessed by two-dimensional echocardiography. Mechanical dyssynchrony was assessed by the presence of septal flash (SF) on echocardiography.*

Results: *The study enrolled 1037 patients (428 females). Female LBBB patients had smaller $QRSD_{LBBB}$ compared to male LBBB patients (142[22]ms versus 156[24]ms, $p<0.001$). In a multivariate analysis, sex and left ventricular end-diastolic diameter (LV_{EDD}) were independent predictors of $QRSD_{LBBB}$. $QRSD_{LBBB}$ can be corrected for sex and LV_{EDD} using a simplified formula: corrected-$QRSD_{LBBB}$ = $QRSD_{LBBB}$ + 0.5 x (50 - LV_{EDD}) – 10 (if male). SF was more prevalent in females compared to males (60% versus 43%, $p<0.001$). Women revealed significantly more SF in narrow $QRSD_{LBBB}$ groups compared to men: 65% versus 13% ($p<0.001$) with $QRSD_{LBBB}$ 120-129ms, 66% versus 18% ($p<0.001$) with $QRSD_{LBBB}$ 130-139ms and 63% versus 31% ($p<0.001$) with $QRSD_{LBBB}$ 140-149ms. At $QRSD_{LBBB}$ >150ms, there were no differences in SF prevalence between females and males.*

Conclusion: *Female patients, show true LBBB morphology at shorter QRSD and have more frequent mechanical dyssynchrony at shorter QRSD compared to males. This might explain the better CRT response rates at shorter QRSD in females.*

1. Introduction

QRS duration (QRSD) and QRS morphology are the key variables to select patients eligible for cardiac resynchronization therapy (CRT).[1, 2] The largest benefit of CRT occurs in patients with left bundle branch block morphology (LBBB) and wide QRSD.[3, 4] Therefore, guidelines favor CRT in patients with LBBB morphology and wide QRSD (>150ms) and do not recommend CRT when QRSD is less than 130ms, even in the presence of LBBB.[1, 2]

Gender disparity in CRT response has been reported previously.[5-7] Although women are underrepresented in clinical trials, female LBBB patients tend to show better CRT response even at shorter QRSD compared to male LBBB patients.

In this study, we hypothesized that differences in LBBB characterization and prevalence of mechanical dyssynchrony might explain gender disparity in CRT selection and CRT response. As such, we evaluated whether, 1) QRSD in patients with LBBB differs between sexes, 2) LBBB QRSD should be corrected for sex differences in body size or cardiac dimensions and 3) prevalence of mechanical dyssynchrony differs between sexes.

2. Methods

2.1. Selection of LBBB patients

Between January 2013 and September 2016, patients presenting with LBBB morphology on a standard twelve lead electrocardiogram (ECG) at the cardiac department of the University Hospital of Ghent were screened and enrolled in this retrospective study. The study was approved by the ethics committee of the University Hospital of Ghent.

ECGs were recorded with MAC 5500 ECG recording devices (GE Healthcare, Waukesha, WI, USA) and stored digitally in a MUSE Cardiology Information system (GE Healthcare).

LBBB diagnosis was defined according to the American Heart Association, American College of Cardiology Foundation and Heart Rhythm Society as a QRSD ≥120ms, QS or rS in lead V1,

broad notched or slurred R waves in two adjacent leads among leads I, aVL, V5 and V6.[8] This definition includes the presence of mid-QRS notching and slurring in the left lateral leads as this differentiates true LBBB from QRS prolongation due to left ventricular hypertrophy. [9, 10]

2.2. LBBB QRSD measurements

QRSD ($QRSD_{LBBB}$) was measured automatically using the Marquette™ 12SL algorithm in the ECG recording devices. This algorithm measures $QRSD_{LBBB}$ as a global QRSD, which is calculated from the earliest beginning until the latest ending of the QRS complex in all leads as recommended by guidelines [8]. This automated algorithm was previously validated by comparing it to manual QRSD measurements using digital calipers.[11]

2.3. Echocardiographic assessment of LBBB patients

Echocardiographic examinations within 3 months of the ECG recording date were considered for further analysis. All echocardiographic examinations were performed by experienced echocardiographers using commercially available systems (GE Healthcare Ultrasound Vivid 7 and GE Healthcare Ultrasound Vivid E9, Vingmed, Horton, Norway; Philips Ultrasound iE 33, Best, Netherlands). Standard two-dimensional cine-loops were recorded for parasternal long and short axis and apical four chamber views. Left ventricular (LV) dimensions were measured in conventional parasternal views: LV enddiastolic diameter (LV_{EDD}), LV endsystolic diameter (LV_{ESD}), interventricular septal wall thickness (IVSD) and posterior wall thickness (PWD). Relative wall thickness (RWT) was calculated as 2 x PWD/LV_{EDD}.[12] LV mass (LV_{MASS}) was calculated as LV_{MASS} (g) =0.8 x (1.04 x ($[LV_{EDD} + IVSD + PWD]^3 - LV_{EDD}^3$)) + 0.6.[13] LV_{EDD}, LV_{ESD} and LV_{MASS} were indexed for body surface area (BSA): LV_{EDDi}, LV_{ESDi} and LV_{MASSi}. The left ventricular ejection fraction (EF) was judged as normal (>55%), moderately reduced (36%-55%) and severely reduced (≤ 35%).

2.4. Assessment of mechanical dyssynchrony

Mechanical dyssynchrony was assessed by the presence of septal flash (SF) on echocardiography. SF refers to a specific echocardiographic pattern in which a rapid, pre-ejection, leftward motion (right to left) of the septum occurs, followed by late contraction of the lateral left ventricular wall, causing a left to right motion of the septum. This SF pattern is an easy and objective parameter to diagnose LV intraventricular dyssynchrony and the presence of SF among LBBB patients is highly predictive of CRT response.[14-17]

Two echocardiography experts, blinded to the ECGs, reviewed all echocardiographic studies offline using EchoPAC version 7.1.13 for the GE scanning systems and Xcelera viewer R3 version 3.3.1 2013 for the Philips scanning system. The presence of SF was assessed visually (parasternal short axis, parasternal long axis or apical views) as validated in prior studies.[17,18] This visual assessment of SF has been shown as a reliable and accurate method to assess mechanical dyssynchrony of the LV.[18] Previously, we validated this 'visual eyeballing' detection of SF at our center with SF assessments by 2-dimensional M-mode and speckle tracking strain analysis showing intraclass correlation coefficients of 0.94 between different SF assessments.[19]

2.5. Statistical Analysis

Categorical variables are expressed as absolute number with percentage (%). Continuous variables are expressed as mean ± standard deviation in case of Gaussian distribution or median [interquartile range (IQR)] if data were non-Gaussian distributed. Shapiro-Wilk test was used to test for normality. Univariate comparison of continuous variables among groups is done by Mann-Whitney U test. Comparison of categorical variables among groups was performed by Chi square test. Associations between continuous variables were assessed using Spearman

rank-order correlation coefficients (r_s). Significant determinants of QRSD in univariate analysis were subsequently tested in a multivariate analysis using multiple linear regression. Non-Gaussian distributed variables (QRSD) were log transformed. Multicollinearity was defined as a variance inflation factor >4. Statistical significance is set at a 2-tailed probability level of <0.05. All statistical analysis was performed using SPSS software (Version 24.0, IBM, Armonk, NY, US).

3. Results

3.1. Patient characteristics

In total, 1037 patients presenting with LBBB on standard twelve-lead ECGs were enrolled for analysis. Mean age was 70±16 years and the cohort compromised 428 (41%) females and 609 (59%) males. All patient characteristics are summarized in Table 6.1. Female LBBB patients were smaller in terms of length, weight and BSA. Female patients also had smaller left ventricular dimensions in terms of LV_{EDD}, LV_{ESD}, LV_{MASS} and RWT compared to male LBBB patients. Male patients were more frequent smokers (8.5 versus 6.1%, p<0.001) and showed more ischemic heart disease (44.5% versus 24.5%, p<0.001).

3.2. Gender differences in LBBB QRSD

Overall, female LBBB patients had smaller $QRSD_{LBBB}$ compared to male LBBB patients (142 [22]ms versus 156 [24]ms, p<0.001) (Figure 6.1). Gender differences in $QRSD_{LBBB}$ remained significant among all age groups except for ages ≤29 years and age group ≥90 years, with this latter group showing a trend to wider QRSD in females (Figure 6.2).

3.3. Gender disparity when selecting patients based on LBBB QRSD

When applying the guidelines' QRSD cutoff of 130ms to implant a CRT [1], 16% (n=67/428) of females versus 9% (n=57/609) of males did not reach this threshold (p=0.002). Using the guidelines cutoff of 150ms (a class 1A guideline to implant a CRT) [1, 2], 68% (n=290/428) of female versus 40% (n=242/609) of male LBBB patients did not reach the threshold (p<0.001).

3.4. Anthropometric determinants of LBBB QRSD

Of all anthropometric characteristics, length, weight and BSA showed a weak but significant linear correlation with $QRSD_{LBBB}$ (r_s = 0.191, r_s = 0.151 and r_s = 0.184 respectively, p<0.001 for all). Body mass index (BMI) showed no significant correlation with $QRSD_{LBBB}$. When analyzing the correlation between anthropometric measurements and $QRSD_{LBBB}$ for each sex separately, none of the body size measurements showed statistically significant linear correlation (p< 0.05).

Table 6.1: Patient characteristics overall, and gender specified

	All Patients n=1037	Female patients n=428	Male Patients n=609	p-value
Age (yrs)	70±16	71±16	69±16	**p=0.002**
Length (cm)	168±11	160±7	172±9	**p<0.001**
Weight (kg)	77±19	69±16	80±16	**p<0.002**
Body mass index (kg/m²)	27±5.5	27±5.7	27±4.9	p=0.735
Body surface area (BSA) (m²)	1.86±0.23	1.72±0.19	1.93±0.21	**p<0.001**
Blood pressure Systolic (mmHg)	120±39	123±39	118±38	p=0.055
Blood pressure Diastolic (mmHg)	62±21	64±22	62±20	p=0.515
Heart rate (beats/min)	75±21	76±19	74±21	p=0.027
Cardiovascular risk factors n(%)				
Smoking	78 (7.5)	26 (6.1)	52 (8.5)	**p<0.001**
Hypercholesterolemia	98 (9.5)	45 (10.5)	53 (8.7)	p=0.373
Arterial hypertension	464 (44.6)	197 (46.0)	265 (43.5)	p=0.228
Diabetes	215 (20.7)	78 (18.2)	137 (22.5)	p=0.149
Underlying heart disease n(%)				
Ischemic heart disease	376 (36.3)	105 (24.5)	271 (44.5)	**p<0.001**
Congenital heart disease	35 (3.4)	14 (3.3)	21 (3.4)	p=0.908
Valvular heart disease	182 (17.6)	74 (17.3)	108 (17.7)	p=0.617
Atrial fibrillation	79 (7.6)	37 (8.6)	42 (6.9)	p=0.136
Medical treatment				
Betablockers	401 (38.7)	125 (29.2)	276 (45.3)	**p<0.001**
ACE-inhibitors	294 (28.3)	110 (25.7)	184 (30.0)	p=0.170
Diuretics	156 (15.0)	48 (11.2)	108 (17.7)	**p=0.011**
Class 1 C antiarrhythmics	15 (1.4)	11 (2.6)	4 (0.7)	**p=0.019**
Class 3 antiarrhythmics	80 (7.7)	21 (4.9)	59 (9.7)	**p=0.005**
Echocardiographic measurements				
Enddiastolic diameter (mm)	51±10	47±8	54±10	**p<0.001**
Enddiastolic diameter/BSA (mm/m²)	28±6	28±5	28±6	p=0.321
Endsystolic diameter (mm)	34±13	30±10	37±13	**p<0.001**
Endsystolic diameter/BSA (mm/m²)	17±9	18±7	19±7	**p=0.015**
Left ventricular mass (g)	212±78	171±62	230±85	**p<0.001**
Left ventricular mass/BSA (g/m²)	116±40	99±33	119±43	**p<0.001**
Relative wall thickness	0.42±0.11	0.44±0.12	0.40±0.11	**p<0.001**

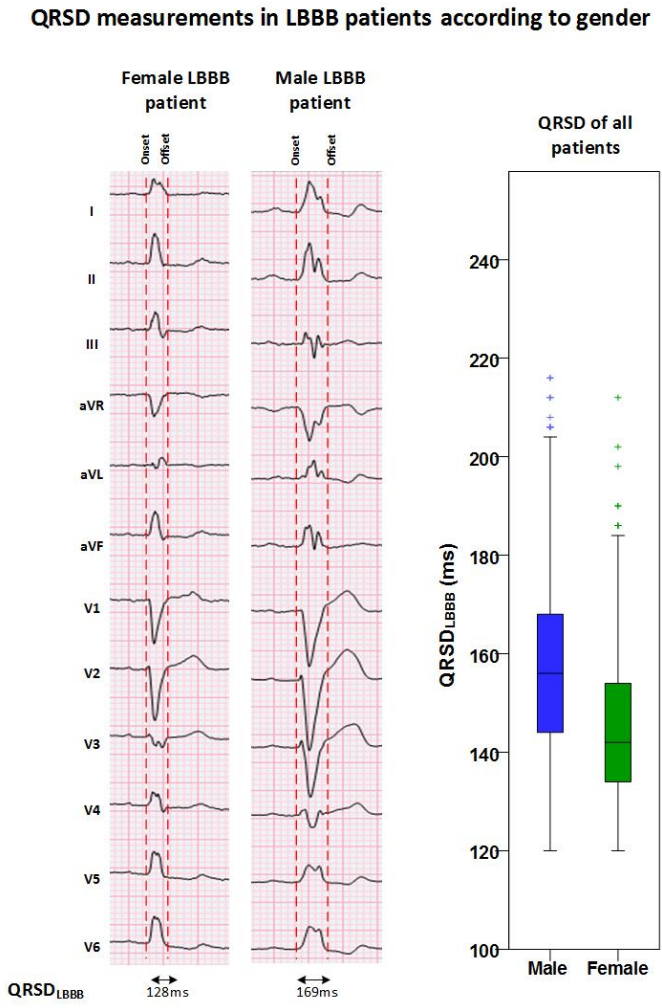

Figure 6.1: *QRS duration measurements in left bundle branch block (LBBB) patients according to sex. LBBB QRS duration ($QRSD_{LBBB}$) is shorter in female LBBB patients compared to males.*

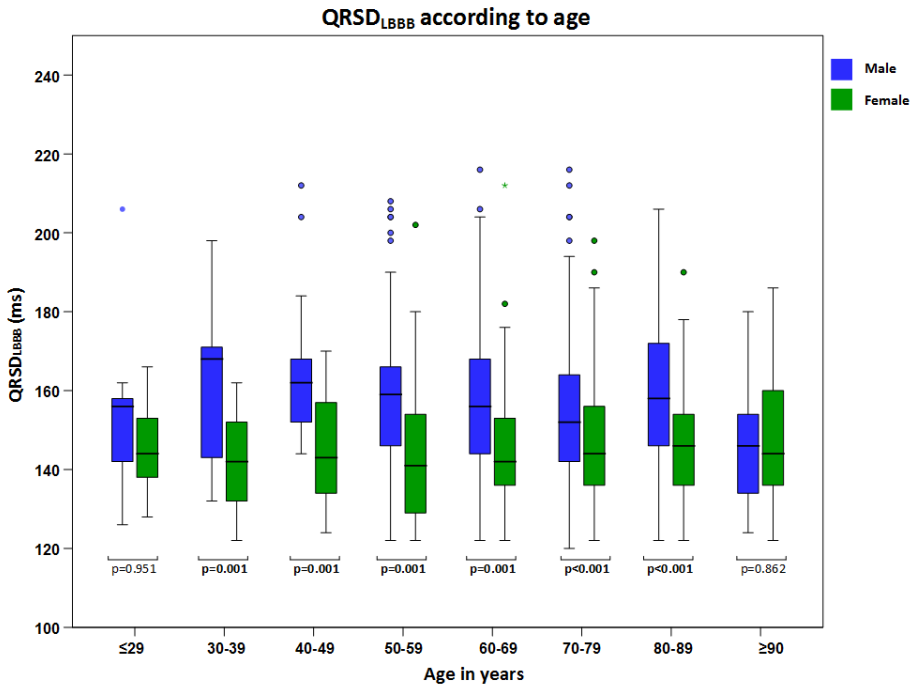

Figure 6.2: *QRS duration (QRSD) in patients with left bundle branch block (LBBB) according to age and sex. For all age groups, except ages <30 and ages ≥90 years old, female LBBB patients have smaller* $QRSD_{LBBB}$ *compared to males.*

3.5. Clinical determinants of LBBB QRSD

$QRSD_{LBBB}$ was not significantly different between patients with ischemic heart disease compared to patients without (150 [24]ms, versus 148 [22]ms, p=0.702). No significant differences in QRSD were found between patients with and without congenital cardiac pathology, valvular heart disease, atrial fibrillation or arterial hypertension.

Patients treated with betablockers (n=401) and class III antiarrhythmics (amiodarone and sotalol, n=80) revealed wider QRSD compared to patients without these drugs (152 [24]ms, versus 146 [22]ms, p<0.001 and 159 [32]ms versus 148 [22]ms, p=0.002 respectively). However, heart rate itself did not correlate with $QRSD_{LBBB}$ (p=0.426). Patients treated with or

without class IC antiarrhythmics (p=0.152), angiotensin-converting-enzyme inhibitor (ACE inhibitor) (p=0.622) or diuretics (p=0.564) showed no significant differences in $QRSD_{LBBB}$.

3.6. Echocardiographic morphometric determinants of LBBB QRSD

In 721/1037 (70%) patients, echocardiographic studies were available. Echocardiographic measurements of left ventricle dimensions showed a weak but significant linear correlation with $QRSD_{LBBB}$: LV_{EDD}: r_s = 0.310, LV_{EDDi}: r_s = 0.149, LV_{ESD}: r_s = 0.276, LV_{ESDi} : r_s = 0.201, LV_{MASS}: r_s = 0.281, LV_{MASSi} : r_s = 0.256, p< 0.001 for all.

Of interest, correlations for $QRSD_{LBBB}$ with LV_{EDD} and LV_{MASS} were larger in female LBBB patients (LV_{EDD}: r_s = 0.275, p< 0.001 and LV_{MASS}: r_s = 0.289, p< 0.001) compared to male LBBB patients (LV_{EDD}: r_s = 0.224, p< 0.001 and LV_{MASS}: r_s = 0.166, p= 0.001).

3.7. Multivariate analysis

In a multiple regression model including sex, BSA, use of betablockers or class III antiarrhythmics and LV_{EDD}, only sex (p<0.001) and LV_{EDD} (p<0.001) were independently associated with $QRSD_{LBBB}$, overall model fit: $F(5,95) = 18.636$, p<0.001.

Therefore, LV_{EDD} and sex were used as variables to normalize $QRSD_{LBBB}$ ($QRSD_{LBBB\text{-}NORM}$), which can be calculated as the following: $QRSD_{LBBB\text{-}NORM} = QRSD_{LBBB} + \beta1 \times (\text{mean } LV_{EDD} - LV_{EDD}) - \beta2 \times \text{sex}$, (with β representing unstandardized coefficients of the multiple regression model). Where β1 = 0.528, mean LV_{EDD} = 51, β2 = 7.560, sex = 1 for males, 0 for females. For simplification, the unstandardized coefficients β1 was rounded to 0.5, mean LV_{EDD} to 50, and β2 to 10. As such, the simplified formula equals: $QRSD_{LBBB\text{-}NORM} = QRSD_{LBBB} + 0.5 \times (50 - LV_{EDD}) - 10 \times \text{sex}$.

3.8. Characteristics of patients with septal flash

Out of 721 patients who had echocardiographic studies, SF could be assessed in 657 patients. When comparing patients with and without SF, patients with SF were more frequent female (47% versus 31%, p<0.001), had less frequent ischemic heart disease (34% versus 49%, p=0.001), had smaller left ventricles as measured by LV_{EDD} (49±10mm versus 52±11mm, p=0.024) and LV_{Mass} (188±74g versus 206±90g, p=0.013) and had wider $QRSD_{LBBB}$ (150 [24]ms versus 146 [24]ms, p=0.014). Differences in clinical characteristics between patients with and without SF are listed in Table 6.2.

Table 6.2: Patient characteristics for patients with and without septal flash

	Septal Flash n=326	No Septal flash n=331	p-value
Age (yrs)	73±14	74±14	p=0.110
Female. n(%)	154 (47)	103 (31)	**p<0.001**
Length (cm)	168±11	169±11	p=0.421
Weight (kg)	75±16	74±17	p=0.821
Body mass index (kg/m²)	26±5	27±5	p=0.964
Body surface area (BSA) (m²)	1.84±0.22	1.84±0.23	p=0.677
Heart rate (beats/min)	71±19	72±20	p=0.570
QRSD Global (ms)	150 [24]	146 [24]	**p=0.014**
Underlying heart disease n(%)			
Ischemic heart disease	111 (34)	163 (49)	**p=0.001**
Congenital heart disease	14 (4.3)	12 (3.6)	p=0.553
Valvular heart disease	63 (19)	90 (27)	p=0.600
Arterial hypertension	169 (52)	167 (51)	p=0.150
Echocardiographic measurements			
Enddiastolic diameter (mm)	49±10	52±11	**p=0.024**
Enddiastolic diameter/BSA (mm/m²)	27±5	27±6	p=0.582
Endsystolic diameter (mm)	33±12	34±14	p=0.261
Endsystolic diameter/BSA (mm/m²)	18±6	18±7	p=0.911
Left ventricular mass (g)	188±74	206±90	**p=0.013**
Left ventricular mass/BSA (g/m²)	101±36	113±44	p=0.060

3.9. Prevalence of septal flash related to sex and LBBB QRSD

Overall, the prevalence of SF in LBBB patients was 45% (326/657 patients). Prevalence of SF in female patients was 60% (154/257 patients), whereas in male patients prevalence of SF was 43% (172/400 patients) ($p< 0.001$).

In a multiple regression model including sex, QRSD, ischemic heart disease and LV_{MASS}, female sex was independently associated with higher SF prevalence, overall model fit: $F(4,95)=7.42$, $p<0.001$.

Analyzing SF prevalence according to QRSD, SF gradually increased from 39% with $QRSD_{LBBB}$ 120-129ms to 59% with $QRSD_{LBBB}$ 160-169ms (red dotted line Figure 6.3). With $QRSD_{LBBB}$ >170ms, prevalence of SF started to decrease to 55% with $QRSD_{LBBB}$ 170-179ms and 48% with $QRSD_{LBBB}$ >180ms.

However, when analyzing sex-specific prevalence of SF according to $QRSD_{LBBB}$, women revealed significantly more SF in narrow $QRSD_{LBBB}$ groups compared to men (Figure 6.3). SF prevalence was 65% in females versus 13% in males ($p<0.001$) with $QRSD_{LBBB}$ 120-129ms, 66% versus 18% ($p<0.001$) with $QRSD_{LBBB}$ 130-139ms and 63% versus 31% ($p<0.001$) with $QRSD_{LBBB}$ 140-149ms. With $QRSD_{LBBB}$ >150ms there were no significant differences in SF prevalence between females and males (Figure 6.3).

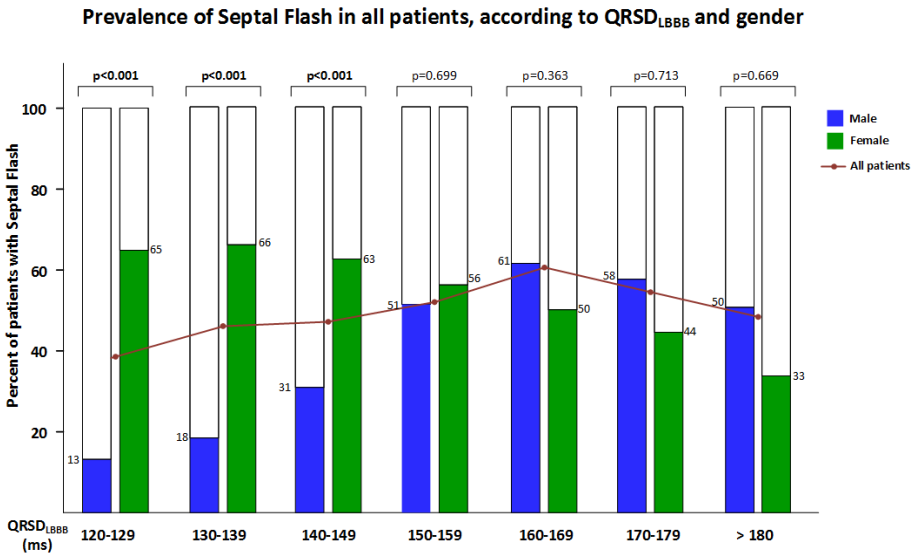

Figure 6.3: *Prevalence of septal flash according to left bundle branch block QRS duration ($QRSD_{LBBB}$) and gender. At $QRSD_{LBBB}$ <150ms, septal flash is more prevalent in female LBBB patients compared to males. At wider $QRSD_{LBBB}$ (≥150ms) differences in septal flash prevalence are not different between males and females.*

3.10. Subanalysis of LBBB patients eligible for CRT

A subanalysis was performed in patients who would meet criteria for CRT (NYHA≥2 and EF≤35%). Out of 1037 LBBB-selected patients, 57 (5.5%) patients (19 females) met this criteria. We observed a trend to shorter $QRSD_{LBBB}$ in female CRT candidates compared to males: 146 [18]ms versus 156 [30]ms, p=0.057. Of interest, in these CRT candidates, 3/19 (16%) female patients and 4/38 (10%) males did not reach the guidelines QRSD threshold of 130ms (p=0.53). Applying a 150ms QRSD cutoff, 11/19 (58%) of females versus 16/38 (42%) of males would not reach this threshold (p=0.26). A trend to higher prevalence of SF was observed in female CRT candidates compared to males: 8/19 (42%) versus 8/38 (21%), p= 0.095.

4. Discussion

4.1. QRS duration thresholds in the era of LBBB

Originally, LBBB was defined by morphologic criteria and a QRSD ≥120ms based on Wilsons' work in dogs in 1941.[20] Recently, insights from endocardial mapping studies proposed QRSD thresholds of ≥130ms in women and ≥140ms in men to diagnose LBBB.[9] To diagnose LBBB, a 10ms sex difference in QRSD is assumed, as it has been shown in normal cardiac conduction that females reveal shorter QRSD compared to males. These wider QRSD cutoffs for LBBB diagnosis in males are generally attributed to larger body size and larger hearts of males and these adjustments are based on observations in subjects with normal cardiac conduction.[10] However, sex differences in QRSD among LBBB patients have not been investigated thoroughly. Our results demonstrate that QRSD is indeed shorter in female LBBB patients compared to males, but rather mounts up to 14ms (+/-10% of $QRSD_{LBBB}$).

In contrast to what has been hypothesized, these sex differences in QRSD cannot be explained by sex differences in body size and only partially by sex differences in cardiac dimensions. Some authors have suggested to individualize QRSD in LBBB patients by correcting QRSD for BMI and LV dimension.[21, 22] However, we found no correlation between BMI and LBBB QRSD. Adjustments for LV dimension will not completely correct for sex differences in QRSD among LBBB patients. Therefore, we suggest, besides QRSD adjustment for LVEDD, also an additional adjustment of 10ms in case of male sex.

Underrepresentation of women in CRT trials and registries

The major clinical trials demonstrating the benefit of CRT, selected patients solely on prolonged QRS durations (≥120ms) and in these trials female patients are underrepresented.[23-25] A meta-analysis by Herz et al. of 183 CRT trials showed that women represent only 24% of the total patient group.[6] As none of the studies specified separate enrollment QRSD thresholds for males

and females, both LBBB females and males have comparable QRSD values in these trials. This is in contrast with our findings in an unselected LBBB population showing that females have true LBBB at narrower QRSD compared to males. Likewise, as guidelines do not present separate QRSD thresholds for males and females, female patients remain underrepresented in registries. In a large Swedish registry, female patients counted only for 16% of CRT-implanted patients and only for 27% of patients eligible for CRT implant when considering guideline recommendations.[26]

Several reasons have been postulated why women are underrepresented in CRT trials and registries: female heart failure patients tend to have less frequent ejection fraction ≤35%, less systolic heart failure and less ischemic heart disease.[6] Our data show that shorter QRSD in female LBBB patients might also be an important reason why female patients are less likely to be considered for CRT.

4.3. Sex differences and outcome in CRT trials

Subanalysis of the MADIT-CRT trial showed that female LBBB patients have better CRT outcome, in terms of all-cause mortality and non-fatal heart failure events when compared to male LBBB patients.[27] Additional analyses by Biton et al. showed that women have clinical benefit both at QRSD <150ms and ≥150ms whereas men benefit from CRT therapy only at QRSD ≥150ms.[5] Similarly, Varma et al showed that CRT response in female LBBB patients was greater compared to men, and women benefit more from CRT at shorter QRSD (<150ms).[7] Our results might explain these gender disparity in CRT outcome: First, women tend to have more frequently true LBBB, as defined by QRS notching or slurring at shorter QRSD compared to men. Secondly, women reveal more mechanical dyssynchrony, as assessed by SF, and at shorter $QRSD_{LBBB}$ compared to men. The presence of SF has been shown to be a strong and robust predictor of long-term CRT response in several large studies.[14, 17, 18] As such, the higher

prevalence of SF among female LBBB patients, both overall and especially with QRSD <150ms, may explain the better CRT response rates in female CRT patients. Interestingly, a decline in CRT response has been observed in females with QRSD >180ms.[7] This is in accordance with the strong decline in prevalence of SF (33%) in female LBBB patients with QRSD >180ms, whereas in men a SF prevalence of 50% was still observed with QRSD > 180ms.

4.4. Is there a need for gender-specific CRT guidelines?

The present observational study selected "healthy" LBBB patients, and care should be taken to apply our observations to a LBBB population with "diseased hearts" that are eligible for CRT. Therefore, we provided an additional subanalysis in LBBB patients who would qualify for CRT indication. Similar to our main data, the same trends for shorter LBBB QRSD and higher prevalence of SF in females CRT candidates were observed, although not reaching statistical significance most likely due to the low number of patients. Therefore, our data justify future studies with emphasis on gender differences in LBBB QRSD and SF prevalence among patients eligible for CRT.

Current guidelines do not recommend to implant a CRT device when QRSD is <130ms, even in the presence of LBBB.[1] Four randomized trials (RethinQ, NARROW-CRT, CRT, EchoCRT and LESSER-EARTH) studied the effect of CRT in patients with narrow QRSD <130ms) and showed conflicting results.[28-31] However in these studies, women are still underrepresented (12 to 38% of the CRT patients) and true LBBB morphology was not an inclusion criterion in these studies. A recent subanalysis of EchoCRT, showed that the lack of CRT benefit in patients with QRSD <130ms was mainly driven by an increased hazard for the primary outcome in male patients.[32] Considering the high response rates of female LBBB patients and the high incidence

of SF in females with QRSD <130ms, further studies to address a potential CRT benefit in these female patients are needed.

Other guidelines still use a class 2a indication for LBBB patients with QRSD ≥120 and <150ms and a class 1 indication of LBBB patients with QRSD≥150ms.[2] As females with QRSD <150ms seem to benefit more from CRT, gender-specific recommendations may be considered in LBBB patients with QRSD between 120 and 150ms.

Furthermore, the intriguing question remains whether septal flash and LBBB patterns could also occur in females with QRS duration < 120ms, as the distribution of LBBB/septal flash in figure 6.3 might suggest such an extrapolation of LBBB/septal flash below 120ms.

5. Limitations

Our population represent a hospital population, with all patients being evaluated at the cardiac department. Patients were selected on LBBB morphology and the majority of patients did not have heart failure or reduced EF. As such, our results should be interpreted with caution, as heart failure patients with LBBB might differ from our population. A single LBBB definition, including QRS notching, was used in this study for reasons mentioned before. Other LBBB definitions may select other patients with other clinical and echocardiographic characteristics. Diagnosis of LBBB was established on the first ECG meeting the criteria for LBBB in the study period between 2013 and 2016. The onset of LBBB for each patient was therefore not known. Mechanical dyssynchrony was only assessed by the presence of SF, and therefore no conclusions can be drawn with respect to other markers of inter- or intraventricular dyssynchrony.

6. Conclusion

Female LBBB patients have true LBBB morphology at shorter QRSD compared to male LBBB patients and this cannot entirely be explained by sex differences in cardiac dimensions. As selection of patients in CRT trials and by CRT guidelines is driven by wide QRSD cutoffs, this may be one of the reasons why women are underrepresented in CRT trials and registries. Moreover, female LBBB patients tend to show more mechanical dyssynchrony and at shorter QRSD compared to males, explaining why women tend to have better CRT response and at shorter QRSD.

7. References:

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Part V

General Discussion

1. Research in the field of CRT

Since its introduction in 1994, the field of CRT has evolved from an experimental therapy to a generally accepted treatment in heart failure patients[1]. Despite the scientific and technical progress since its first introduction, not all CRT patients achieve the expected response[2-4]. Except for achieving higher CRT response rate and avoiding CRT non-response, the limited healthcare budgets and high socio-economics costs of CRT devices require further efforts to maximize the benefit of CRT[5]. The search to increase the benefit of CRT has triggered an increasing number of publications the past decades (Figure V.1). This research has been focusing on better selection of CRT candidates, better implantation strategies and optimizing CRT to the individual patient by device programming. The present thesis contributes to this research field by a thorough and in depth electrocardiographic study of patients eligible for CRT.

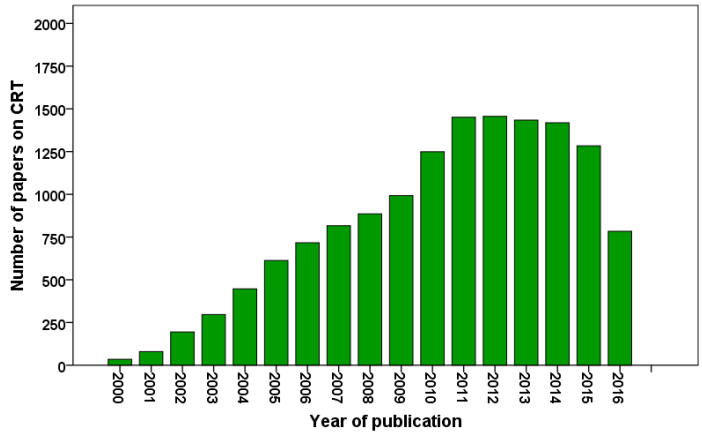

Figure V.1: *Number of publications regarding cardiac resynchronization therapy in the last two decades (Source: https://www.ncbi.nlm.nih.gov/pubmed).*

2. QRS duration in CRT

2.1. QRS duration: a historical parameter revisited

In the large clinical CRT trials, QRSD was used as main inclusion parameter to enroll patients[6-15]. This emerged from the idea that CRT should correct electrical dyssynchrony, as reflected by prolonged QRSD, by pre-excitation of the delayed ventricular contraction. From these CRT trials and sub-analyses, it became clear that CRT benefit is more likely to occur in patients with wider QRSD[9, 12-14]. The better response rate with wider QRSD was also confirmed by two meta-analyses, combining data form several CRT trials[16, 17]. Based on these trials, QRSD used to be and currently still is the main determinant to select or exclude patients from CRT according to international guidelines[3, 18-20].

Despite the major role of QRSD in selecting patients for CRT, no specific recommendations on how to measure QRSD are specified in guidelines, and accuracy of different QRSD assessments have been poorly investigated. The first two chapters of this thesis focused on the methodology to measure QRSD. In the individual patient, different methods yield significant differences in QRSD and therefore become clinically relevant when tailoring CRT based on a patients' individual QRSD[21-23]. These findings imply two important consequences. First, there is a need for standardization of QRSD measurements in the selection of CRT candidates. Secondly, QRSD parameters should not be considered as a sole parameter to decide whether a patient should have or be denied from a CRT device. Current European guidelines use both QRSD and QRS morphology to include patients for CRT[18]. However, these guidelines do exclude patients from CRT based on QRSD alone. Indeed, patients with QRSD less than 130ms are excluded from CRT according to most recent European guidelines[18]. We showed that a substantial number of LBBB patients could be withheld from CRT because QRSD was scored below the 130ms cutoff by one single QRSD assessment, whereas other methods yield QRSD values >130ms. Therefore, excluding patients from CRT based on QRSD alone should be avoided.

2.2. Shortening of QRS duration: a valuable concept to predict CRT response?

The electrocardiographic changes that occur during BV pacing have been of particular interest. As a wide QRSD is used as a surrogate marker for LV dyssynchrony, it sounds logic that shortening of QRSD after CRT, might implicate successful resynchronization. Different studies have shown that shortening in QRSD predict both clinical and echocardiographic CRT response[24, 25]. Conversely, QRSD prolongation during BV pacing after CRT predicts non-response[26]. A recent meta-analysis, including 12 observational studies (1545 patients), concluded that QRSD narrowing after CRT implantation is associated with a favorable clinical and echocardiographic response[27]. Interestingly, both acute shortening of QRSD (occurring immediately after CRT implant) and shortening at six months turned out to be a good predictor of future CRT response. However, a subanalysis of the REVERSE trial (610 patients) was unable to show any predictive effect (reverse modeling and NYHA benefit) of CRT-induced QRSD narrowing[28].

In chapter 1 and 2 of this thesis, we showed that paced QRSD varies strongly according to the method by which QRSD is measured[21-23]. Lack of agreement on the predictive value of QRSD shortening could therefore, at least partially, be explained by the different methods used to measure QRSD. We have showed that paced QRSD and shortening in QRSD is best assessed using a manual, global QRSD assessment which reveals low inter- and intra-observer variability. The high accuracy of this global QRSD emerges from its global approach which considers all leads of the twelve lead ECG. By taking into account all leads, iso-electric segments at the beginning of the QRS or blurred transitions at the end of the QRS complex are less likely to be considered as false onset or end of the QRS waveform. As such, this global approach leads to a more accurate detection of the beginning and end of the QRS waveform and hence a more accurate assessment of QRSD. Our studies showed that when measuring

QRSD shortening accurately by a global QRSD approach, this shortening in QRSD by BV pacing can predict CRT response.

However, even accepting that QRSD narrowing is predictive for CRT response, its practical use might be limited at the individual level. The degree of QRSD shortening that discriminates responders from non-responders ranges from 14 to 24ms[22, 27]. Though, even with the most accurate QRSD assessment, variability in measurements up to 11ms are unavoidable. As such, the degree of QRSD shortening becomes too small with respect to the inevitable variability of QRSD measurements, and may therefore impede its practical use to differentiate CRT response from non-response in the individual patient.

3. QRS duration or QRS morphology: what matters in CRT?

3.1. LBBB versus non-LBBB patients: data derived from CRT trials and registries

Although QRSD was the main enrollment criterion in large CRT trials, QRSD cannot be considered the sole determinant of CRT response as not all patients with wide QRSD benefit to the same extent from CRT. Subanalyses of large CRT trials revealed that patients presenting with LBBB benefit most from CRT[28-32]. The benefit of CRT in patients with RBBB or non-specific intraventricular conduction delay (NIVCD) is less clear, as studies showed only modest or even absent response to CRT in these patients[28, 32]. Long term follow up of the MADIT-CRT trial and data from CRT registries showed even a concerning trend towards increased mortality risk of non-LBBB patients compared to LBBB patients[33, 34]. Whether this increased mortality can be attributed to an harmful impact of CRT implantation in non-LBBB patients should be interpreted with caution as none of the studies included a control group of non-LBBB patients having no CRT. It has been shown that patients with non-LBBB reveal more ischemic heart disease, diabetes, pulmonary disease, atrial fibrillation and renal dysfunction compared to

LBBB patients, which may contribute to a worse outcome[35]. Conversely a recent study showed a mortality benefit of CRT over ICD in patients with bundle branch block and very wide QRSD (>180ms)[36]. However, this study did not report the percentage of ventricular pacing in these patients with very broad BBB in the ICD-arm. This is an important issue, as a possible benefit of CRT might arise from a compensation for the deleterious effects of high percentage RV-pacing in the ICD-arm, explaining the relative benefit in the CRT arm (no control group "without or with less pacing" was used).

3.2. What to prefer: QRS morphology or QRS duration?

Whether either QRSD or QRS morphology should be preferred for the selection of CRT patients has been a matter of debate. One study of Dupont et al. stated that QRS morphology is a more important determinant of CRT response compared to QRSD[37]. Likewise, Khidir et al. found that QRS morphology was associated with long-term survival after CRT, whereas QRSD showed no significant association with long-term survival. Conversely a large individual patient meta-analysis of five large CRT trials by Cleland et al. stated that QRSD is a powerful predictor of CRT benefit and QRS morphology did not predict clinical CRT response in this study[38]. Post hoc analyses of large randomized CRT trials concluded that both in LBBB patients and non-LBBB patients a trend to better CRT response is found with wider QRSD[29]. We believe that several reasons can explain the discrepancy in literature.

- First, QRSD and QRS morphology are strongly correlated, with patients presenting with RBBB and non-specific intraventricular conduction delay (NIVCD) having shorter QRSD compared to LBBB patients[32, 39]. When putting two strongly related parameters such as QRSD and QRS morphology together in a multivariate analysis, the strongest of the two variables might nullify a possible predictive effect of the other variable.

- Meta-analyses using aggregate data ignore the relation between QRSD and QRS morphology for each patient individual. Therefore only individual patient data analyses can accurately assess the relation of QRSD and QRS morphology[40].
- Several studies were conducted on subanalyses which may not be powered to reveal a dominant effect of QRSD over QRS morphology and vice versa. In this regard, we should recall that QRS morphology was never a primary inclusion criterion in CRT trials. Subgroup criteria for QRS morphology were therefore often based on statistics to avoid small subgroups. As the majority of patients had LBBB, patients presenting with other conduction delays (RBBB, NIVCD, …) were lumped into a single "non-LBBB" group. As such, lumping these groups together might dilute a possible benefit of CRT in some of these patients groups[40].
- Definitions of LBBB, RBBB and NIVCD may differ among the different studies. The use of different definitions might affect the predictive value of QRS morphology or QRSD on CRT response. It has been shown that when using a "liberal LBBB" definition, patients with non-LBBB tend to have smaller QRSD compared to patients with LBBB[32]. However, when applying more strict criteria to define LBBB, no differences in QRSD between patients with LBBB and non-LBBB occur and QRSD was not found to be a predictor of CRT response[41-43].
- Another important explanation might be related to the read-out and how CRT response is defined. It has been shown that agreement among different CRT response criteria is poor[44]. This is also illustrated in the paper of Dupont et al., where QRS morphology is not associated with endpoints as death, heart transplant and left ventricular assist device placement but is also associated with change in ejection fraction[37].
- At last, not all LBBBs are equal. Several activation patterns among LBBB patients have been described[45]. We showed that SF, a strong predictor of CRT-response[46-48], is only

present in half of the LBBB patients and the twelve lead ECG cannot accurately discriminate those patients with LBBB and SF from those without SF.

To our opinion, there should be no doubts that patients with wider QRSD benefit more from CRT compared to patients with narrow QRSD. Likewise, it should be clear that patients with LBBB show better CRT response compared to patients with non-LBBB. We assume, that as one defines LBBB more strictly by morphology characteristics (e.g. mid-QRS notching) and echocardiographic criteria (such as SF), the additional effect of wider QRSD on CRT response might become smaller.

4. Towards new electrocardiographic parameters in the field of CRT

4.1. QRS area: combining QRS duration and morphology

Given the limitations of QRSD, new electrocardiographic parameters have been developed to better select patients that will respond to CRT. Recently, QRS area has been proposed as a new parameter for better prediction of CRT response among CRT candidates[49, 50]. This new parameter combines the information of both QRSD and QRS morphology into a single parameter. Furthermore, measurements of QRS area are highly reliable in terms of reproducibility and can be measured automatically. Current ECG devices can convert ECGs to VCGs using an inverse Dower or Kors matrix. Calculating QRS area then only requires a mathematical formula to integrate the QRS waveform. As such, assessment of QRS area has some unique advantages: non-invasive, cheap, easily obtainable, high reproducibility, automated measurements possible and little time-consuming.

4.2. Paced QRS area: an easy tool to optimize CRT?

In chapter 3, we showed that the reduction in QRS area occurring with BV pacing predicts CRT response better than shortening of QRSD[51]. Moreover, we were able to define the optimal AV-delay and best LV lead position by pursuing the largest reduction in QRS area. As such, assessment of BV-paced QRS area can be used as a tool during CRT implant or optimization. One could even hypothesize to use far field electrograms, recorded by the CRT device, to calculate QRS areas. Templates of far field electrograms are already used to differentiate between ventricular and supraventricular arrhythmias based on changes in the QRS waveform. By automatically calculating the QRS area of a paced configuration and comparing this to a baseline QRS area, a novel approach for automated optimizing CRT may be envisaged in the future.

Some authors prefer to use 3D QRS areas, calculated by all three VCG leads[49, 50]. In our studies, both 3D QRS area and QRS area in the vectorcardiographic Z-lead were useful to assess CRT response. The high accuracy of QRS areas in the Z-lead in our studies can be explained as we preferentially enrolled patients with LBBB. In LBBB patients, 3D QRS areas are mainly determined by large areas in the Z-lead as those patients have typically a delayed activation of the posterobasal segments of the LV[51]. As the Z-lead is oriented in an anteroposterior direction, shifts in QRS areas from LBBB to BV pacing are best detected in this lead. For the same reasons, LBBB QRS areas calculated in lead V1 and V2 of the standard twelve lead ECG correlate best with 3D QRS areas of the VCG. However, when applying measurements of QRS area to all type of heart failure patients, both LBBB and non-LBBB, 3D QRS areas might be preferred as these will be less dependent on the orientation of the delayed ventricular activation.

5. Towards the "optimal" electromechanical substrate

5.1. Electromechanical dyssynchrony

The ideal substrate for CRT is thought to be dyssynchronous ventricular contraction caused by an electrical conduction problem, so-called electromechanical dyssynchrony. Current guidelines use QRSD and QRS morphology as the two major selection criteria[18, 52]. These criteria are considered markers of electrical dyssynchrony, but do not necessarily reflect mechanical dyssynchrony as patients with wide QRSD may not all have LV dyssynchrony and those with a narrow QRSD may reveal "dyssynchrony"[53]. On the other hand, mechanical dyssynchrony can be assessed by echocardiography using tissue Doppler imaging or other techniques[54-57]. However, due to previous controversial studies[4], these echocardiographic assessments of mechanical dyssynchrony are not considered in the current guidelines to select CRT patients[18, 52]. Several reasons for the disappointing results of echocardiographic prediction of CRT response have been put forward: large inter-observer variability, lack of validation and no differentiation between electrical and mechanical dyssynchrony[55]. Indeed, mechanical dyssynchrony can have several causes, however, it is primarily mechanical dyssynchrony caused by an electrical conduction delay that will lead to an optimal CRT response[55]. From a conceptual point of view, a selection parameter which reflects both the electrical and mechanical dyssynchrony of the diseased heart could be the ideal parameter to select CRT patients.

5.2. The genesis of septal flash

In this thesis we compared electrocardiographic parameters with a simple visual assessment of mechanical dyssynchrony, called septal flash (SF). This abnormal motion of the septum, is specific for an LBBB-induced contraction pattern[58]. The early systolic right-left motion of the septum has been attributed to both an active septal contraction and a passive pressure-related

modulation. From early pacing studies it was known that a septal motion, resembling SF, could be generated by transient increase in RV pressure relative to LV pressure[59]. Similarly but more recently, it was shown that SF might result from an early RV activation that is unopposed because contraction of the lateral LV wall is delayed, as typically seen with LBBB[60]. Another argument for RV involvement in the generation of SF, is that pacing at the left side of the septum does not generate SF, whereas pacing the RV side of the septum did result in SF[61]. On the other hand, Gjesdal et al. showed that ablation of the proximal left bundle branch in dogs resulted in SF, even when LV pressure was higher than RV pressure[62]. Therefore they attributed SF to a contraction of the septum, occurring early (pre-ejection) relative to the lateral wall of the LV. However, it seems that an active septal contraction is not an essential condition to reveal SF. In a simulation model, SF could be induced by an early RV activation preceding simultaneous activation of the LV septal and lateral wall[60]. As an early septal activation was now excluded, SF was attributed solely to a passive mechanism. As this simulation model used simultaneous activation of the LV septum and lateral wall preceding RV activation, it is not clear to which physiological condition this might rely. Indeed, such an activation cannot correspond to an LBBB activation pattern, as the hallmark of LBBB is delayed lateral LV activation with regard to the septum.

Electrophysiological (EP) studies have been performed in patients with SF, and these data showed a long transseptal activation time (due to slow muscle to muscle conduction within the septum) and functional lines of block in the left ventricle[63]. These EP characteristics were also described by Auricchio et al., but no echocardiographic data of dyssynchrony (no SF mentioned) were reported in that study[45]. Importantly, in many other patients with LBBB, no such EP characteristics were present and often, several early breakthrough sites in the septum occurred and were associated with much shorter transseptal activation times. These latter characteristics may be compatible with LBBB patients who do not have septal flash, but his

remains to be investigated. Therefore, it appears that not all LBBBs are created equally and the heterogeneous EP findings in LBBB may relate to the variable anatomy of the left bundle[64], the site and/or the extent of conduction block in the left bundle and the diseased myocardial tissue (e.g. scar, hibernation, stunning and other myocardial cell dysfunctions)[45, 65, 66].

5.3. Septal flash: the ideal electromechanical substrate for CRT?

We showed that septal flash (SF) is present in 50% of patients with LBBB, and patients with SF fulfilled more LBBB criteria compared to patients without SF[67]. Importantly, we could not detect SF in patients with LAHB, LPHB or RBBB patients. Based on our data and the aforementioned literature we hypothesize that SF in LBBB patients result from a proximal block of the left bundle branch. A proximal bundle branch block will not cause an early septal breakthrough. Therefore, the septum will likely be activated by an intact right bundle branch, followed by right to left and slow cell to cell conduction resulting in long transseptal activation times. According to this hypothesis, the presence of SF requires both an intact right bundle branch and relatively intact septal myocardium. As such one might speculate on whether SF might be a criterion for true LBBB, redefines true LBBB or identifies a particular "subset" of LBBB patients with an optimal electromechanical substrate for CRT. Indeed, SF has been shown to be an accurate, reproducible and strong predictor of reverse remodeling and long term CRT response[46-48]. Although multicenter, randomized prospective trials are further needed, LBBB patients with SF might represent the optimal electromechanical substrate to be corrected by CRT.

5.4. Can we identify electromechanical dyssynchrony on the surface ECG?

Given the heterogeneity and discordance between electrical and mechanical dyssynchrony, several electro- and vectorcardiographic parameters have been proposed as markers of electrical and mechanical dyssynchrony. These parameters generally use either a well-defined part of the QRS duration interval or calculate the surface of the QRS waveform (QRS area) [49, 50, 68, 69]. Of all electro- and vectorcardiographic parameters, VCG-calculated QRS area correlated best with SF. This is in line with a previous study showing that large QRS areas are associated with a higher degree of mechanical dyssynchrony, measured by electro-anatomic mapping[49]. However, we showed that the accuracy of ECG or VCG parameters to discriminate LBBB patients with SF from those without SF remains low (chapter 5). Given the high CRT response rates among patients with SF and because no ECG or VCG parameter can accurately identify SF among LBBB patients, SF might be considered as an independent and additional parameter to select CRT-candidates. On the other hand, patients without SF also appear to respond to CRT, although much less frequent and with much less reverse remodeling[46].

6. Gender differences in electromechanical characteristics of LBBB

6.1. Gender differences in LBBB QRS duration

In chapter six we showed that female LBBB individuals have smaller QRSD compared to male LBBB patients. Previous computer simulations suggested different QRSD cutoffs for males (140ms) and females (130ms) to diagnose LBBB[66]. In that study, a 10ms sex difference in QRSD is assumed, as it has been shown in normal cardiac conduction that females reveal shorter QRSD compared to males. Our results show that QRSD is indeed shorter in female LBBB patients compared to males, but rather mounts up to 15ms. As such, current CRT guidelines, favoring wide QRSD, may disadvantage female patients in the selection of CRT.

Wider QRSD in males is generally attributed to larger body size and larger hearts of males. In contrast to what has been hypothesized[66], sex differences in LBBB QRSD cannot be explained by sex differences in body size and only partially by sex differences in cardiac dimensions. From the 15ms differences in LBBB QRSD between males and females only 5ms could be attributed to differences in cardiac dimensions. As such, an additional adjustment of 10ms is further needed to account for differences between males and females. For that reason we developed a simple formula to correct LBBB QRSD for differences between males and females.

6.2. Gender differences in electromechanical dyssynchrony

In chapter six we also assessed the gender-specific prevalence of SF in LBBB patients. According to our study, female LBBB patients reveal more mechanical dyssynchrony (as defined by SF) and at smaller QRSD compared to men. Given the high probability of CRT response in the presence of SF[47, 48], our results might explain why female LBBB patients respond at smaller QRSD compared to men[70-73].

Interestingly, our data also showed that 60% of female LBBB patients with QRSD between 120 and 130ms have SF. This high prevalence may lead to the hypothesis that SF could also be present in female patients with QRSD <120ms, as it is very unlikely that a natural distribution of SF prevalence would start abruptly at such a high prevalence. If female patients show SF at QRSD <120ms and accepting the hypothesis that SF is an echocardiographic marker of LBBB, this might indicate that women can reveal true LBBB at QRSD < 120ms, which would require revision of current LBBB criteria.

Furthermore, we believe that our findings justify further research to assess whether CRT may be effective in female LBBB patients with narrow QRSD (<130ms) and SF. This idea is supported by a recent subanalysis of the Echo-CRT trial showing that the absence of CRT benefit in patients with mechanical dyssynchrony and narrow QRSD (<130ms) was mainly

driven by a worse outcome in males[74]. As the study was terminated prematurely, a possible benefit of CRT in female patients could not be evaluated.

7. Limitations of the studies

As all conducted research, our studies have limitations. We consider three limitations, worth to mention in our final discussion. First, one of the limitations we encountered in chapter 1 and 2 is that the gold standard for assessing ventricular depolarization time is not known. Therefore, we cannot state that our global QRS duration approach is the best method to assess real depolarization time of the heart, but at least it is a measurement which is least prone to inter- and intra-observer variability and therefore can serve as standard approach to assess QRS duration. A validation with high density intracardiac mapping would be a method to assess how accurate global QRSD is to assess ventricular activation time. Secondly, several of our research studies were not conducted in a CRT population, but quite often in a general LBBB population. As such, we should be cautious to extrapolate our study results to a specific CRT population. Our findings should therefore be seen as a potential challenge/pitfall within current clinical practice and questioning current selection parameters in the CRT guidelines. Thirdly, all our studies had a retrospective design with its restrictions inherent to retrospective analyses. Therefore further validation of global QRS duration, QRS area and gender differences in electromechanical characterization needs prospective study designs before translating our concepts into clinical practice.

8. Future perspectives and thoughts on CRT

8.1. New insights from cardiac electromechanics should be considered in future CRT guidelines

With the current CRT selection criteria (QRSD and QRS morphology), up to one third of the patients fail to respond to CRT[2, 3], indicating that current established selection criteria might be suboptimal. We showed that selecting or excluding patients for CRT, based on a single selection parameter, is neither advisable nor desirable. Apart from co-morbidities, the heterogeneity and complex dynamic nature of the electro-mechanical substrate precludes that a single parameter will be able to discriminate with high accuracy CRT responders from non-responders. Therefore we need a paradigm shift from single parameters towards multi-parametric scoring models for better selection of CRT responders. Two such scoring models have been introduced in the last years and are summarized in table V.1[75, 76].

Table V.1: Multi-parametric score models to predict CRT response

Score model	Author	Year	Parameters
L_2ANDS_2	**Brunet-Bernard**	**2014**	- LBBB (2 points) - Age > 70years (1 point) - Non-ischemic cardiomyopathy (1 point) - LVEDD <40 mm/m^2 (1 point) - SF (2 points)
CAVIAR	**Maass**	**2017**	- Age - QRS Area - Interventricular mechanical delay - Apical rocking

These scoring systems provide better predictive power than clinical, echocardiographic and electrocardiographic parameters separately. Interestingly, in both score models,

electrocardiographic characteristics and echocardiographic assessments of mechanical dyssynchrony are combined. Therefore, it seems that electrophysiologists and echocardiographists meet again when tailoring patients for CRT, and future guidelines on CRT should might consider these multi-parametric models.

8.2. Identifying variable(s) that predict significant ventricular dysfunction in patients who require (frequent) right ventricular pacing

The right ventricular apex has been the preferred site for pacing as it offers stable lead positions and is easily accessible. However, several studies reported on detrimental effects of RV apical pacing with an increased risk of heart failure and mortality[77, 78]. Prevalence of new-onset heart failure after RV apical pacing varies between 9 to 26%, depending on the percentage and long-term duration of ventricular pacing[79]. Given the observed benefits of CRT, one might assume that implanting a CRT instead of regular DDD or VVI pacemaker might prevent the potential deleterious effects of RV pacing in patients with a standard pacemaker indication and high RV pacing burden. Two large randomized trials (BIOPACE and BLOCK HF) compared RV versus BV pacing in patients with normal or only moderate depressed LV function and a standard indication for pacing[80, 81]. Whereas the BLOCK HF trial suggested beneficial results of CRT on a composite endpoint (mortality, heart failure and increase of >15% in LVESV), preliminary results of the BIOPACE trial (endpoint death or first heart failure hospitalization) could not confirm this superiority of CRT in those patients. For patients with a standard pacing indication, current guidelines consider CRT as first implant only when LV ejection fraction is moderately depressed and a high percentage of ventricular pacing is expected[18]. If a patient received a pacemaker or ICD and subsequently develops heart failure, an upgrade for CRT might be considered if patients exhibit a high percentage of pacing.

Currently, we are not able to accurately select those patients who will develop heart failure with RV pacing and might benefit from CRT. Obviously, patients who do not experience detrimental effects of standard RV pacing, should not be considered for CRT as CRT bears a higher risk of complications. Recently it has been shown that SF, as marker of LV dyssynchrony, is present in the majority of patients with high burden (>99% RV pacing) and long duration of RV apical pacing[82]. It should be further evaluated if the presence of SF or its magnitude is a good predictor for the development of heart failure and might identify those patients who will benefit from CRT upgrade. Another potential selection tool for selecting those patients who will benefit from CRT upgrade might be QRS area. One of our hypothesis is that those patients who have large baseline QRS areas and do not reveal any reduction in QRS area with RV pacing might be considered candidates for upgrade to CRT.

8.3. Should RV pacing (always) be omitted in CRT?

To our opinion, biventricular pacing by CRT might not be the ideal pacing modality for every heart failure patient. Biventricular pacing still implicates RV pacing which may harm ventricular function. It is possible that some of the non-responders to CRT are caused because of the deleterious effects of this RV pacing, which cannot be rescued by the LV pacing component during BV pacing in some. This hypothesis is supported by studies showing that LV pacing (both with and without fusion with intrinsic conduction) might result in similar hemodynamic effects compared to BV pacing[83-86]. Moreover, the GREATHER-EARTH study showed that LV pacing could improve non-responders of BV pacing[86]. Modern CRT algorithms, like Adaptive CRT™ (Medtronic) already apply left univentricular pacing allowing fusion with intrinsic AV conduction. This algorithm has shown non-inferiority compared to echocardiographic CRT optimization in the Adaptive-CRT trial[87]. Sub-analyses of this trial

demonstrated that patients randomized to the algorithmic optimization had more CRT response (clinical composite score)[88] and less all-cause and heart failure hospitalizations[89].

8.4. Single lead transseptal pacing might open new perspectives for patients requiring ventricular pacing

The negative effects of RV apical pacing are attributed to the abnormal electromechanical activation (e.g. dyssynchrony) of the heart and reduced myocardial work[79, 90-92]. On the other hand not all patients with RV apical pacing experience deleterious effects of RV pacing. Patients with ischemic heart disease, pre-existing conduction disorders and depressed LV ejection fraction might be at higher risk for developing heart failure after RV apex pacing[93-95], but the precise mechanism by which some patients experience heart failure and others not, remains unclear.

In earlier studies it has been shown that RV septal pacing results in long transseptal activation times causing the left ventricle to contract with a significant delay (LV dyssynchrony)[96]. Conversely, pacing at LV septum better preserves LV function compared to RV septal pacing[96]. The loss of the septal contribution to the overall ventricular activation pattern may be an important determinant of heart failure development in patients with chronic RV pacing[91]. Additionally, abnormal septal motions (resembling septal flash) could be induced by pacing at the right side of the septum and not by pacing at the left side of the septum[61]. This triggers some hypothetical thoughts on why some patients develop heart failure after RV pacing and others not. During normal ventricular conduction, the electrical activation of the heart starts at the left sided endocardium and the septum is activated from left to right[97]. We hypothesize that depending on how close the screw-in lead of the right ventricular pacing lead approximates the LV septal endocardial conduction system, the more physiologic the pace-induced mechanical

activation will be. When the screw-in lead does not approximate the left sided endocardial tissue, delayed activation of the septum may result and ventricular contraction becomes dyssynchronous and septal work decreases[91]. In fact, this hypothesis is supported by a new concept of left ventricular pacing through the interventricular septum[98]. Mafi-Rad et al. used a pacing lead with an extendable helix and placed it through the interventricular septum towards he LV septal endocardium. LV septal pacing with this custom-made lead resulted in preserved LV pump function (measured as dP/dt max) when compared to RV septal pacing. Although, the clinical benefit, safety issues and whether the hemodynamic benefit of LV septal pacing is preserved on the long term should be further validated, this concept clearly opens new perspectives as an alternative and hemodynamically preferable approach for standard RV (or even BV) pacing[98].

9. Key conclusions of this thesis:

1. **When measuring QRSD manually, a global approach** taking into account the first onset until the latest offset among all leads is preferred as this method provide better accuracy compared to single lead measurements.
2. **Nominal values of QRSD are dependent on the measurement method**, which may hamper the selection of CRT-candidates based on QRSD as sole parameter.
3. **Female LBBB patients present true LBBB at smaller QRSD** compared to men, which may disadvantage females in the selection of CRT as current guidelines favor wide QRSD to implant CRT.
4. **Paced QRSD**, should preferentially be assessed by manually measured **global QRSD,** as computer-calculated QRSD are inaccurate to assess paced QRSD.
5. **Shortening in QRSD,** occurring with biventricular pacing, **can predict CRT response**, although the clinical use may be limited due to small differences with regards to its inevitable measurement variability.
6. **Paced QRS area, predicts better acute hemodynamic CRT response** compared to QRSD shortening, and can be a useful tool during CRT implant and optimization
7. Mechanical dyssynchrony, assessed by **septal flash is present in half of LBBB patients.**
8. **Patients with septal flash, fulfil more LBBB criteria** (including mid-QRS notching) compared to patients without septal flash.
9. **QRS area correlates better with mechanical dyssynchrony** compared to QRSD, however overall accuracy to identify those LBBB patients with SF remains low.
10. **Female LBBB patients show more mechanical dyssynchrony and at smaller QRSD** compared to men, which may explains better CRT response rates of females.

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Part VI

Summary

Summary

QRS duration (QRSD) and QRS morphology, are two major selection criteria to select patients for cardiac resynchronization therapy (CRT). Despite this major role for QRSD in selecting CRT patients, guidelines do not specify a preferred technique to measure QRSD. QRSD, measured in single leads of the standard twelve lead electrocardiogram have shown significant inter- and intra-observer variability. For that reason we introduced a global QRSD measurement, taking into account all leads simultaneously. This global QRSD measures QRSD on the standard twelve lead electrocardiogram (ECG) from the earliest onset to the latest offset among all leads. This way of measuring QRSD has been recommended in guidelines on general ECG interpretation, but has not been applied within the field of CRT. Our research showed that global QRSD measurements perform better in terms of inter- and intra-observer variability compared to single lead measurements when assessing biventricular (BV) paced and LBBB QRSD. Additionally, QRSD can be measured by automated computer-calculated QRSD assessments. We showed that these computer-calculated QRSD reveal significant inter-manufacturer variability between different commercial systems. These findings emphasize the need for standardization of QRSD measurements within the field of CRT.

In paced ECGs manual global QRSD assessments outperform computer-calculated and single lead QRSD measurements in terms of accuracy. Single lead and computer-calculated QRSD assessments are not accurate enough to detect the small changes in QRSD occurring between baseline QRSD and BV pacing. When measuring QRSD shortening by a global QRSD assessment, shortening in QRSD has the best potential to predict CRT response in the individual patient.

The area of the QRS complex (QRS area) combines both the information of QRSD and QRS morphology in one single parameter. QRS area has been recently introduced as a promising parameter which allows better selection of CRT patients compared to QRSD alone. However,

a possible role for paced QRS area has not been established. We provided the first study showing that reduction in QRS area by BV pacing can predict acute CRT response better than changes in QRSD. Moreover, QRS area is less prone to inter- and intra-observer variability compared to QRSD. Pursuing the largest reduction in QRS area can be used to optimize atrioventricular intervals and help to identify favorable left ventricular lead locations during CRT implantation. As such, paced QRS area may be an easy, non-invasive tool to guide CRT implantation and optimization.

Mechanical dyssynchrony, assessed by presence of septal flash (SF) on echocardiography, is present in half of the patients with left bundle branch block (LBBB) and is not present in non-LBBB patients. Patients with SF fulfil more LBBB criteria compared to patients without SF. However, no ECG- or vectorcardiography-derived parameter can accurately predict the presence of SF among LBBB patients. Given the high rate of CRT response in LBBB patients with SF, this echocardiographic parameter might be considered as a selection parameter in CRT.

Finally, we analyzed gender differences in electromechanical characterization of LBBB patients. Female patients tend to have true LBBB (as defined by QRSD notching) at shorter QRSD compared to males. As patients are selected for CRT based on wide QRSD, women are less likely to be selected for CRT. This might be one of the reasons why women are underrepresented in CRT trials and registries. On the other hand, females LBBB patients show more SF and at smaller QRSD compared to males. This might explain why women tend to have better CRT response and at shorter QRSD compared to males.

Part VII

Samenvatting

Samenvatting

De duur (QRS-duur) en de morfologie van het QRS-complex worden momenteel gebruikt als de belangrijkste selectiecriteria in de indicatiestelling voor cardiale resynchronisatie therapie (CRT). Ondanks het feit dat QRS-duur één van de belangrijkste parameters is bij de selectie van CRT patiënten, specifiëren de internationale richtlijnen niet hoe de QRS-duur te meten. Wanneer men de QRS-duur meet in individuele afleidingen van het twaalf afleidingen elektrocardiogram (ECG) leidt dit tot belangrijke inter- en intra-waarnemer variabiliteit. Hiertoe introduceerden we bij CRT-kandidaten het concept van globale QRS-duur, dewelke rekening houdt met alle afleidingen. Deze globale QRS-duur meet in het twaalf afleidingen ECG de QRS-duur van het vroegste begin tot het laatste einde over alle afleidingen heen. Deze meting van globale QRS-duur wordt door richtlijnen aangaande algemene ECG-interpretatie aanbevolen, maar werd tot op heden nog niet toegepast in de selectie van CRT-patiënten. We konden aantonen dat deze globale QRS-duur beter scoort in termen van inter- en intra-waarnemer variabiliteit vergeleken met metingen van QRS-duur in individuele afleidingen. De QRS-duur kan ook automatische berekend worden op basis van computeralgoritmen in ECG-toestellen. Deze metingen vertonen echter ook belangrijke variabiliteit tussen verschillende commerciële algoritmes. Onze studies beklemtonen het belang van standaardisatie bij het meten van de QRS-duur in de selectie van CRT-patiënten.

In gepacete QRS-complexen zijn automatische bepalingen van de QRS-duur niet accuraat. Manuele metingen in individuele afleidingen zijn evenmin accuraat. Het verkorten van de QRS-duur als gevolg van biventriculaire (BV) pacing wordt preferentieel dan ook gemeten met behulp van een globale QRS-duur bepaling. Metingen van QRS-duur in individuele afleidingen en computer berekende waarden zijn immers niet accuraat genoeg om de soms subtiele verkortingen in QRS-duur op te meten. Het optreden van verkorting in QRS-duur, gemeten met een globale methode, voorspelt bovendien het best CRT-respons.

De oppervlakte van het QRS-complex (QRS-oppervlakte) combineert de QRS-duur en de QRS-morfologie in één enkel parameter. Deze QRS-oppervlakte werd recent voorgesteld als een parameter die beter CRT-responders kan identificeren dan QRS-duur alleen. De waarde van het QRS-oppervlakte tijdens BV-pacing was echter nog niet onderzocht. Wij toonden als eerste aan, dat het verkleinen van de QRS-oppervlakte als gevolg van BV-pacing acute CRT-respons beter voorspelt dan verkortingen in QRS-duur. Bovendien is deze QRS-oppervlakte ook minder onderhevig aan variabiliteit in metingen. Het streven naar de grootste reductie in QRS-oppervlakte kan ook gebruikt worden om het optimale atrioventriculair-interval alsook de meest gunstige locaties van een linker ventriculaire pacing elektrode te bepalen. Op deze wijze kan QRS-oppervlakte als een eenvoudige, niet-invasieve methode helpen bij CRT-implantatie en -optimalisatie.

Mechanische dyssynchronie, gemeten als septale flash (SF) op echocardiografie, is aanwezig bij ongeveer de helft van patiënten met linker bundeltakblok (LBTB) en quasi niet aanwezig bij patiënten zonder LBTB-morfologie. Patiënten met SF voldoen aan meer LBTB-criteria in vergelijking met patiënten zonder SF. Echter, geen enkele ECG- of vectorcardiografie-parameter kan accuraat LBBB patiënten met SF onderscheiden van deze zonder SF. Gezien patiënten met SF meer kans op CRT-respons hebben, dient deze echocardiografische parameter overwogen te worden als selectie criterium bij het plannen van CRT.

Als laatste analyseerden we de verschillen in elektromechanische kenmerken van LBTB tussen mannen en vrouwen. Vrouwen vertonen een LBTB-morfologie bij een smallere QRS-duur in vergelijking met mannen. Vermits patiënten in de eerste plaats geselecteerd worden op basis van een breed QRS-complex, kan deze smaller QRS-duur bij vrouwelijke LBTB-patiënten een oorzaak zijn waarom vrouwen ondervertegenwoordigd zijn in CRT-studies en -registers. Vrouwelijke LBTB-patiënten vertonen bovendien meer SF en dit bij een smallere QRS-duur in

vergelijking met mannen. Dit is één van de redenen waarom vrouwen een betere CRT respons vertonen en meer voordeel hebben van CRT bij een kortere QRS-duur.

Part VIII

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Coeman M en **De Pooter J.** Minimalisatie van rechter ventrikel pacing in elke pacemaker patiënt? Tijdschrift voor Cardiologie, accepted november 2017

Abstracts- Posters

- 2014: Cardiostim 2014, Nice. Global QRS duration as marker for CRT response
- 2016: Cardiostim 2016, Nice. Arrhythmic events in the HoRRACLE's trial are predicted by slow VT
- 2016: BSC 2016, Brussels, Belgium. Electrocardiographic characteristics of the paced QRS complex according to different positions of the left ventricular lead in CRT patients
- 2017: HRS 2017, Chicago, Illinois, US. Automated verification of pulmonary vein isolation in radiofrequency and cryoballoon guided ablation
- 2017: HRS 2017, Chicago, Illinois, US. Electrogram based mapping of repetitive atrial activation patterns during ongoing persistent atrial fibrillation
- 2017: EHRA 2017, Vienna. Accuracy of computer-calculated QRS duration assessments: clinical implications to select candidates for cardiac resynchronization therapy
- 2017: EHRA 2017, Vienna. Comparison of local activation time annotation algorithms in high density mapping of regular atrial tachycardias

Oral Presentations (international only)

- 09/06/2016 Cardiostim 2016, Nice France. Vectorcardiographic parameters of the biventricular paced QRS complex to predict acute CRT response
- 12/05/2017 HRS 2017 Chicago, Illinois, US. Clinical assessment and comparison of local activation time annotation algorithms in high density mapping of atrial tachycardias
- 06/10/2017 BHRM 2017 Brussels, Belgium. Gender differences in electromechanical characteristics of left bundle branch block.
- 07/12/2017: Euro Echo-Imaging 2017, Lisbon, Portugal. Gender differences in electromechanical characteristics of left bundle branch block potential implications in the selection for CRT.

Reviewer for journals

- Europace
- Acta Clinica Belgica
- European Heart Journal: Acute Cardiovascular Care