Simplicity is key in CRT

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Simplicity is key in CRT

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Simplicity is key in CRT

Patient selection and management in cardiac resynchronization therapy

PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof.dr. Rianne M. Letschert
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op **vrijdag 21 juni 2019 om 14.00 uur**

door

Antonius Martinus Wilhelmus van Stipdonk

Geboren op 17 augustus 1983
te Nuenen

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Contents

General introduction and thesis outline.

11

Part 1. Patient selection

Why QRS duration should be replaced by better measures of electrical activation to improve patient selection for cardiac resynchronization therapy

J. of Cardiovasc. Trans. Res. 2016 Aug;9(4):257-65

23

Large variability in clinical judgement and definitions of left bundle branch block to identify candidates for cardiac resynchronization therapy.

Int J Cardiol. 2019 Jan 15. pii: S0167-5273(18)32345-3. (Epub ahead of print)

41

The definition of left bundle branch block influences the response to cardiac resynchronization therapy.

Int J Cardiol. 2018 Oct 15. 269:165-169

55

Evaluating ECG-based identification of CRT responders beyond current LBBB definitions.

Revisions

71

Identifying delayed left ventricular lateral wall activation in patients with non-specific intraventricular conduction delay using coronary venous electro-anatomical mapping

Netherlands Heart Journal. 2016;24(1):58-65.

Editorial comment: To implant or not to implant? That is the unsolved question concerning heart failure patients with non-LBBB

89

QRS area is a strong determinant of outcome in cardiac resynchronization therapy.
Circ Arrhythm Electrophysiol. 2018 Dec; 11(12):e006497. (Epub ahead of print)

105

Part 2. Patient Management

Consensus of a Standardized Cardiac Resynchronization Therapy Care Pathway.

127

Development and Implementation of a Structured Cardiac Resynchronization Therapy Care Pathway.

147

General Discussion

163

Summary

Valorization

Samenvatting

Dankwoord

List of publications

Curriculum Vitae

175

General introduction

The background of the slide is a light gray color. It is decorated with several thin, diagonal lines that cross the frame from the top-left towards the bottom-right. There are two black lines and two red lines, creating a geometric pattern.

Heart Failure

Heart Failure (HF) is a clinical syndrome of signs and symptoms resulting from structural and/or functional cardiac abnormality, leading to reduced output and/or elevated intracardiac filling pressures [1]. HF is a common disease occurring in 1-2% of the adult population, mainly affecting older people. Despite significant advances in HF therapies over the last decades, prognosis of HF remains poor with high annual rates of mortality (7-17%) (due to progressive HF and sudden cardiac death), and hospitalisation (32-44%), and overall poor quality of life [2]. Moreover, HF patients usually have one or more serious comorbidities affecting general well-being and prognosis apart from HF [3]. Therefore HF entails high health care costs, averaging 1.1% of the total health care budget in the Netherlands [4].

Treatment

Current HF treatment has significantly improved prognosis, especially in patients with a reduced left ventricular ejection fraction (LVEF) [5]. The mainstay of HF treatment consists of lifestyle changes and pharmacotherapy to reduce cardiac stress (reducing neurohormonal activation) and filling pressures, and to induce reverse remodelling of structural changes. Implantable cardioverter defibrillators (ICD) are used to prevent sudden cardiac death in patients at increased risk of life threatening arrhythmias. Biventricular pacemakers are used in cardiac resynchronization therapy (CRT) in patients with electrical conduction delay. In case of progressive HF despite optimal medical treatment, interventions like left ventricular assist devices (LVAD) and cardiac transplantation can be considered [1]. Above all, treatment should aim at taking away the cause of the underlying structural and/or functional disease and factors aggravating the disease.

Causes of Heart Failure

Different aetiologies in HF encompass differences in prognosis, particularly because some can be treated and others cannot. Causes of HF are numerous; with ischemic, valvular and hypertensive heart disease as classic aetiologies, while inflammatory, infiltrative, toxic, genetic, tachycardia, irregularity, dyssynchrony and adrenergic stress are increasingly recognized as causes of HF [1]. Moreover, many times these causes interact within one patient, and surface at different moments in the course of the disease. In order to effectively treat HF, the cause and aggravating factors have to be recognized and treated.

Cardiac Resynchronization Therapy

CRT aims to correct a dyssynchronous ventricular electrical activation, and hence dyscoordinate ventricular contraction. The dyssynchronous electrical activation amenable to CRT classically entails an early activation and contraction of the septum and delayed activation and contraction of the left ventricular lateral wall. This dyscoordinate contraction leads to a reduction in stroke volume and LVEF, which over time is associated with LV dilatation and increased filling pressures [6, 7].

CRT aims at reducing the dyssynchrony of the left ventricle by biventricular pacing [8]. The biventricular pacemaker typically uses leads in the right atrium, right ventricular (RV) apex and left ventricular (LV) postero-lateral epicardium. Atrial sensing triggers a sequence of pre-set delays and activations resulting in electrical stimulation at the LV and RV pacing electrodes, leading to a synchronous activation and coordinate contraction of the myocardium.

The very first observation of the benefit of biventricular pacing comes from the early '70s, when Gibson et al compared the behaviour of implanted aortic valve prostheses during RV, LV and biventricular pacing [12]. Since the 1990's CRT has been shown to improve cardiac pump function in terms of LV systolic pressure build up and stroke volume [9]. On the long-term, reverse remodelling (reduction of the increased LV dimensions) has been observed as well as an increase in LVEF, which continues to increase even years after implantation of the device [10]. In terms of patient benefit, CRT leads to pronounced increase in quality of life, and reduction of HF hospitalizations and mortality [11].

Patient selection in CRT

The very first studies on CRT already used a wide QRS complex on the 12-lead electrocardiogram (ECG) as selection criterion [13]. Soon after the establishment of CRT as an HF therapy, studies showed increased QRS duration to be associated with outcome in CRT [15]. Subsequent studies showed the association of ECG markers of specific types of ventricular conduction delay (QRS morphology) with outcome of CRT. Especially differentiation between left bundle branch block (LBBB), right bundle branch block (RBBB), and non-specific intraventricular conduction delay (IVCD) seems relevant. While LBBB is consistently associated with the presence of delayed LV lateral wall activation, this is much less the case for RBBB and IVCD [16]. In substudies of the landmark CRT trials, an LBBB morphology was shown to be associated with significantly more benefit from CRT than other QRS morphologies [17-20]. Based on the aforementioned findings, QRS duration and QRS morphology are currently guideline recommended markers of the presence of dyssynchrony [1, 21].

The role of LBBB as an ECG marker has changed considerably over time. Initially, it was described as an (innocent) electrocardiographical phenomenon. Later LBBB was described as a marker of worse prognosis in heart failure. Only recently, since the demonstration of structural remodelling in canine LBBB models [22] and its reversal by CRT [23], LBBB is regarded as a possible cause of the development of heart failure. Strikingly and most important for research presented later in this thesis, there are multiple definitions of LBBB, each using their own criteria derived from the ECG. Most of these definitions of LBBB consist of elaborate and complex morphological features, which are highly sensitive to subjective interpretation.

In order to improve patient selection for CRT, many other parameters that can be deduced from the 12-lead ECG like QRS axis, QRS fragmentation and left ventricular activation time (LVAT), have been evaluated [24-26]. More recently, the development of ECG-imaging has made it possible to more precisely determine the ventricular activation pattern [27]. In addition, assessment of mechanical dyssynchrony using imaging techniques like echocardiography [28] and cardiac magnetic resonance imaging (CMR) [29] have been employed. However, none of the abovementioned parameters have made it to clinical practice, primarily because these analysis and techniques are more complicated and therefore less robust in clinical practice.

Patient Management in CRT

CRT starts after implantation of the biventricular pacing device. However, in many patients this does not mean that this therapy leads to optimal benefit. Not only does the device need individualization, as every patient's heart shows different electrical, structural and mechanical properties, but also treatment of the underlying cause of HF, general HF treatment and consideration of relevant comorbidities is needed to achieve optimal clinical benefit.

As CRT has proven to be of great benefit in many patients, research has focussed on finding factors reducing the odds of response to therapy. Over time, many aspects of both device and HF management have been identified as important conditions that need to be met in order to ensure that the patient optimally benefits from therapy [30]. Achieving effective resynchronization needs reassurance of the presence of significant intrinsic dyssynchrony (patient selection); optimization of timing (AV and VV delays) and location of the pacing-electrode on the LV lateral wall outside of scar, and optimization of the 'dosage' of resynchronization (over 98% biventricular pacing). Moreover, in order to be able to establish beneficial effect, the heart needs a reduction of elevated filling pressures, optimization of general HF treatment (which often allows for rigorous up-titration of HF drugs after implementation of CRT), treatment of underlying cause(s) and triggers of HF, and diagnosis and treatment of relevant comorbidities like supraventricular and ventricular tachyarrhythmias, hypertension, kidney dysfunction, anaemia and iron-deficiency, thyroid dysfunction, and obstructive sleep-apnoea. Finally, in order to maintain long term beneficial effects, patients need education and support of lifestyle changes and individualized rehabilitation [30-32].

In general HF management, it is well established that multidisciplinary care management leads to a reduction in HF hospitalizations and mortality [33]. However, as CRT is an electrical therapy, it is often left to the electrophysiologists to manage it. Therefore, in current practice CRT patients often get separate appointments with several specialized cardiologists, device technicians and specialized HF nurses. On top of the additional investigations, this creates a large burden for these mostly fragile patients, their family as well as for the health care system. Moreover, as elucidated above, the complex natures of both HF disease management and CRT management necessitate elaborate and structured evaluation of this patient group. Although CRT has been shown to be the most effective therapy for HF patients in the last decades, a single missing link in the chain of disease management may be the difference between 'response' and 'non-response'. Therefore, patient management in CRT profits from a multidisciplinary approach [34], moreover efficient organization of care for these patients could lead to great improvements in patient and health care burden, as well as improved clinical outcome.

Aim of this thesis

The overarching theme of this thesis is to maximize the benefit of CRT for HF patients. The specific topics this thesis will target are;

- (1) **Improving patient selection;** evaluating current ECG selection criteria and investigate possibly better ones.
- (2) **Improving patient management;** introducing a comprehensive re-organization of patient management in CRT; making patient management governable, effective and efficient.

Outline of this thesis

Part I focuses on patient selection for CRT. **Chapter 2** provides a critical appraisal of current ECG selection methods and a proposal of potentially better markers known in literature. Continuing on this critical evaluation, **chapter 3** investigates the correlation between the various definitions of LBBB and clinical judgement of LBBB, as well as the inter- and intra-observer variability of applied methods. In **chapter 4** and **5** we set out to compare the different LBBB definitions in CRT patients with respect to their association with reverse remodelling and clinical endpoints. Moreover, we dissect the definitions' morphological criteria to evaluate their specific value with respect to outcomes in CRT.

Subsequently, we investigated to what extent patients that do not exhibit LBBB characteristics (non-LBBB) on their 12-lead ECG still may harbour the substrate amenable to CRT (**chapter 6**). To this purpose electro-anatomical mapping was used in CRT candidates. In **chapter 7** we compared the predictive value of vectorcardiographic QRS area to that of established parameters QRS duration, LBBB morphology and their combination in a large cohort of CRT patients.

Part II tackles the important issue of effective patient management in CRT. In **chapter 8** we elaborate on a comprehensive CRT care pathway, designed by CRT experts from 4 large implanting centres in Europe. Proposing a benchmark for clinics, naive to a patient care pathway to evaluate their current practice. The next step in optimizing local organization of CRT care is described in **chapter 9**. Here we show the strategy used to implement the proposed CRT care pathway into our own practice in the Maastricht University Medical Centre. With the help of expert consultants the local care process was assessed, compared and effectively reorganized in order to optimize CRT care.

This thesis ends with a general discussion (**chapter 10**) with special emphasis on the clinical implications of the results described in this thesis and future directions of research.

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Part 1. Patient selection

**Why QRS duration should be
replaced by better measures of
electrical activation to improve
patient selection for cardiac
resynchronization therapy**

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ABSTRACT

Cardiac resynchronization therapy (CRT) is a well-known treatment modality for patients with a reduced left ventricular ejection fraction accompanied by a ventricular conduction delay. However, a large proportion of patients does not benefit from this therapy. Better patient selection may importantly reduce the number of non-responders. Here we review the strengths and weaknesses of the electrocardiographic (ECG) markers currently being used in guidelines for patient selection, e.g. QRS duration and morphology. We shed light on the current knowledge on the underlying electrical substrate and the mechanism of action of CRT. Finally, we discuss potentially better ECG-based biomarkers for CRT candidate selection, of which the vectorcardiogram may have high potential.

Introduction

Cardiac resynchronization therapy (CRT) is an effective therapy for patients with a decreased left ventricular ejection fraction (LVEF) in combination with a ventricular conduction delay, especially due to left bundle-branch block (LBBB). CRT creates a more coordinated and efficient contraction of the heart, improves LV systolic function and quality of life, and reduces heart failure (HF) symptoms, hospitalizations, and mortality [1, 2].

Nevertheless, there is still an incomplete understanding of the mechanism of the therapy and unsatisfying selection of patients. On the one hand, a significant portion (30–50%) of patients that are implanted according to current guidelines [3, 4] benefit little from this therapy, whereas ~20% of patients show complete normalization of LVEF [5]. Possible explanations for this huge range of benefit are variation in substrate that is amenable to resynchronization, inadequate device settings, suboptimal medical treatment, arrhythmias, and variable lead position [6].

The most important selection criteria in current CRT implantation guidelines are derived from the electrocardiogram (ECG): QRS duration and morphology [3, 7]. Here, we review the strengths and weaknesses of these ECG markers in the light of the current knowledge on the underlying electrical substrate and the mechanism of action of CRT and discuss potentially better ECG-based biomarkers for selection of CRT candidates.

The Role of the 12-Lead ECG in the Selection of CRT Candidates.

The clinical application of CRT began in 1994 when the first cases of atrio-biventricular pacemaker implantations in patients with severe congestive HF were described [8, 9]. The surface ECG of these patients often showed a prolonged PR interval and a widened QRS complex due to ventricular conduction disturbances.

The first randomized crossover trial investigating the clinical efficacy of CRT was the MULTIsite STimulation In Cardiomyopathy (MUSTIC) study [10]. This trial in patients with chronic severe HF (New York Heart Association (NYHA) III), reduced LVEF (<35%) and a broad QRS complex (>150ms), showed that biventricular (BiV) pacing improved the 6-min walking distance, peak oxygen uptake, quality of life score, and NYHA class. The Multi-centre Insync RANdomized CLinical Evaluation (MIRACLE) study confirmed these results in patients with a QRS duration ≥ 130 ms [2, 11]. This study also showed a clear reduction in LV volumes, reduced HF hospitalization, and better survival. Similar results were shown by the Comparison of Medical therapy, Pacing and Defibrillation in Chronic Heart Failure (COMPANION) [12] and the CARDiac RESynchronization (CARE)-HF [1] trials, which included patients with QRS duration ≥ 120 ms and NYHA class III–IV.

These favourable and consistent results led to the recommendation of CRT in patients in NYHA class III–IV despite optimal medical treatment, with a reduced LVEF (<35%), in sinus rhythm, and a wide QRS complex (≥ 120 ms) [13]. Subsequent trials investigated the effect of CRT in less symptomatic patients (the Resynchronization Reverses Remodelling in Systolic Left Ventricular Dysfunction (REVERSE) [14], Multicentre Automatic Defibrillator Implantation Trial (MADIT)-CRT [15], and Resynchronization/defibrillation for Ambulatory heart Failure Trial (RAFT) trials [16]. Again, LV function improved, and both all-cause mortality and non-fatal HF events improved. However, subgroup analyses of these three trials demonstrated that these effects were predominantly confined to patients with a QRS duration ≥ 150 ms (Fig. 1) [17]. This evidence resulted in the addition of a class I indication for CRT in patients presenting with NYHA class II, a reduced LVEF, and a QRS duration >150ms, in the 2010 guidelines [18].

Figure 1.

Effect of CRT on composite clinical events in patients with moderately prolonged (QRS duration of 120-150ms) and severely prolonged QRS duration (>150ms) (reprinted from Bryant et al. [17]).

Even though most studies show an increased response rate after CRT in patients with a severely prolonged QRS duration, these studies used the fairly crude division of the cohorts in patients with a QRS duration < and >150ms. However, the best cut-off value for QRS duration is unclear.

More recently, attention has shifted from QRS duration to QRS morphology. Small single-centre studies [19, 20] and sub-analyses of the MADIT-CRT [21], REVERSE [22], and RAFT [16] study showed that patients with a LBBB morphology benefit most from CRT. In contrast, patients with right bundle-branch block (RBBB) or intra-ventricular conduction delays (IVCD) had no benefit or even a worse outcome from CRT (figure 2). These observations led to the adaptation of the guidelines in 2012/2013, including LBBB as the primary ECG criterion and QRS duration >150ms only if a non-LBBB morphology is present [3, 4].

Figure 2.

Cumulative probability of HF event or death (top) and of death alone (bottom) according to QRS morphology in the CRT with defibrillator (CRT-D) arm of the MADIT-CRT (adjusted from Zareba et al. [21])

Interesting and important, however, is that the definition of complete LBBB from the 12-lead ECG varies between European and American guidelines and between large clinical trials [21, 22] or studies [23] that investigated LBBB as a predictor of CRT effectiveness. The refinement of LBBB morphology with the presence of notching or slurring appears to significantly improve the prediction of CRT response and clinical outcome, at least in small single-centre studies [20, 24].

While QRS morphology is now one of the primary indicators for CRT, a recent meta-analysis, combining data from CARE-HF, MIRACLE, MIRACLE ICD, REVERSE, and RAFT showed that QRS duration is a more powerful predictor of CRT outcomes (mortality and morbidity) than QRS morphology [25]. This conclusion is in contrast to several reports derived from some of the individual trials and to a meta-analysis of the MADIT-CRT, RAFT, and REVERSE study (figure 1) [26]. One possible explanation for this discrepancy is the use of liberal LBBB criteria. In that case, it is likely that QRS duration provides additional information. Indeed, when using liberal LBBB criteria the non-LBBB patients tended to have a lower QRS duration than the LBBB patients [21], but this difference could not be observed when stricter LBBB criteria were used [20]. Furthermore, in the studies where strict LBBB criteria as defined by Strauss et al. [23] were used, QRS duration was not a predictor of response while LBBB was [20, 27].

In conclusion, currently it is not clear whether QRS duration or morphology should be preferred as primary marker for selection of CRT patients. QRS duration may not be specific, but LBBB criteria may be too complex and/or dependent. In order to come to a possible solution, it may be worthwhile to go back to the basic physiology of dyssynchronous HF and the mechanisms of CRT.

Electrophysiological Evaluation of the Electrical Substrate for CRT.

Delayed electrical activation of the LV is considered the underlying substrate of LV dysfunction in patients with systolic dysfunction and a conduction delay, mainly due to LBBB [28]. CRT aims to correct the underlying electrical substrate by paced pre-excitation of late depolarized and contracting LV regions, thereby restoring synchronous ventricular electrical activation and contraction [28]. Experimental studies have confirmed that in hearts with delayed LV activation due to LBBB, LV-only or BiV pacing creates a more synchronous contraction pattern, which is accompanied by marked hemodynamic improvement [28, 29]. The clinical importance of LV activation delay has become evident in studies showing that a greater delay in time from onset of the QRS complex to the local intrinsic activation at the LV stimulation site (Q-LV) is associated with a greater likelihood of benefit from CRT. Singh et al. measured Q-LV intra-procedurally as a percentage of the baseline QRS interval in 71 patients undergoing CRT device implantation [30]. A longer Q-LV was related to superior acute LV hemodynamic improvement, whereas a reduced Q-LV (<50% of QRS duration) was related to a worse clinical outcome [30]. A secondary analysis of the prospective multicentre SmartDelay determined AV optimization (SMART-AV) trial showed that patients with a Q-LV >95ms show significantly improved odds of reverse remodelling and quality of life response [31]. Conversely, experimental studies and computer simulations have shown that pacing induced pre-excitation in a heart without a significant electrical delay (narrow QRS complex) widens the QRS complex and consequently worsens LV pump function [32–34]. The clinical significance of these findings has become evident in the results of the recent Cardiac Resynchronization Therapy in Heart Failure with a Narrow QRS Complex.

(EchoCRT) trial [35]. This was a randomized trial that evaluated the effect of CRT in patients with a narrow QRS complex (<130ms) and evidence of mechanical dyssynchrony at echocardiographic examination. The trial was prematurely stopped because the CRT group did not derive any detectable clinical benefit and even showed a significant increase in mortality compared to the control group [35].

All the aforementioned data support the notion that an electrical substrate, consisting of a sufficient amount of LV activation delay, needs to be present for CRT to be efficient. LBBB is considered the hallmark conduction disturbance that is associated with delayed LV activation. In canine hearts where proximal ablation of the left bundle-branch was performed, electrical mapping showed that earliest electrical activation occurs inside the right ventricle and that the electrical wave front then slowly propagates through the interventricular septum towards the lateral wall of the LV [36]. Induction of LBBB in healthy canine hearts leads to electrical and mechanical dyssynchrony that in turn causes loss of LV pump function and ventricular remodelling [37]. In these hearts, CRT largely reverses functional and structural abnormalities [28]. The key clinical investigation to detect and evaluate the extent of LV activation delay remains the surface ECG. However, identifying true LBBB on the ECG is not as straightforward as one might presume. As discussed earlier, numerous dissimilarities in ECG criteria for the diagnosis of LBBB between different definitions complicate a uniform diagnosis.

The most accurate way to evaluate the cardiac electrical activation sequence in patients is by invasive mapping using conventional point-by-point technique or three-dimensional electro-anatomical reconstruction contact (CARTO, NOGA) or non-contact (EnSite) mapping. Studies that performed endocardial mapping in patients with HF and LBBB according to conventional ECG criteria have shown that the sequence of LV endocardial activation in these patients is heterogeneous [38–41]. The activation wave front originating from the right ventricle was shown

to cause LV endocardial breakthrough in different septal regions [39, 40]. In some patients, breakthrough occurred in the vicinity of the conduction system in the mid-septal region, which suggests activation by slow conduction through the left bundle-branch, in others, LV endocardial activation occurred as a result of right-to-left transseptal spread of activation [40]. A characteristic finding in true LBBB patients also seems to be a long (>40 ms) trans-septal conduction time [42].

Endocardial non-contact mapping has also identified two different patterns of electrical wave front propagation in the LV of these patients. The first entity, observed in approximately two thirds of patients, is characterized by a U-shaped pattern of activation that turns around the LV apex and inferior wall in order to activate the lateral wall [39, 41, 43], which is similar to the activation pattern that has been observed during endocardial non-contact mapping in canine hearts where proximal ablation of the left bundle-branch has been performed [44]. The second entity is characterized by homogeneous propagation of electrical activation throughout the left ventricle [41, 43]. The varying conduction patterns observed in these mapping studies could be explained by variations in left bundle-branch anatomy [45] and the location of the block, but also by the fact that cellular uncoupling as a consequence of LV hypertrophy or fibrosis can give rise to a wide QRS complex with morphological features that meet conventional ECG criteria for LBBB [46, 47].

In contrast to LBBB, RBBB is typically associated with delayed RV activation, but not delayed LV activation. However, in some RBBB patients, the QRS morphology differs significantly from the characteristic RBBB pattern. These patients show a specific electrocardiographic pattern previously defined as RBBB masking LBBB [48, 49], which is characterized by precordial lead findings consistent with RBBB and limb lead findings consistent with LBBB. Extensive measurements of both RV and LV endocardial electrical activation in heart failure patients with RBBB using CARTO 3D contact mapping showed that patients with RBBB masking LBBB have LV activation delay similar to that found in LBBB [50].

Although the aforementioned mapping techniques provide accurate characterization of cardiac electrical activation, the application of these techniques in clinical practice is time-consuming, cumbersome, and not without risk. Measuring the Q-LV as described above provides a relatively simple manner of assessing the extent of LV activation delay. However, this technique provides limited information on LV electrical activation because usually measurements are only performed at the anatomically targeted region. A technique that provides a middle ground between complete mapping and single Q-LV measurement is intra-procedural coronary venous electroanatomic mapping. In a recent study, we assessed the LV electrical activation in a cohort of 51 CRT candidates using this technique [51]. A guidewire that allows for unipolar sensing and pacing was inserted into the coronary sinus and connected to an EnSite NavX system. The wire was then manipulated to various coronary sinus branches creating an anatomic map along with determining the electrical activation time associated with each anatomic region. Significant LV activation delay ($>75\%$ of QRS duration) was found in 38 of 51 patients. QRS duration was shown to perform poorly in identifying delayed LV activation (area under the curve = 0.49). Twenty-nine of the 51 patients had LBBB according to specific ECG criteria which included broad, notched, or slurred R waves in leads I, aVL, V5, and V6, an occasional RS pattern in leads V5 and V6 attributed to displaced transition of the QRS complex, and absent q waves in lead I, V5, and V6 (in the absence of a large anterior-apical infarction). As described earlier, this refined LBBB definition, which includes the presence of QRS notching and slurring, has previously been shown to significantly improve the predictive value of LBBB QRS morphology for CRT response [52].

Of the remaining 22 patients, 7 met ECG criteria for RBBB and 15 met neither criteria for LBBB nor RBBB and were classified as IVCD. QRS duration did not differ between different QRS morphologies. However, LV activation time was significantly larger in LBBB patients as compared to RBBB and IVCD patients. Significant LV activation delay was found in all patients diagnosed with LBBB according to specific ECG criteria, but also in 8 of 15 patients with IVCD and even in 1 of 7 patients with RBBB (examples shown in Fig. 3). The findings of this mapping study indicate that (1) a prolonged QRS duration by itself is not a reliable marker of delayed LV activation. Thus, patient selection based on QRS duration alone will most likely include a substantial number of patients without the appropriate electrical substrate to benefit from CRT, and (2) the refined LBBB definition, which includes QRS notching and slurring, is highly specific for delayed LV activation, but lacks sufficient sensitivity. As a consequence, a substantial number of patients that have delayed LV activation are not identified as such, and in these patients, CRT may be withheld erroneously.

Figure 3.

Coronary venous electro-anatomic map of a LBBB patient demonstrating delayed activation of the LV anterolateral wall (A), an IVCD patient demonstrating delayed activation of the LV inferolateral wall (B), and a RBBB patient with a potential left anterior hemiblock demonstrating delayed activation of the LV anterolateral wall (C). AIV=anterior inter-ventricular vein, ALV=anterolateral vein, ILV=inferolateral vein, CS=coronary sinus, AT=electrical activation time, AP=antero-posterior, L/RAO=left/right anterior oblique, RV=right ventricle (adapted from Mafi Rad et al. [51])

Instead, the above described technique of coronary venous electro-anatomic mapping can be used at the time of CRT implantation for a more precise characterization of the electrical substrate at only minor prolongation of procedure time (~20 min) [51, 53]. However, ideally the decision whether or not to implant a CRT device is made in advance. In this respect, electrocardiographic imaging (ECGi) provides an entirely non-invasive alternative [54]. ECGi provides high-resolution non-invasive electrical mapping of the epicardial electrical activation. The technique acquires electrical data from more than 200 body surface electrodes using a multi-electrode vest. Epicardial anatomy and body-surface electrode positions are registered simultaneously by a thoracic computed tomography scan. The

body-surface electrical data and the anatomical data are then processed with algorithms to construct epicardial depolarization and repolarization patterns, using a single heartbeat [54]. In this way, detailed information on LV electrical activation can be readily obtained prior to CRT implantation, which may be used to guide the decision on whether or not to implant a CRT device. However, the requirement for a multi-electrode vest in combination with a computed tomography scan may preclude widespread application of this technique in clinical practice.

Better Electrocardiographic Identification of the Electrical Substrate: New ECG Parameters.

The demand for easy and widely applicable non-invasive techniques that can be used to accurately characterize the electrical substrate in CRT candidates has renewed the interest in finding additional/alternative electrocardiographic markers of dyssynchrony. Sweeney et al. carefully analysed standard 12-lead ECGs of 202 CRT candidates with LBBB according to specific ECG criteria that included QRS notching/slurring and identified new measurements that predict volumetric CRT response [19]. The time difference between the first notch after 40ms of QRS onset and the end of the QRS on the baseline ECG was indicated as the LV activation time (LVATmax, Fig. 4). A longer LVATmax was shown to be predictive of CRT response (OR [CI]= 1.30 [1.11, 1.52] for each 10ms increase up to 125ms). In addition, the Selvester QRS score for LBBB was used to quantify LV scar extent. A higher Selvester score was negatively associated with reverse remodelling (OR [CI] = 0.49 [0.27, 0.88] for each 1-point increase from 0 to 4; 0.92 [0.83, 1.01] for each 1-point increase > 4) [19].

Figure 4.

Example of a left ventricular activation time (LVAT) measurement. LVATmax is measured as the time difference between the first notch after 40ms of QRS onset and the end of the QRS.

Recently, the value of the vectorcardiogram (VCG) for characterizing the electrical substrate and predicting CRT response has been explored. VCG is a technique that records the magnitude and direction of the electrical forces that are generated by the heart over time, resulting in a resultant electrical force depicted by a vector for each time point. Connecting the arrow heads of all vectors, a vector loop is constructed. The VCG thus contains 3D information of the electrical forces within the heart, which might provide more valuable information than the 1D-ECG. It was hypothesized that large electrical dyssynchrony, amenable to CRT, would lead to large unopposed electrical forces during ventricular depolarization and that the size of these forces may be well represented by the QRS area, the area of the QRS complex in the three principle directions. Van Deursen et al. assessed the area of the QRS complex (QRS area) on the VCG in 81 consecutive CRT candidates and showed that a large QRS area was associated with high odds of long-term volumetric CRT response. Moreover, QRS area predicted CRT response better than QRS duration and conventionally defined LBBB, and as least as good as the most refined LBBB definition [24]. The notion that QRS area represents the extent of unopposed electrical forces is supported by the observation that QRS area is larger in patients with LBBB as compared to patients with IVCD and that QRS area is lower in ischemic than in non-ischemic patients [24], the latter may be explained by the presence of non-conductive fibrotic tissue. Further support comes from observations in the abovementioned study on coronary venous mapping. In this study, VCGs were constructed from pre-procedural standard 12-lead ECGs for all patients using the Kors algorithm. A large QRS area ($>69 \mu\text{Vs}$) on the VCG was shown to be highly predictive of delayed LV lateral wall activation as determined by coronary venous mapping (Fig. 5) [51]. Taken together, these observations suggest that QRS area is not only useful to determine the extent of electrical dyssynchrony, but that it may also reflect the presence of determinants known to reduce the chance of CRT benefit, such as an ischemic aetiology of heart failure. However, more research is required to better understand all determinants of QRS area.

Figure 5.

QRS area plotted as a function of maximal LV lateral wall activation time (maxLVLW-AT) expressed as % of QRS duration (QRSd) for all patients (each dot represents a patient, $n=51$) with LBBB diagnosed according to the definition provided by the REVERSE trial (left) and the American Heart Association (AHA) definition (right). This figure demonstrates the excellent diagnostic performance of QRS area $> 69 \mu\text{Vs}$ for delayed LV lateral wall activation, defined as a max LVLW-AT exceeding 75% of QRS duration, and illustrates the difference in QRS morphology classification caused by disparity in LBBB definitions (adapted from Mafi Rad et al. [51])

Interestingly, two studies showed that VCG-derived measures of repolarization predict CRT response even better than QRS area. Engels et al. assessed the T-wave area from VCGs of 244 CRT recipients (VCG examples shown in Fig. 6c, d). The VCG-derived T-wave area was shown to predict echocardiographic CRT response better than QRS area [55].

Figure 6.

Typical example of VCGs constructed from standard 12-lead ECGs for a patient with a large (a and c) and a patient with a small (b and d) T-wave area, despite being both classified as having LBBB. Panels e and f show Kaplan-Meier estimates of the probability free of the composite endpoint (heart failure hospitalization, heart transplantation, LVAD implantation, death) after 3 years of CRT. Large QRS or T-wave area are values $\geq$ median value and small QRS or T area are values $<$ median value (adapted from Engels et al. and Vegh et al. [55,56])

In a larger cohort consisting of 335 CRT recipients in which the primary endpoint was the composite of heart failure hospitalization, cardiac transplantation, left ventricular assist device implantation, or death during a 3-year follow-up period, the predictive power of T-wave area for CRT response was found to be primarily evident in the group of patients with LBBB (Fig. 6e, f) [56]. A large T-wave area in LBBB patients was associated with less HF hospitalizations and a higher chance of survival [56]. The size of the T-wave area is a reflection of the extent of unopposed electrical forces during the repolarization phase. The T-wave area is partially determined by the size of the QRS area [55], but other factors such as changes in K^+ and Ca^{2+} ion channel expression might also play a role. In this study, a larger T-wave area was primarily caused by a larger amplitude and not so much by a longer JT-interval. Further research is needed to investigate which other factors are exactly reflected in the T-wave area.

A limitation of all these studies regarding the QRS area is that relatively small sample sizes were used. Furthermore, the studies related to the prediction of CRT response using the QRS area were all retrospective. Therefore, these results need to be validated in a larger prospective study. The great practical benefit of QRS area and T-wave area is that these parameters are measured in an objective manner and quantified as continuous variables, as opposed to LBBB which is a dichotomous measurement that is subject to the use of different definitions and subjective interpretations of QRS notching/slurring. Another practical feature of QRS area and T-wave area is that they can easily be derived from the standard 12-lead ECG. Most commercially available ECG machines have algorithms to construct VCGs from standard 12-lead ECGs using the inverse Dower or Kors' regression transformation [57, 58]. These VCGs provide a good resemblance of the gold standard Frank VCG and have recently also been validated for use in patients with dyssynchronous heart failure [59]. The non-invasive and simple nature of VCG analysis combined with the excellent predictive power of QRS area and T-wave area for CRT response indicates that these parameters can be easily applied in clinical practice to identify appropriate candidates for CRT, thereby potentially improving response to this therapy.

Conclusion

Based on the evidence obtained from electro-anatomic mapping that QRS area reflects LV activation delay, the primary electrical substrate for CRT, and on the better prediction of CRT response by QRS area as compared to QRS duration, we propose to include QRS area in the guidelines as a selection criterion for CRT implantation. The possibly even better prediction of CRT response by using the T-wave rather than the QRS complex requires further investigation.

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**Large variability in clinical judgement
and definitions of left bundle branch
block to identify candidates for
cardiac resynchronization therapy**

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ABSTRACT

Background Left bundle branch block (LBBB) morphology is associated with improved outcome of cardiac resynchronization therapy (CRT) and is an important criterion for patient selection in the current CRT guidelines. There are, however, multiple definitions for LBBB. Moreover, applying these definitions requires careful examination of the ECG and seems subjective. We investigated the intra- and inter-observer variability in the determination of LBBB and the agreement between the various definitions and their correspondence to clinical judgement of the presence of LBBB.

Methods Observers were provided with 12-lead ECGs of 100 randomly selected CRT patients. Four observers judged the ECGs based on different LBBB-definitions (ESC, AHA/ACC/HRS, MADIT, and Strauss). Additionally, four implanting cardiologists scored the same 100 ECGs for the presence of LBBB based on their clinical judgement.

Results The probability of classifying an ECG as LBBB by available definitions varied considerably (range 0.20-0.76). Relative intra-observer agreement (Kappa) with LBBB definitions is moderate (k ranging from 0.47 to 0.74). Intra-observer agreement in clinical judgement of LBBB as well was moderate ($k=0.76$ (0.14)). Relative inter-observer agreement for LBBB definitions was minimal to weak (k ranging from 0.19 to 0.44). Clinical judgement showed weak relative agreement as well ($k=0.35$ (0.20)). The agreement between different definitions of LBBB ranged from good ($P=0.95$ (0.07)) to weak ($P=0.40$ (0.22)). AHA/ACC/HRS LBBB definition showed the poorest agreement with other definitions. Furthermore, correlation between clinical judgement and the LBBB definitions was poor (0.33-0.55), with poorest correlation with AHA/ACC/HRS definition.

Conclusion Overall significant variation in the probability of classifying a patient as showing LBBB is present in using different LBBB definitions or clinical judgement. Considerable intra- and inter-observer variability in classification using both LBBB criteria or clinical judgement by experienced implanting physicians, adds to this variation. Inter-definition agreement varies significantly and correlation of clinical judgement and LBBB classification by definitions is modest at best.

Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for heart failure patients with ventricular conduction disturbances [1, 2]. Studies have shown that the presence of left bundle branch block (LBBB) is one of the best predictors for response to CRT [3-6]. Therefore, current guidelines use LBBB QRS morphology next to QRS duration as a tool for patient selection for CRT [2]. Currently, patients with a LBBB QRS morphology have a class I recommendation for CRT, whereas patients with non-LBBB QRS morphology have a class IIa or IIb recommendation depending on QRS duration.

The use of the LBBB morphology in clinical practice is, however, not straightforward. LBBB morphology has been defined differently by the European and American cardiology societies [1, 7], landmark trials (REVERSE and MADIT-CRT) [4, 6] and by experts [8]. In addition, applying these different definitions requires careful evaluation of the ECG. Therefore, implanting cardiologists' judgement of the presence of LBBB may not be in concordance with these definitions. Even when the LBBB definitions would be used in clinical practice, they are extensive (many criteria) and sensitive to different interpretations, which may result in significant variation in patient selection for CRT.

In this study we aim to investigate (1) the agreement in identification of LBBB by clinical judgement of implanting cardiologists; (2) the agreement in identification of LBBB using the available definitions; (3) the agreement between the different LBBB definitions and (4) the relationship between LBBB definitions evaluated by observers and clinical judgement of implanting cardiologists.

Methods

From a large cohort of over 500 consecutive patients implanted with a CRT device in the University Medical Centre Utrecht, 100 baseline 12-lead ECGs were randomly selected. The ECGs were recorded at 25mm/s paper speed and displayed in a 2x6 lead fashion. Four expert cardiologists involved in CRT in daily clinical practice (JL, AA, AM, KV) classified the presence of LBBB on the ECG according to their clinical judgement. The ECGs were provided as printed 12-lead ECGs. For the classification of LBBB according to the different LBBB definitions, four independent, trained observers judged the ECGs according to four currently used LBBB definitions (Table 1). As can be seen in table 1, REVERSE-trial and ESC definition contain the same morphological features. Therefore the REVERSE-trial LBBB definition was not investigated as a separate definition.

The evaluation of the four different LBBB definitions was performed on digital ECGs (using up to 400% zoom to judge the individual LBBB criteria. QRS duration was determined by the automated ECG algorithm.

Table 1. Left bundle branch block definitions

Definitions	Criteria
ESC[1]/REVERSE[4]	<ul style="list-style-type: none"> • QRS $\geq$ 120ms • QS or rS in V1 • Broad (frequently notched/slurred) R in I, aVL, V5 or V6 • Absent Q in V5 and V6
AHA/ACC/HRS [7, 21]	<ul style="list-style-type: none"> • QRS $\geq$ 120ms • Notch-, slurred R in I, aVL, V5 and V6 • Occasional RS pattern in V5-6 • Absent q in I, V5-V6 and aVL • R peak time > 60ms in V5 and V6 • Normal R peak time in V1-V3 • No negative concordance • Usually discordant ST-T segments
MADIT [6]	<ul style="list-style-type: none"> • QRS $\geq$ 130ms • QS or rS in V1 • Broad (frequently notch-/slurred) R in I, aVL, V5 or V6 • Absent q in V5 and V6
Strauss [8]	<ul style="list-style-type: none"> • QRS $\geq$ 130ms in women, $\geq$ 140ms in men • QS or rS in V1 and V2 • Mid QRS Notching/Slurring in $\geq$ 2 congruent leads V1, V2, V5, V6, I or aVL

Statistical analysis

Intra-observer agreement for all five ways to determine LBBB was investigated using repeated independent observations from two observers; both for definitions and clinical judgement. Inter-observer agreement was defined between pairs of observers. Intra-observer and inter-observer agreement levels were quantified in two ways: through the probability to agree and through the kappa coefficient. While the first measure accounts for disagreement on the classification of the ECGs themselves, the kappa coefficient also accounts for disagreement on the probability to be classified as LBBB with the different definitions (including inter-observer variability). Kappa coefficients therefore mix two sources of disagreements. The effect of predictors (type of criterion and QRS duration larger than 150ms for clinical classification) on the intra- and inter-observer agreement levels and the probability of LBBB were analysed using a multilevel approach [9]. Random effects relative to the patients were introduced in the models to capture the dependency between the multiple measurements made on each patient (different pairs of observers using the same definition or the same observers using different definitions). Large values of the variance of the random effects indicate heterogeneous agreement levels, while small values indicate homogeneous agreement levels. A Bayesian approach with vague priors was used to estimate the parameters in the model. A predictor is said to be significant if the 95% equal-tailed posterior credibility interval relative to the predictor does not contain the value 0. Posterior marginal distributions were obtained by averaging over the random effects and are summarized using posterior mean (posterior standard deviation). Data analysis was conducted using R (version 3.2.5 for Windows) and JAGS statistical packages.

Results

Mean QRS duration of the patients was 160 ± 24 ms. Baseline characteristics reflect a typical CRT population. Three patients had a QRS duration shorter than 120ms, and were implanted with a CRT device for an ablate-and-pace indication.

General variation in observation of LBBB

There was a considerable difference in the probability of classification as LBBB between the four available definitions and clinical judgment, ranging between 0.20 (0.27) for AHA/ACC/HRS definition and 0.76 (0.29) for ESC definition (Figure 1). The error bars in figure 1 indicate large variability in scoring LBBB between the four observers, even when using the same definition. The probability of being classified as LBBB with clinical judgement was higher in patients with QRS duration above 150ms than in patients with a QRS duration < 150 ms, 0.68 (0.36) versus 0.26 (0.34) respectively.

Intra-observer agreement in LBBB classification

Overall absolute intra-observer agreement between LBBB definitions is strong (P range 0.87 – 0.95), however relative agreement (kappa), corrected for probability of the presence of LBBB, is only moderate (k range 0.47 – 0.74). Intra-observer (absolute and relative) agreement was lower with AHA/ACC/HRS definition than with ESC and MADIT definitions (table 2). Within the AHA/ACC/HRS definition, the agreement level on the detection of notched and slurred R criterion was lower ($P=0.81$ (0.09)) than on other criteria. Agreement on morphological criteria of other LBBB definitions did not significantly differ.

Figure 1. Prevalence of LBBB according to available definitions and clinical judgement

Summary of the estimated prevalence of LBBB according to four definitions each used by 4 observers and clinical judgement made by 4 clinicians. Data are presented as mean (cross), median (bar), 25-75 percentiles (box) and minimum and maximum (dotted line). AHA = American Heart Association, American College of Cardiology and Heart Rhythm Society conjoint definition of LBBB [21], CLI = clinical judgment, ESC = European Society of Cardiology [1], MADIT = MultiCentre Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) [6], Strauss = LBBB definition according to Strauss et al. [8]

Absolute Intra-observer agreement on clinical judgement was good ($P=0.93$ (0.05)) for clinical judgement of LBBB, but only moderate relative agreement was found ($k=0.76$ (0.14)) (table 2). Agreement did not differ for patients with QRS duration below and above 150ms ($P=0.96$ (0.09) and $P=0.88$ (0.16), respectively). Similar conclusions were found for kappa coefficients.

Table 2. Intra- and inter-observer agreement in LBBB classification

Criterion	Prevalence	intra-observer agreement		inter-observer agreement	
		Probability (P)	Kappa (K)	Probability (P)	Kappa (K)
ESC	0.75±0.29	0.94±0.05	0.67±0.22	0.85±0.08	0.27±0.25
AHA/ACC/HRS	0.20±0.27	0.87±0.08	0.47±0.28	0.81±0.09	0.19±0.25
MADIT	0.71±0.31	0.95±0.04	0.74±0.19	0.88±0.07	0.44±0.22
Strauss	0.65±0.32	0.92±0.06	0.65±0.22	0.85±0.08	0.40±0.22
Clinical judgement	0.50±0.35	0.93±0.05	0.76±0.14	0.81±0.08	0.35±0.20

Inter-observer agreement in LBBB classification

Absolute inter-observer agreement levels were good for all LBBB definitions (P range 0.81 – 0.88), however relative agreement (kappa) was minimal to weak (range k 0.19 – 0.44) (Table 2). Agreement level in AHA/ACC/HRS definition was reduced by variability in scoring notching/slurring of the R-wave in leads I, aVL, V5 and V6, the absence of a Q-wave in leads I, V5, V6 and aVL and R-peak time criteria ($P=0.73$ (0.06), $P=0.75$ (0.07) and $P=0.71$ (0.07), respectively).

The same trend was visible for clinical judgement of LBBB. Whereas there was good absolute agreement of clinical judgement ($P=0.81$ (0.81)), relative agreement is weak ($k=0.35$ (0.20)) (table 2). QRS duration did not influence inter-observer variability ($P=0.73$ (0.34) and $P=0.82$ (0.19), for QRS duration below and above 150ms respectively) for clinical judgement.

Inter-definition agreement in LBBB classification

Highest inter-definition agreement was observed between ESC and MADIT definitions ($P=0.95$ (0.07)), whereas lowest agreement was seen between the AHA/ACC/HRS and the ESC, MADIT and Strauss criteria ($P=0.40$, (0.22), $P=0.44$, (0.23), and $P=0.50$ (0.23) respectively).

Correspondence of clinical judgement with available definitions

As shown in figure 2, the clinical judgement of the presence of LBBB correlated only modestly (phi coefficient range 0.10-0.68) to LBBB according to the available definitions of LBBB. Clinical judgement correlated best with Strauss definition (phi=0.52 (0.10)) and worst with AHA/ACC/HRS definition (phi=0.30 (0.10)).

Figure 2. Correlation of clinical LBBB classification with classification according to available LBBB definitions.

Summary of the correlation (phi coefficient) between LBBB according to clinical judgement and the four LBBB definitions. Data are presented as mean (cross), median (bar), 25-75 percentiles (box) and minimum and maximum (dotted line). Symbols and abbreviations are explained in the legends to figure 1.

Discussion

The present study shows that the probability of classifying an ECG as LBBB by clinical judgement and available definitions varied considerably. Clinical judgement as well as classification by use of definitions of LBBB shows significant inter-observer variability and seems to depend on the complexity of the definition of LBBB. Furthermore, the correlation between clinical judgement and the LBBB definitions was poor. These results are important in the light of LBBB being an important selection criterion for CRT. The lack of a standardized and well-defined classification of LBBB may hamper consistent selection of patients and proper comparison of studies, irrespective of whether they used the same or a different LBBB definition.

Classification according to clinical judgement of LBBB

Clinical judgement of LBBB seems reproducible as it showed good intra-observer agreement. Although still close to 1 in 10 ECGs will be classified differently by the same observer. However, inter-observer agreement is only 0.81, which implies that implanting cardiologists will disagree on 1 in 5 ECGs. This large inter-observer variability exists despite the fact that the observers in this study are experienced and have been dealing with this issue extensively in research and clinical settings. Although QRS duration influences the likelihood for a patient to be classified as LBBB, no evidence of an influence of QRS duration on the intra- and inter-observer agreement was found. Meaning that the subjectivity in LBBB classification depends predominantly on morphological features. The $50 \pm 0.35\%$ prevalence of LBBB by clinical classification adds to the low kappa-value (0.35 ± 0.20). Which translates to the poor correlation with LBBB definitions.

The poor correlation of clinical judgement with LBBB classification according to the definitions implies that the abundance of research showing the relation of LBBB to improved outcomes in CRT may not be applicable to LBBB based on clinical judgement. Since all observers were from Europe, a larger correlation of the clinical judgement with the ESC definition was expected than with the other definitions. However, the correlation was the highest MADIT and Strauss definitions, the two least complex definitions. These definitions also incorporate a larger QRS duration criterion, which could reflect that clinical judgement is sensitive to wider QRS duration, as was shown in this study.

Classification using different LBBB definitions

There is great variability in classification of LBBB according to different definitions. With AHA/ACC/HRS definitions classifying every other ECG different from ESC, MADIT and Strauss definitions. This obviously leads to great differences in implantation practice. However even Strauss and ESC or MADIT definition will lead to a different classification in 1 out of 5 ECGs.

The probability of observing LBBB according to the definitions investigated in this study correlates well to findings in earlier studies [4, 6, 10]. The REVERSE-trial subanalysis reported 60% patients to have LBBB, whereas 70% of MADIT-CRT patients had LBBB. The REVERSE definition differs from the MADIT definition by the inclusion of a shorter QRS duration, which would make it less specific. The difference can also be explained by the difference in populations, with a larger mean QRS duration in the MADIT-trial (158ms) as compared to the REVERSE-trial (151ms). Studies incorporating the Strauss LBBB definition report approximately 40% of patients classified as LBBB [11]. Interestingly, a recent study investigated the effect of the application of Strauss (strict) LBBB definition on CRT patients that were included for 'less' strict criteria, according to the AHA/ACC/HRS definition in the CRT MORE registry. In this subanalysis only 39% of patients classified as LBBB by AHA/ACC/HRS definition, were classified as LBBB by Strauss definition [12]. According to the current analysis however AHA/ACC/HRS LBBB definition is far more specific than the definition Strauss and colleagues used. This once more shows the complex nature of the morphological features the definitions are composed of. The standard deviations shown in figure 2 confirm these issues, even within our own group.

Intra-observer variability in LBBB classification using different LBBB definitions is generally good, leading to less than 1 in 10 ECGs classified differently by the same observer. Inter-observer variability however is a little higher, with 1 in every 5 to 6 ECGs being classified differently by different observers. The lower kappa values in comparison to the probabilities reflect the respective prevalence of LBBB by different definitions. Therefore the percentage of patients (0.20 ± 0.27) classified as LBBB by AHA/ACC/HRS definition leads to relatively large difference in probability (0.87 ± 0.08) and kappa (0.47 ± 0.28) values. The small difference in absolute probability between LBBB definitions therefore increases with taking into account the prevalence of LBBB by the different definitions. Moreover variability seems to depend on the complexity of the definition. As the AHA/ACC/HRS definition entails judgement of the presence of 8 separate criteria, this is by far the most complex definition. Easily misinterpreted morphological criteria as 'notching or slurring' seem to contribute to the higher intra- and inter-observer variability. This becomes even more clear when reviewing previous studies' summary of 12-lead ECG characteristics of LBBB. Gold et al. [4] in the REVERSE-trial subanalysis, Zareba et al. [6] in the MADIT-CRT-trial subanalysis, Birnie et al. [3] in the RAFT-trial subanalysis, all refer to the WHO classification [7] also used by the AHA/ACC/HRS guidelines. The summary of these characteristics in the respective papers however differ significantly from the original WHO criteria that are referred to. Furthermore in the determination of the presence of LBBB (according to the aforementioned definitions) these

trials all had a (trained) core-laboratory at their disposal. The results in the current analysis clearly show that this is not a good representation of clinical practice as this reduces inter-observer variability apart from inter-definition and intra-observer variability present in every day clinical practice. Furthermore interpretation of morphological criteria might also depend on the format and filtering of the ECG. When a digital ECG is used, zooming in on the QRS-complex may reveal (or seem to reveal) distinct criteria. When using a printed ECG however, this is not possible. This has also been shown for the interpretation of QRS duration. [13]

LBBB, dyssynchrony, and outcome

Recent studies have looked into the value of different LBBB definitions (more specifically Strauss LBBB definition) to identify electrical and mechanical dyssynchrony, as well as outcomes to CRT. Mafi Rad et al. [14] have shown the Strauss definition to be associated to the presence of electrical dyssynchrony as measured by delayed LV lateral wall activation. Whereas van Deursen et al. [15] and Jackson et al. [16] showed the presence of LBBB according to this definition to predict clinical and echocardiographic outcomes after CRT better than other definitions. Although the 'best' correlation of LBBB classification according to clinical judgement was with the Strauss definition, the correlation still is too low to apply above mentioned study results to general daily practice of clinical judgement of LBBB.

Limitations

This study did not include outcomes to CRT. Therefore this analysis cannot show the implication for patient benefit from CRT. Although this would further establish the importance of reaching consensus on the definition of LBBB, this was not the primary aim of the current analysis. A limitation in the selection of ECGs in this study, was that all ECGs were from patients actually implanted with a CRT device. This may have caused selection bias in the probability of scoring LBBB. It is unlikely that this affected the variability in the classification of LBBB. However, as observers using clinical judgement were different from observers using LBBB definitions for classification, inter-observer variability could have influenced the relationship between clinical judgement and LBBB definitions.

Clinical relevance

The observed variability in LBBB classification might in part be an explanation for the high variations in patient selection for CRT and abiding existence of non-response in every day practice [17, 18]. The present results also indicate that combining studies on outcome of CRT using different LBBB definitions may produce unreliable indications about the value of LBBB as selection criterium [19]. Finally, while results from subanalyses of the MADIT and REVERSE trials have led to the introduction of LBBB as a selection criterion in all CRT guidelines, this study shows considerable difficulties in application and that novel objectively determined electrocardiographical indices may be worth to investigate further [16, 20].

Conclusions

Classification of LBBB on the ECG is not straightforward at all. There is considerable difference in identification of LBBB by the clinical judgement of experienced cardiologists as well as between current LBBB definitions. Furthermore, clinical judgement of LBBB correlates poorly with any of the LBBB definitions. These data indicate that great variability in LBBB classification is bound to be present between clinical trials and between physicians selecting patients for CRT in daily clinical practice.

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The definition of left bundle branch block influences the response to cardiac resynchronization therapy

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ABSTRACT

Background CRT has been proven to achieve most benefit in patients with left bundle branch block morphology (LBBB). However, ECG criteria to define LBBB significantly differ from each other. Objective of the study was to evaluate the impact of different ECG criteria for LBBB definition on survival, hospitalization for heart failure and reverse remodelling in patients who received cardiac resynchronization therapy (CRT).

Methods and results Three-hundred-sixteen consecutive patients were included in the analysis. Six different definitions were assessed in baseline ECGs of patients who received a CRT device: a QRS duration of ≥ 150 ms and LBBB according to AHA/ACC/HRS, ESC 2006, ESC 2009, ESC 2013 and the classification proposed by Strauss and colleagues. In univariate analysis, the ESC 2009 and 2013 and the Strauss definitions were significantly associated with a reduction in cumulative probability for heart failure (HF) hospitalization and mortality (HR 0.60, 95%CI 0.42-0.86, HR 0.61, 95% CI 0.43-0.87 and HR 0.57, 95% CI 0.40-0.80, respectively). In multivariate analysis, there was a significant association with the combined endpoint only for ESC 2009 and 2013, and for Strauss LBBB definition. Moreover, the cumulative probability of HF hospitalizations and mortality and was higher in patients who were negative for all the 5 LBBB definitions.

Conclusions This study shows that the strength of the association of LBBB to outcome in CRT depends on the ECG classification used to define LBBB. With the simplest definitions (ESC 2009 and 2013) providing the best association with clinical endpoints in CRT.

Introduction

Cardiac resynchronization therapy (CRT) improves symptoms, quality of life, and survival in patients with reduced left ventricular (LV) ejection fraction, heart failure symptoms, and prolonged QRS duration. The randomized clinical trials that lead to the initial widespread adoption of CRT used only QRS duration of more than 120ms as entry criteria [1-4]. Ever since, multiple subanalyses of large randomized trials showed QRS morphology to be associated to the measured benefit by CRT [5]. Where the benefit in patients presenting with left bundle branch block (LBBB) on their baseline ECG was shown to be very robust [6,7], in non-LBBB patients the benefit is still controversial [6,7]. Moreover, the specific criteria that should be used to classify LBBB are not properly indicated in clinical practice guidelines [7,8].

Currently, there are multiple ECG definitions for LBBB proposed by scientific organizations [6,9-11] and research groups [12]. Moreover, the European Society of Cardiology (ESC) has changed the definition of LBBB a few times over the last decade [6,10,11]. While initially these ECG criteria were used to classify the conduction abnormality per se, the more recent ones implicitly assume that LBBB represents the most important substrate for CRT. The lack of uniformity of LBBB definitions and uncertainty about the differences in association with outcomes to CRT can contribute to the still remaining group of patients not experiencing benefit from CRT.

Therefore, we aimed to evaluate a population of patients implanted with a CRT for (1) the consistency of a CRT patient to be classified as having LBBB, and (2) the association of the different LBBB definitions with both reverse remodelling and HF hospitalization and all-cause mortality.

Methods

Study population.

All consecutive patients who received a CRT at two different European centres (Cardiocentro Ticino, Lugano, Switzerland and Maastricht University Medical Centre, Maastricht, The Netherlands) from 2006 to 2016 were retrospectively analysed for the inclusion in the study. Patients were indicated for CRT according to European guidelines indications available at time of CRT implantation. All patients underwent implantation of a CRT system, with or without implantable cardioverter-defibrillator capabilities based upon clinical and patient decision. Exclusion criteria were unavailability or poor quality of the baseline ECG, baseline right ventricular pacing, incomplete follow-up data and inadequate biventricular pacing after implantation ($\leq 95\%$ biventricular pacing). The study protocol was approved by the locally appointed ethics committee and complied with the Declaration of Helsinki. Written informed consent has been obtained from all subjects (or their legally authorized representative).

ECG acquisition and analysis.

Standard supine 12-lead ECGs (filter range, 0.15 to 100 Hz; AC filter, 60 Hz, 25 mm/sec speed, 1 mm/mV) were obtained at baseline and before discharge. Blinded to outcomes, one experienced reader interpreted QRS morphology based on morphological features of the five different definitions. LBBB definitions used were the ones recommended by the AHA/ACC/HRS [9], the ones suggested by the ESC in 2006 [10] and 2009 [11] textbooks and the 2013 ESC guidelines [6], and finally the ECG definition proposed by Strauss et al. [12]; the criteria are summarized in Table 1. Notching in the QRS complex and slurring were defined according to Almer et al. [13]. Notching was defined as a sudden change, within a slope (waveform), in direction $\geq 90^\circ$; slurring was defined as sudden change in the slope of a waveform with a change in direction 0° - 90° . QRS duration was always automatically measured by using ECG machine of two different vendors (Schiller CARDIOVIT CS-200 Excellence, Doral, FL, USA and ELI 350, Mortara Instrument, Inc., Milwaukee, WI, USA). In order to qualify for LBBB according to a specific definition, the ECG should comply with all required criteria for that definition.

Table 1. ECG criteria to define left bundle branch block.

	AHA (2009)	ESC 2006	ESC 2009	ESC 2013	Strauss (2011)
QRS duration	$\geq 120\text{ms}$	$\geq 120\text{ms}$	$\geq 120\text{ms}$	$\geq 120\text{ms}$	$\text{♂} \geq 140\text{ms}, \text{♀} \geq 130\text{ms}$
QS or rS pattern	-	V1	V1,V2	V1	V1,V2
QS pattern	-	aVR	-	-	-
Positive concordance	Yes	V1,aVR	-	-	-
Delayed ID-time ($\geq 60\text{ms}$)	V5,V6	I,V6	-	-	-
Discordant T-waves	usually	usually	-	-	-
Notch/slurred R-wave	I,aVL,V5,V6	-	I,aVL,V5,V6	I,aVL,V5,V6	I,aVL,V1,V2,V5,V6
Negative T-wave in leads					
with upright QRS	Yes	-	I,aVL,V5,V6	-	-
Absent Q-wave	I,V5,V6	-	I,aVL,V5,V6	V5,V6	-

AHA = AHA/ACC/HRS, ID = intrinsecoid deflection.

Echocardiographic measurements.

Echocardiographic evaluation was performed at baseline and at 6 months after device implantation. Images were acquired in the left lateral decubitus position with a commercially available system (GE Healthcare, Horten, Norway) with a 3.5-MHz transducer at a depth of 16 cm in conventional parasternal and apical views. LV end-systolic volume (LVESV) and end-diastolic volume (LVEDV) were measured in apical 2- and 4-chamber views; LV Ejection Fraction (LVEF) was calculated with the use of the biplane Simpson method. Reverse remodelling was defined as a reduction of LVESV of at least 15% assessed at 6 months after CRT implantation compared to baseline.

Follow-up.

Clinical follow-up of patients consisted of physical examination, ECG and echocardiogram performed at least every 6 months. Follow-up of the device was performed at 1 and 3 months after CRT implantation and every 6 months thereafter. Data on hospitalization for acute heart failure were systematically collected. The diagnosis of heart failure required symptoms and signs consistent with congestive heart failure that was responsive to intravenous decongestive therapy.

Statistical analysis.

Continuous data are presented as median and 25th-75th percentiles (IQR) and categorical data as counts and percentages. Comparisons between groups were performed with Mann-Whitney U and Fisher's exact tests, respectively for these data. Each patient's ECG was classified as LBBB or not according to the five classification methods described above. Therefore, each patient could have from 0 to 5 LBBB definitions satisfied. Comparisons according to the number of LBBB positive classification per patient were performed using the Kruskal-Wallis test for continuous variables and the Fisher's exact test for categorical variables. The test for trend was also applied. Significance was set at 0.003 for pairwise post-hoc comparisons.

The association of LBBB and reverse remodelling was assessed using a logistic regression model. Odds ratios (OR) and 95% confidence intervals (95%CI) were computed. Median follow-up (IQR) was computed with the inverse Kaplan Meier method. Event rates per 100 person year and 95%CI were computed.

Event-free survival was estimated by Kaplan-Meier method and compared with the logrank test. Hazard ratios (HR) and 95%CI were calculated with a Cox regression model. The proportional hazard assumption was satisfied in all cases. Endpoints for these analyses were HF hospitalization, all-cause mortality and the combination of these clinical endpoints. For both modelling procedures, both univariable and multivariable models with adjustment for a priori selected clinical confounders were fitted. Harrell's c concordance statistic was computed for all Cox regression models including in turn each LBBB classification (the higher the Harrell's c, the better model discrimination); classifications were informally compared by ranking the Harrell's c. Statistical analyses were conducted using the Stata 15.1 software (Stata Corporation, College Station, TX, USA). A 2-sided p-value less than 0.05 was considered statistically significant.

Results

From January 2006 to December 2016, 498 patients received a CRT-device at the two participating institutions. Of those patients, 45 were excluded because of poor quality baseline ECG, 15 patients because of baseline paced QRS, 25 patients because of biventricular pacing <95%, and 97 patients were excluded due to incomplete follow-up data. Three-hundred sixteen patients were finally included in the analysis (Lugano n: 156; Maastricht n: 160). Demographic characteristics of the study cohort are summarized in Table 2.

Table 2. Demographic data, baseline clinical parameters of the 316 CRT patients included in the study.

Parameter	All patients (n=316)
Male gender, n (%)	230 (73)
Age, years, median [IQR]	71 [62-77]
Ischemic aetiology, n (%)	196 (62)
Persistent atrial fibrillation, n (%)	56 (16)
NYHA functional class II/III-IV, n (%)	129 (41) /164 (52)
ECG parameters	
Heart rate, bpm, median [IQR],	71 [62-83]
QRS duration, ms, median, [IQR]	156 [140-170]
QRS ≥ 150 ms, n (%)	198 (63)
LBBB + by ESC criteria 2006, n (%)	106 (33)
LBBB + by ESC criteria 2009, n (%)	145 (46)
LBBB + by ESC criteria 2013, n (%)	148 (47)
LBBB + by AHA/ACC/HRS, n (%)	92 (29)
LBBB + by Strauss et al. , n (%)	194 (61)
Medication, n (%)	
Beta-blocker	297 (94)
ACE inhibitor or ARB	278 (88)
MRAs	230 (73)
Diuretics	230 (73)
Amiodarone	38 (12)
Echocardiographic parameters, median [IQR]	
LV ejection fraction, %	28 [23-33]
LV end-diastolic volume, ml	184 [147-227]
LV end-systolic volume, ml	133 [101-172]

NYHA = New York Heart Association, LBBB+ = Left bundle branch block positive according to the indicated classification, ACE = Angiotensin-converting-enzyme, MRAs = mineralocorticoid receptor antagonists, ARB = Angiotensin receptor blocker; LV = Left Ventricle.

The frequency of LBBB strongly depended on the definition used, the proportion of patients meeting LBBB criteria ranged from 29% (AHA) to 61% (Strauss). One-hundred ninety-eight patients (63%) had a LBBB according to at least one definition; of these, of which 33% was positive for all five ECG classifications. As illustrated in Supplemental Table 1, overlap among the LBBB definitions is present.

QRS morphology and reverse remodelling.

One-hundred seventy-six patients (55%) out of the 316 patients had a $\geq 15\%$ reduction of baseline LVESV at 6-month follow-up. The proportion of patients with reverse remodelling varied according to different LBBB definitions and QRS duration (Supplemental Figure 1). Among all considered LBBB definitions, the ESC definitions showed the strongest association with reverse remodelling. When adjusted for confounding factors (age, gender, renal impairment, anti-remodelling therapy), the association with reverse remodelling was significant only for ESC 2009 and ESC 2013 definitions (OR 8.8, 95%CI 1.3-56.5, p 0.01 and OR 8.7, 95%CI 1.4-56.4, p 0.01, respectively).

QRS morphology and HF hospitalization.

During a median follow-up time of 55 months (IQR 25-79 months), 104 patients (33%) were admitted to the hospital for acute heart failure after CRT implantation. The cumulative probability of HF hospitalization during follow-up, overall was lower among patients with LBBB than in those without LBBB. However, statistical significance was only met in patients with LBBB according to the ESC 2009 (Logrank test $p=0.002$, HR = 0.54, 95% CI 0.34-0.85), the ESC 2013 (HR= 0.55, 95% CI 0.36-0.82, $p=0.003$), the Strauss (HR= 0.55, 95% CI 0.38-0.82, $p=0.002$) and the AHA definitions (HR= 0.60, 95% CI 0.37-0.97, $p=0.03$). Whereas LBBB according to the ESC 2006 definition was not significantly associated to HF hospitalization.

Figure 1. Combined survival estimate free of HF hospitalization or all-cause death for QRS duration and five LBBB definitions.

*HR adjusted for age, gender, NYHA class, atrial fibrillation, baseline EDV. HF = Heart Failure, LBBB = Left Bundle Branch Block, NYHA = New York Heart Association class, EDV = end-diastolic volume

QRS morphology and mortality.

During the follow-up period, 81 patients (25%) died. Overall, survival rate between LBBB and non-LBBB patients differed significantly. However when LBBB definitions were evaluated individually, results differed. The cumulative probability of the combined event (HF hospitalization and all-cause mortality) was significantly reduced in patients with LBBB according to ESC 2009, ESC 2013 and Strauss definitions. (Figure 1)

When adjusted for confounding factors, the probability of the combined event was significantly lower only for patients with LBBB according to ESC 2009 and ESC 2013 definitions (HR 0.75, 95%CI 0.68-0.83, $p=0.004$ and HR 0.74, 95%CI 0.66-0.83, $p=0.006$, respectively) and for Strauss definition (HR 0.50, 95%CI 0.17-1.49, $p=0.001$).

As shown in supplemental figure 2, ESC 2103 and Strauss classifications ranked highest by the Harrell's c statistic of the Cox models assessing the combined endpoint of HF hospitalization and all-cause mortality. Classification based on QRS and AHA ranked lowest. The ESC 2013 and AHA definitions consistently ranked highest and lowest, respectively, for HF hospitalization and all-cause mortality.

Figure 2. Combined survival estimate free of HF hospitalization or all-cause mortality according to number of LBBB definitions positive.

No LBBB classification-positive (blue line), 1 classification-positive (red line), 2 or more classifications-positive (green line). HF = Heart Failure, LBBB = Left Bundle Branch Block.

Notably, cumulative probability of the occurrence of the combined clinical event was significantly higher in those patients who did not fulfil any of the five LBBB definitions' criteria ($n=118$) compared to those who were positive for one or more LBBB definitions (Figure 2).

Discussion

To the best of our knowledge, this is the first study that systematically investigated how the ECG definition of LBBB is related to the clinical benefit of CRT. We demonstrated that different definitions currently used to define the LBBB on ECG differ in their classification of patients, and are not equally associated to the clinical benefit of CRT with regards to the proportion of patients showing reverse remodelling, HF hospitalization and all-cause mortality. Strikingly, the "simpler" LBBB definitions provided an equal or better differentiation between CRT responders and non-responders as compared to so-called "stricter" LBBB criteria. The highly selective AHA criteria resulted in high percentages of CRT response in both LBBB-positive and LBBB-negative patients. The elegance of these results is that the use of simple ECG definitions provide good selection for CRT device implantation. By comparing the criteria of the three simple definitions to those of the other definitions, it seems that QS or rS pattern in V1, notching/slurring in V5, V6 and absence of Q in V5, V6 are the most important criteria, whereas intrinsic time and T wave morphology seem to contribute less to the prediction of clinical response.

LBBB definition influences CRT outcome prediction.

The data from the present study confirm findings from previous studies that the extent of LV volumetric changes (i.e., reverse remodelling), and clinical outcomes are affected by baseline ECG characteristics [14,15]. Sweeney et al. demonstrated that an ECG pattern representing complete LBBB is a strong predictor of response to CRT [16]. This observation was consistent with results from substudies of the COMPANION [17], MADIT-CRT [2] and RAFT [3] studies. However, our findings significantly expand these findings, indicating that the definition of LBBB influences the association with both echocardiographic and clinical response to CRT. Among the herein studied ECG

classifications, the ESC 2009 and 2013 definitions and the Strauss definition are the only ones that significantly stratify the probability of HF hospitalization and the combined clinical endpoint. These results are in partial agreement with other recent studies. For the first time, we showed that patients who did not fulfil any definition of the herein considered ECG classification of LBBB, thus possibly being the “true non-LBBB” patients, had worse prognosis. In contrast, fulfilling at least 2 or more LBBB definitions’ criteria, significantly reduced the clinical adverse event rate.

Tian et al. [18] found that LVEF increased significantly after CRT in 22 patients with a strict definition of LBBB, but not in 17 patients who had less than two notches. These data seem therefore to be in line with the present study, where LBBB according to all definitions that include QRS notching were predictive of CRT response. Our data are in partial disagreement with Bertaglia et al. [19] who included 335 CRT patients. They found on average no significantly different response (echocardiographic change and time to cardiovascular hospitalization or death) between patients with “strict LBBB” vs. “traditional LBBB”. However, in this study, only patients with LBBB according to AHA criteria were included and “strict LBBB” definition was obtained by applying the Strauss definition on top of the AHA definition. On the other hand, the results by Bertaglia et al. support our observation that CRT response can be predicted equally good by using less restrictive LBBB definitions, when they include QS or rS pattern in V1 and notches and no Q in lateral leads.

Critical components of the LBBB definition.

As compared to the ESC 2009 criteria, the ESC 2013 definitions consider the absence of Q-wave in V5 and V6 as criterion of LBBB. Even if the presence of Q waves in leads I, V5, and V6 cannot exclude patients from a diagnosis of LBBB [11], this addition may be useful for predicting CRT response because such Q-wave may indicate the presence of a scar tissue in the lateral/postero-lateral wall, that likely limits the response to CRT.

Of note, in the present study 42% of patients missed a LBBB classification according to AHA due to lack of a discordant T-wave. In a subanalysis of MADIT-CRT, it was observed that LBBB patients with concordant T wave had a better outcome in terms of hospitalization and survival, regardless of the treatment by CRT [20]. Therefore, the subgroup of non-LBBB patients according to AHA/ACC/HRS criteria is likely composed of a mix of “true” CRT non-responders and well-performing complete LBBB patients. This may in part explain why in the present study there was a relatively small difference in long-term prognosis (combined endpoint of HF hospitalization and all-cause mortality) between patients qualified as LBBB and non-LBBB according to AHA/ACC/HRS definition. The present study shows that using QRS morphology, can help identify patients that will probably benefit of CRT. However, the study also shows that the choice of the LBBB definition and its’ criteria used is associated with the outcome to CRT. In this regard, the proper determination criteria like ‘notching and slurring’ is a key element, which may be user- and system-(filtering) dependent; moreover, recent reports imply the presence of large inter-observer and intra-observer variability in manual ECG reading [21]. There is no standard definition of QRS notching and slurring patterns in modern quantitative electrocardiology, likely because they remain difficult to apply manually by clinicians since they rely on very small amplitude and duration measurements. From a conceptual point of view, in a recent patient-specific computer simulation study, Nguyen et al. showed that notching/slurring patterns in the precordial leads V1, V2, V5, and V6 and ID-time were affected by the position of the heart in the patients’ chest and by appropriate positioning of electrodes on the chest [22]. These variations affected the LBBB/non-LBBB diagnosis,

based on AHA/ACC/HRS, ESC 2006 and Strauss definitions. In addition, measurement of QRS duration has its uncertainties [23]. This difference in QRS duration measurement may exceed the level of 10-15ms, which might be considered clinically significant in patient selection for CRT [24]. Therefore, it is imperative to develop a universally accepted standard on ECG classification for ventricular conduction disturbance, to request its implementation by all ECG vendors, and to mandatorily prescribe its use in future CRT studies and in clinical practice guidelines.

Limitations

This study has some limitations. The retrospective design implies that comparisons were only performed within the same patients, without a control group in which CRT was deactivated. Although quadripolar LV lead technology was clinically introduced around 2012; the proportion of patients that received a quadripolar LV lead was negligible (<5%). Furthermore, none of the devices was capable of multipoint pacing. Functional capacity was assessed using NYHA class only, which considering the retrospective design of the study could be considered acceptable.

65

Conclusions

The ECG definitions adopted to define LBBB morphology have a significant influence on clinical outcome and reverse remodelling in patients who receive CRT. A consensus view needs to be established on how best to define QRS morphology and standardize the diagnostic criteria for LBBB, in order to optimize the selection of patients suitable for CRT.

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Supplemental material

Table 1. Overlap of LBBB classifications, n* (%).

	ESC 2006	ESC 2009	ESC 2013	AHA	Strauss
ESC 2006	-	83 (42)	85 (43)	66 (33)	102 (51)
ESC 2009		-	151 (76)	93 (47)	144 (73)
ESC 2013			-	93 (47)	149 (75)
AHA				-	91 (46)
Strauss					-

**118 patients were not classified as LBBB by any of the 5 classifications.*

68

Figure 1. Reverse remodelling ($\geq 15\%$ reduction in baseline LVEF at 6-months follow-up) according to LBBB morphology and to QRS duration.

Figure 2. Discrimination of all-cause death, hospitalizations for heart failure and combined event according to QRS duration and to each LBBB classification.

Harrell's c values are reported on the x-axis, endpoints on the Y-axis. Bars, representing the Harrell's c for each LBBB classification are ranked according to the value of the Harrell's c for the combined endpoint.

Evaluating ECG-based identification of CRT responders beyond current LBBB definitions.

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Revisions

ABSTRACT

Introduction Left bundle branch block (LBBB) morphology is associated with positive response to cardiac resynchronisation therapy (CRT). There are, however, multiple LBBB definitions. We investigated the association of four LBBB definitions and their individual ECG criteria with clinical outcome. Furthermore, we aimed to combine relevant outcome-associated ECG characteristics into a novel outcome-based definition.

Methods A retrospective multicentre study was conducted in 1,492 CRT patients. Patients were classified as LBBB or non-LBBB according to definitions provided by the European Society of Cardiology (ESC), American Heart Association (AHA), MADIT-CRT trial and Strauss. Primary endpoint was LV assist device implantation (LVAD), cardiac transplantation and all-cause mortality.

Results LBBB classification differed significantly between the four definitions (kappa-coefficients 0.09-0.92). The AHA definition correlated the least (0.09-0.12) with the other definitions. Only 13.8% of patients were classified as LBBB by all definitions. During a 3.4 ± 2.4 years follow-up period, 472 (32%) patients experienced the primary endpoint. For each LBBB definition survival analysis showed a significant association of LBBB with outcome, with relative risk reduction (RRR) ranging from 39 to 43%. Each LBBB definition included characteristics that were not associated with outcome. Combining outcome-associated ECG characteristics into a novel prediction-model did not significantly improve diagnostic performance (RRR 43%).

Conclusion The classification of LBBB is highly dependent on the LBBB definition used. However, each LBBB definition provides a comparable difference in risk of adverse clinical events between LBBB and non-LBBB patients. Combining individual outcome-associated ECG-characteristics into a novel prediction model does not improve association with outcome.

Introduction

Since the first observation of left bundle branch block (LBBB) in humans by Cater et al. in 1914, the perception of LBBB has changed. LBBB was first perceived as an (innocent) electrocardiographic phenomenon (1), but more recently it was found to be associated with worse prognosis in both general heart disease and heart failure.(2) In addition, after the clinical implementation of cardiac resynchronization therapy (CRT), it evolved into a sign of suitability for this therapy, because the presence of LBBB on the 12-lead ECG is considered to reflect electrical dyssynchrony that is amenable to CRT.(3-5)

Over time several different definitions of LBBB have been proposed in large clinical CRT trials (6,7) and CRT guidelines.(8,9) It is unclear to what extent these different LBBB definitions lead to differences in LBBB classification, and whether these different classifications lead to a difference in association with outcome in CRT patients.

The present study was undertaken to evaluate different LBBB definitions and their association with clinical outcome. Furthermore, we evaluated the contribution of the various individual ECG-criteria that compose the various definitions, and their association with outcome. Using associated ECG-criteria we designed a novel outcome-based definition and evaluated whether this might improve clinical outcome prediction in CRT patients.

Methods

Patient population

The Maastricht-Utrecht-Groningen (MUG) cohort consists of 1,492 consecutive patients, with baseline 12-lead ECG available, who received a CRT device in three University Hospitals in the Netherlands from January 2001 up to January 2015. For the present study, we considered patients with a de novo CRT device implantation, following standard guideline indications.(8) Baseline data were retrieved from local hospital patient information systems. Patient characteristics like heart failure (HF) cause and classification, comorbidities, and medication were retrieved from patient history and referral letters. HF cause was deemed ischemic when there was clear evidence of myocardial infarction or coronary artery bypass graft (CABG) in the medical history. Device data were retrieved from specific device databases. Left ventricular lead location was judged from the fluoroscopic images or chest X-ray. At the time of this study, the Dutch Central Committee on Human-related Research (CCMO) allowed the use of anonymous data without prior approval of an institutional review board provided that the data are acquired for routine patient care. All data used were handled anonymously.

Electrocardiography

Recorded baseline 12-lead ECGs were stored digitally in the MUSE Cardiology Information system (GE Medical System) and were evaluated for QRS duration and baseline ECG parameters using automated ECG readings. Four trained, independent observers judged the ECGs for the presence of LBBB morphology according to four different definitions derived from major guidelines and large clinical trials: the European Society of Cardiology (ESC guideline) definition (8), the American Heart Association/American College of Cardiology Foundation/Heart

Rhythm Society (AHA/ACC/HRS) guideline definition (9,10), the Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy (MADIT-CRT) trial and the REsynchronization reVErses Remodeling in Systolic Left vEntricular dysfunction (REVERSE) trial LBBB definition (6,7), and the LBBB definition proposed by Strauss et al.(11) An example ECG is shown in figure 1.

Clinical study end point

The primary endpoint was a combination of LV assist device implantation (LVAD), cardiac transplantation and all-cause mortality. Information was obtained from hospital records, linked to municipal registries. Outcome data was collected until end of follow-up December 2015.

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics software version 25 (SPSS Inc., Chicago, IL, USA). Continuous and discrete variables are presented as mean $\pm$ standard deviation (SD) and counts (percentages), respectively. Dichotomous variables were compared using the X² test. Continuous variables were compared using the Student-t test.

The degree of association between stratification by LBBB definitions was assessed using Cohen's kappa coefficient for correlation. Diagnostic performance (sensitivity, specificity, positive and negative predictive value) of the different LBBB definitions for identifying patients without the clinical endpoint was evaluated using unadjusted receiver operating characteristic curve (ROC) analysis. Area under the curve for tested variables were compared statistically using the Delong method.(12) Kaplan-Meier survival analyses were used when appropriate to evaluate the association between LBBB according to different definitions and clinical outcome. The log-rank test was used to determine probability values. Cox regression analysis was used to assess univariable and multivariable adjusted effects of LBBB according to different definitions on the association with the clinical study endpoint. Multivariable models were adjusted only for ECG characteristics in these analyses. A two-sided P value < 0.05 was considered statistically significant.

76

Results

Baseline Characteristics

A total of 1,492 patients were included in the current analysis. Baseline characteristics of the total cohort are displayed in table 1. This represents a typical CRT cohort, with a mean age of 67 ± 11 years, predominantly male (71%) population. An ischemic cause of heart failure was present in 49% of patients; most patients were in NYHA functional class II-III (93%). QRS duration was 160 ± 21 ms, 15% of patients had atrial fibrillation (AF). The subgroup of patients, qualified as LBBB by AHA/ACC/HRS consisted of slightly but significantly more women and in that group LVEF was higher and LVEDV and LVESV were lower. (Table 1)

Data on the primary endpoint of LVAD implantation, cardiac transplantation and all-cause mortality was available in 1,491 patients. One patient was lost to follow-up due to emigration.

Table 1. Baseline characteristics of the total population and different LBBB populations.

	Total	ESC LBBB	AHA LBBB	MADIT LBBB	Strauss LBBB
Patients %*	100	78	14	75	69
Demographics and History					
Age (years)*	67 (11)	67 (11)	66 (10)	67 (11)	67 (11)
Female gender %*	29	32	34	32	34
BMI (m/kg ²)	27 (5)	27 (5)	28 (5)	27 (5)	27 (5)
Atrial fibrillation %	15	13	9	13	12
Ischemic CMP %	50	45	38	45	45
Diabetes Mellitus %	25	25	23	25	23
Hypertension %	41	43	44	43	43
Echocardiographic Characteristics					
LVEF %*	25 (9)	25 (9)	26 (8)	25 (9)	24 (9)
LVEDV (ml)*	218 (88)	217 (90)	205 (82)	217 (90)	220 (90)
LVESV (ml)*	167 (77)	167 (79)	156 (71)	167 (80)	170 (81)
Functional Status					
NYHA I %	2	2	3	2	2
NYHA II %	39	41	48	41	41
NYHA III %	54	52	45	52	52
NYHA IV %	5	5	4	5	5
Laboratory					
NTproBNP (pmol/l)	2866 (5017)	2868 (5098)	1856 (2796)	2892 (5188)	2920 (5283)
Creat Clear (ml/min)	71 (32)	71 (33)	76 (35)	71 (32)	71 (33)
Medication					
Beta-blocker %*	82	85	83	85	83
ACEi/ARB %	90	91	90	91	91
MRA %	45	44	41	44	45
Device Characteristics					
Device (% CRT-D)	93	93	93	93	93
ECG Characteristics					
QRS duration (ms)#	160 (21)	161 (20)	166 (18)	163 (19)	166 (18)

* $p < 0.05$ for significance

QRS duration was not tested for significant differences as this is included as a criterion in LBBB definitions.

ACEi/ARB = angiotensin converting enzyme inhibitor and/or angiotensin receptor blocker, AHA/ACC/HRS = the American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society, BMI = body mass index, CMP = cardiomyopathy, CRT-D = cardiac resynchronization therapy with defibrillator function, ESC = European Society of Cardiology, LVEF = left ventricular ejection fraction, LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, MADIT = the Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy trial, MRA = mineralocorticoid receptor antagonist, NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

Presence of LBBB according to different LBBB definitions.

Figure 2. depicts the distribution of LBBB and non-LBBB QRS morphology at baseline according to the different LBBB definitions. The AHA/ACC/HRS LBBB definition was the most stringent, classifying only 14% of patients as having LBBB. The other definitions (ESC, MADIT and Strauss) provided rather similar percentages of LBBB positive patients (78, 75 and 69%, respectively).

Only 13.6% of patients were classified as having LBBB according to all four definitions. The correlation of LBBB classification between the different definitions varied significantly, with kappa coefficients ranging from 0.09 between ESC and AHA to 0.92 between ESC and MADIT. (Table 2)

Table 2. Correlation of classification as LBBB and non-LBBB between different definitions. Cohen's kappa between one and another LBBB definition for each possible pair of LBBB definitions.

	ESC	AHA/ACC/HRS	MADIT	Strauss
ESC	-			
AHA/ACC/HRS	0.09	-		
MADIT	0.92	0.11	-	
Strauss	0.41	0.12	0.50	-

AHA/ACC/HRS = the American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society, ESC = European Society of Cardiology, MADIT = the Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy trial.

Frequency of morphological characteristics of different LBBB definitions.

Table 3 shows the frequency of individual ECG characteristics of all LBBB definitions used in this study. While almost all ECG characteristics were highly prevalent in this CRT population (79.3-95.6% of patients), a broad R wave (57.5%) and the absence of a Q wave in the lateral leads were significantly less prevalent (63.4%). As these characteristics both belong to the AHA LBBB definition, these may explain the low number of LBBB positive patients according to this definition.

Table 3. Association and diagnostic accuracy of each of the LBBB definitions for LVAD implantation, cardiac transplantation and all-cause mortality

LBBB definition	Sens (%)	Spec (%)	PPV (%)	NPV (%)	HR (95% CI)
ESC	0.82	0.31	0.72	0.44	0.57 (0.47 – 0.69)
AHA/ACC/HRS	0.21	0.87	0.77	0.33	0.61 (0.46 – 0.79)
MADIT	0.79	0.34	0.72	0.42	0.59 (0.49 – 0.72)
Strauss	0.73	0.40	0.72	0.40	0.61 (0.51 – 0.73)

Sens = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value. Univariable Cox regression was used to calculate hazard ratios and 95% confidence intervals. AHA = AHA/ACC/HRS definition for LBBB; HR = hazard ratio; 95% CI = 95% confidence intervals.

Performance of different LBBB definitions.

In a mean follow-up of 3.4 ± 2.4 years, 472 patients (31.7%) experienced the primary endpoint. Primary event rates for patients with and without LBBB morphology according to each of the definitions are shown in Figure 3. Event rates in the LBBB groups ranged from 22.9% (AHA/ACC/HRS) to 33.3% (MADIT), and in non-LBBB groups from 33.3% (AHA/ACC/HRS) to 44.1% (ESC).

Kaplan-Meier estimates of survival free from the primary endpoint showed significant associations with LBBB morphology for each definition ($p < 0.001$ for all). (Figure 3) Relative risk reduction in LBBB patients compared to non-LBBB patients according to the four different definitions ranged from 39% (AHA/ACC/HRS and Strauss) to 43% (ESC).

Figure 3. Kaplan-Meier estimates of the time to primary endpoint (combination of LVAD implantation, cardiac transplantation or all-cause mortality) for A) ESC, B) AHA/ACC/HRS, C) MADIT, and D) Strauss LBBB definitions.

In each panel the black line represents patients classified as non-LBBB QRS morphology and the red line LBBB QRS morphology according to the respective definition.

Diagnostic properties of the LBBB definitions are presented in table 4. LBBB according to the AHA/ACC/HRS definition had the highest specificity for predicting survival free from the primary endpoint (0.87) with a corresponding positive predictive value (PPV) of 0.77. The ESC LBBB definition had the highest sensitivity (0.82) with a corresponding negative predictive values (NPV) of 0.44. (Table 4) The AUC of the various LBBB definitions was similar for all LBBB definitions (0.53, [0.50, 0.56]), except for the ESC definition, which showed a significantly higher AUC (0.57, [0.54, 0.59], $P=0.004$).

Table 4. Frequencies and uni- and multivariable association of ECG characteristic per LBBB definition and overall with event free survival.

ECG criteria	Frequency % (n=)	HR [95% CI] Univariable	HR [95% CI] Multivariable Within definition	HR [95% CI] Multivariable Overall
ESC				
QS or rS in lead V1	92.9 (1388)	0.56 [0.41-0.76]	0.63 [0.46, 0.84]	0.10 [0.01-0.75]
Broad R lead V5-6, I or aVL	95.6 (1427)	0.90 [0.55-1.49]	0.97 [0.64, 1.47]	-
No Q in lead V5 and 6	83.9 (1254)	0.66 [0.51-0.85]	0.70 [0.56, 0.89]	-
AHA/ACC/HRS				
Notch in lead V5-6, I or aVL	29.2 (436)	0.69 [0.55-0.88]	0.73 [0.58, 0.93]	0.79 [0.63-0.99]
No Q in lead V5-6, I, and aVL	63.4 (947)	0.54 [0.44-0.66]	0.55 [0.45, 0.66]	0.56 [0.45-0.69]
R peak > 60 in lead V5 and 6	57.5 (858)	0.91 [0.74-1.12]	1.04 [0.85, 1.26]	-
No neg concordance	82.6 (1234)	0.99 [0.78-1.26]	0.96 [0.78, 1.19]	-
MADIT				
QRS ≥ 130ms	93.5 (1408)	1.10 [0.71-1.71]	1.01 [0.70, 1.47]	-
QS or rS in lead V1	92.9 (1388)	0.56 [0.41-0.76]	0.63 [0.46, 0.85]	-
Broad R lead V5-6, I or aVL	95.6 (1427)	0.90 [0.55-1.49]	0.96 [0.63, 1.48]	-
No Q in lead V5 and 6	83.9 (1254)	0.66 [0.51-0.85]	0.70 [0.55, 0.89]	-
Strauss				
♀ QRS ≥ 130ms, ♂ QRS ≥ 140ms	86.3 (1300)	0.75 [0.56-0.99]	0.79 [0.62, 1.02]	-
QS or rS in lead V1 and V2	91.0 (1359)	0.67 [0.50-0.92]	0.73 [0.55, 0.97]	-
Notch in 2 consecutive leads V1, V2, V5, V6 and I, aVL	79.3 (1184)	0.74 [0.58-0.95]	0.78 [0.62, 0.98]	-

* interaction effect significant with $p < 0.05$

Uni- and multivariable Cox regression was used to calculate hazard ratios and 95% confidence intervals. Multivariable regression within the LBBB definitions was conducted including all ECG characteristics composing the definition. Multivariable regression overall was conducted with univariably significantly associated ECG characteristics, not significantly interacting with each other.

HR = hazard ratio; 95% CI = 95% confidence intervals.

Performance of morphological characteristics.

Three of the 11 individual ECG characteristics that made up the four definitions were independently associated with primary endpoint occurrence; QS or rS in lead V1; notching or slurring in lead V5-6, I or aVL and absence of a Q in lead V5-6, I, and aVL (table 3). Strength of the associations ranged from 0.10 to 0.79.

Performance of outcome based LBBB characteristics.

The aforementioned individual ECG characteristics that were independently associated with occurrence of the primary endpoint, were combined into a novel outcome-based model. In the entire cohort, 21.7% of patients fulfilled the criteria of this model.

Of patients fulfilling model criteria, 21.9% experienced the endpoint during follow-up, compared to 33.9% in the patient group not fitting this model ($p < 0.001$). Kaplan-Meier estimates of survival free of events showed significant associations with the presence of this outcome-based model ($p < 0.001$; Figure 4). Unadjusted hazard ratio for event free survival was 0.63 [0.50, 0.78]. Diagnostic properties showed sensitivity and specificity of 24.7% and 84.8%, respectively with corresponding NPV and PPV of 33.9% and 78.1%, respectively. Diagnostic performance was not different from aforementioned LBBB definitions (AUC 0.55 [0.50, 0.56]).

Discussion

In this real-world CRT cohort, we show that there are pronounced differences in qualification of LBBB morphology and related diagnostic properties among four frequently used LBBB definitions. In this cohort only 13.6% of ECGs fitted all criteria of the four LBBB definitions. The presence of LBBB is significantly associated with survival free of the primary endpoint, without significant differences in hazard ratios between the definitions. Interestingly, only 3 out of the 11 characteristics, included in any of the four LBBB definitions showed a significant association with clinical outcome. However, combining these 3 characteristics into an outcome-based model does not improve diagnostic characteristics beyond that of current LBBB definitions.

Differences in LBBB classification

Despite the fact that currently LBBB is regarded as an important electrophysiological substrate for CRT response, only few previous studies have addressed the issue of the different LBBB definitions. A first finding of the present study is the large range of percentages of patients with LBBB according to the different definitions (between 18 and

78%). This may explain the large differences in the percentage of LBBB patients in landmark trials, ranging from 67 to 94%. (13) One recent study, also assessing differences in LBBB definitions, showed equally large differences ranging from 29 to 61% of patients being classified as LBBB between multiple definitions (including definitions beyond the ones included in the present study). The difference in classification between various LBBB definitions seems to relate to the extensiveness of the definitions, as the AHA and Strauss definitions (being the most extensive and complicated) classify the lowest proportion of patients as LBBB. Definitions agree on the presence of LBBB in only 13.6% of patients. This low agreement is confirmed by the fact that correlation between definitions that result in similar prevalence of LBBB (MADIT; 75% and Strauss 69%) is only moderate (k-coefficient 0.50). Obviously, an LBBB definition, like AHA definition, with low prevalence is more selective as compared to definitions with higher prevalence. These differences should be recognized because they may influence decision making.

Association of LBBB definitions to event free survival

Despite the difference in prevalence of LBBB according to the various definitions, the difference in clinical outcome (event free survival) between LBBB and non-LBBB subgroups are consistently present. Although crude prevalence and definition of endpoints differ from earlier studies showing differences in outcome between LBBB and non-LBBB patients, we describe a similar difference in endpoint occurrence (33-44% in non-LBBB patients versus 23-33% in LBBB patients). Gold et al conducted a post hoc study in the REVERSE population, in which they found a 10% event rate (worsening composite clinical score, including death) in LBBB patients, versus 26% event rate in non-LBBB patients in the CRT-ON group within 2 years of follow-up.(4) In the MADIT-CRT post hoc study event rates for the combined endpoint of heart failure events or mortality were 23-33% in non-LBBB patients and 16% for LBBB patients, as well as mortality alone (12-15% for non-LBBB patients versus 7% for LBBB patients) over a 3-year follow-up period.(3) The present cohort shows higher overall event rates than in the aforementioned randomized trials. This is a known phenomenon in real life cohorts compared to randomized clinical trials. Furthermore, follow-up was slightly longer in the current analysis than in the aforementioned trials. The endpoint used in this analysis also differs from that used in MADIT-CRT and REVERSE, as it does not include heart failure hospitalisations or other heart failure events.

Contribution of individual morphological characteristics to association with outcome

This study is the first to evaluate individual ECG characteristics (from existing LBBB definitions) and their association with outcome in CRT patients. Theoretically, individual morphological characteristics are all related to the change in sequence and durations of electrical activation of the myocardium typically seen in LBBB (14), and therefore possibly related to clinical outcome.

QRS duration reflects the slowed activation of the myocardium without using the specialised conduction system, but lacking any specific information on the direction of activation. This has been considered the main drawback of QRS duration as a diagnostic measure in patient selection for CRT.(3,4,13,15,16) The current analysis confirms a lack of association of QRS duration with outcome, as none of the QRS duration related criteria remained significantly associated with outcome in a model including characteristics from all LBBB definitions.

A hallmark feature of the more recent Strauss and AHA LBBB definitions is notching and/or slurring of the QRS complex. This aspect is thought to reflect endocardial breakthrough at the left side of the interventricular septum (first notch), after which LV activation reaches the epicardial side of the left ventricular posterolateral wall (second

notch), typical to LBBB activation.(11) Occurrence of this ECG characteristic varies significantly among AHA/HRS/ACC and Strauss definitions (29 vs 79%) as the AHA/ACC/HRS definition demands the presence of notching in all leads with a leftward orientation, whereas Strauss definition requires only 2 consecutive leads with notching or slurring. The AHA notching/slurring criterion remained significantly associated with the endpoint in a multivariable model of ECG characteristics (HR 0.79).

The presence of a QS or rS pattern in the first precordial leads (V1 or V1 and V2) in LBBB definitions are explained by absence of normal initial septal left to right activation facilitated by the posterior fascicle of the left bundle branch (absence of r in V1) and subsequent slow right to left ventricular activation (broad S). A QS or rS pattern in V1 appears to be a significant contributor to both individual LBBB definitions, as well as overall ECG characteristics association with outcome.

Furthermore, the initial activation of the intraventricular septum normally results in an initial Q wave in leads V5, V6, I and aVL, as activation travels from left to right. All but the Strauss LBBB definition dictate that the initial Q wave in the lateral leads should be absent. Strauss et al (11) however argue that this is not the case in the presence of septal myocardial infarction, as initial unopposed right ventricular activation will give an initial Q wave as well. In the current analyses, however, we see that the absence of an initial Q is independently associated with event free survival in CRT patients. This contradiction to the sound argument of Strauss and colleagues could be the result of the known lower probability of response in ischemic cardiomyopathy patients, which would explain the presence of Q waves in LBBB activation.

Association of outcome-based characteristics to event free survival

This is the first study to recombine individual ECG characteristics from different LBBB definitions, associated with clinical endpoint occurrence, into an outcome-based model. Unfortunately, the model failed to improve differentiation between clinical responders and non-responders to CRT. This suggests that ECG parameters, recommended for classification of LBBB by current guidelines and experts are simply not sensitive enough to truly identify patients able to respond, and specific enough to identify those that are not. Potential reasons for this mismatch are that 1. the definition LBBB is originally not meant to predict CRT response and that late LV activation, presumably linked to CRT response, also occurs in some non-LBBB patients.(5,17) Accordingly, small studies using more extensive mapping indicate that the use of such techniques can improve response prediction in CRT.(18,19) However, both ECG and mapping techniques lack the potential to clearly identify structural abnormalities such as scar, factors that also influence the response to CRT even in the presence of a good electrical substrate.

Limitation

The current study has several limitations, inherent to its real-world observational study design. There was no control group of patients not receiving CRT. Therefore we cannot ascribe the association of LBBB with outcome to the effect of CRT based on the current study. However, previous analyses of landmark CRT trials including untreated patients, have shown that the association of LBBB with outcome, is indeed a treatment effect. The significant association with outcome in CRT as shown in this study, can therefore be translated to a significant association with effectiveness of CRT. As this study aims to study the size of effect of the therapy, we feel this does not impair the conclusion of the current study.

Conclusion

Currently used LBBB definitions differ significantly in the patient populations which are classified as LBBB. Regardless of the definition used, outcome is significantly better in LBBB than in non-LBBB patients. Only three individual ECG criteria used in LBBB definitions were associated with clinical outcome, suggesting that LBBB definitions may be simplified. Combining these three criteria to a novel model performed as good as the more complicated LBBB definitions.

Implications and perspectives

CRT remains an important part of current heart failure therapy. Current patient selection is largely based on QRS morphology criteria, which are diverse and complex. The results reassure that no matter which LBBB definition is used it is associated with better outcome in CRT. However as different LBBB definitions classify different patients as LBBB, this will lead to heterogeneity in global CRT practice. In trying to combine individual ECG characteristics associated with outcome, this does not improve diagnostic properties and thus it appears that in trying to improve patient selection methods, we need to find another method identifying the same electrical substrate of LBBB, but presenting it in a way that it can be easily and objectively interpreted.

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Identifying delayed left ventricular lateral wall activation in patients with non-specific intraventricular conduction delay using coronary venous electro-anatomical mapping

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ABSTRACT

Background Delayed left ventricular (LV) lateral wall (LVLW) activation is considered the electrical substrate that characterizes patients suitable for cardiac resynchronization therapy (CRT). Although typically associated with left bundle-branch block, delayed LVLW activation may also be present in patients with non-specific intra-ventricular conduction delay (IVCD). We assessed LVLW activation in CRT candidates with IVCD using coronary venous electro-anatomic mapping (EAM), and investigated whether QRS characteristics on the ECG can identify delayed LVLW activation.

Methods Twenty-three consecutive CRT candidates with IVCD underwent intra-procedural coronary venous EAM using EnSite NavX. QRS morphology, -duration, -fragmentation, -axis deviation, and left anterior/posterior fascicular block were assessed on baseline 12-lead ECGs.

Results Delayed LVLW activation (activation time > 75% of QRS duration) occurred in 12/23 patients. In these patients, the latest activated region was consistently located on the basal lateral wall. QRS duration and prevalence of QRS fragmentation, left/right axis deviation, and left anterior/posterior fascicular block did not differ between patients with and without delayed LVLW activation.

Conclusion Coronary venous EAM can be used at the time of CRT implantation to determine the presence of delayed LVLW activation in patients with IVCD. Delayed LVLW activation is present in over 50% of patients with IVCD. QRS characteristics on the ECG seem unable to identify delayed LVLW activation in this subgroup of patients.

Background

The supposed mechanism of the benefit of cardiac resynchronization therapy (CRT) is that delayed activation of the left ventricular (LV) lateral wall causes mechanical dysfunction, which can be reverted by paced pre-excitation of this delayed LV region. Left bundle branch block (LBBB) is typically associated with early septal activation and delayed activation of the LV lateral wall [1-3]. Non-specific intraventricular conduction delay (IVCD), on the other hand, is considered a more heterogeneous group of conduction disorders exhibiting a more variable pattern of ventricular electrical activation [3]. This may explain why, in contrast to patients with LBBB, patients with IVCD show a variable response to CRT [4]. The reduced benefit of CRT observed in this subgroup of patients has led international guidelines to assign a lower level of recommendation to CRT in patients with IVCD [5]. However, recent studies have suggested that CRT may be beneficial in a subset of IVCD patients with evidence of LV activation delay [6-9]. Recently, we introduced coronary venous electro-anatomical mapping as a tool to assess LV electrical activation at the time of CRT implantation in patients with LBBB [10].

The objectives of the present study were (1) to investigate whether coronary venous electro-anatomical mapping can be used at the time of CRT implantation to determine the presence of delayed LV lateral wall activation in patients with IVCD, and (2) to investigate whether QRS characteristics on the ECG, other than QRS morphology, can identify delayed LV lateral wall activation as determined by coronary venous electro-anatomical mapping in this subgroup patients.

Methods

Study population

Twenty-three consecutive patients referred for CRT device implantation, with LV ejection fraction (LVEF) <35%, New York Heart Association (NYHA) functional class II, III or ambulatory IV, and IVCD with QRS duration ≥ 120 ms were enrolled. IVCD was defined as a QRS duration ≥ 120 ms without typical features of LBBB or RBBB, according to accepted criteria [11]. The study protocol was approved by the Institutional Review Board.

Electro-anatomical mapping

Coronary venous 3D electro-anatomical mapping was performed at the time of CRT implantation as described previously [10]. In brief, prior to LV lead placement, a 0.014 inch guidewire (Vision Wire, Biotronik SE & Co.KG), which permits unipolar sensing and pacing, was inserted into the coronary sinus and connected to an EnSite NavX system (St Jude Medical, St Paul, MN, USA). The guidewire was manipulated to all coronary sinus branches located on the inferolateral or anterolateral LV wall as defined by the American Heart Association (AHA) 17-segment heart model [12], creating an anatomic map along with determining local electrical activation time during intrinsic ventricular activation. Local activation time was measured in milliseconds (ms) from QRS onset on surface ECG and expressed as percentage of total QRS duration. Activation of the LV lateral wall was considered delayed if maximal activation time measured at the LV lateral wall (maximal LVLW-AT) exceeded 75% of the total QRS duration. This definition was chosen because epicardial mapping via the coronary veins is limited by coronary venous anatomy, which means that some areas cannot be mapped because they do not contain any veins. Therefore, the latest activated LV region

can only be identified using coronary venous mapping by relating the electrical activation time of the anatomical region to its time point within the QRS complex. We believe that an electrical activation time exceeding 75% of QRS duration is a reasonable definition for delayed LV lateral wall activation, especially since previous studies have shown that positioning of the LV lead over a region of the heart with an electrical delay of just over 50% of the total QRS duration is associated with a superior CRT outcome [9, 13].

After the mapping procedure, the LV lead was positioned in or as close as possible to the region of maximal electrical delay based on current evidence and recommendations [14, 15].

ECG assessment

Twelve-lead ECGs were assessed by two experienced clinicians blinded to patient data and mapping results. Any disagreement was reviewed together before achieving consensus. QRS duration was assessed in the lead with the widest QRS. The QRS axis was derived from the automatically computed value on the ECG. Left and right axis deviation, as well as the presence of left anterior and posterior fascicular block, were defined according to AHA/ACC/HRS criteria [11], excluding the criterion of QRS duration <120ms because of coexisting IVCD. QRS fragmentation was defined according to Das et al. [16]; >2 notches in at least 2 contiguous leads, or multiple notches in the R wave, or >2 notches in the nadir of the S wave. The region of notching was classified as anterior when observed in leads V1-5, inferior when observed in II, III, aVF and lateral when observed in leads I, aVL, V6.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation and were compared using the Mann-Whitney U-test. Categorical variables are expressed as observed numbers and percentage values, and were compared using Fisher's exact-test. Statistical significance was accepted at the 95% confidence interval ($p < 0.05$). Statistical analysis was performed using SPSS version 22.0 (SPSS Inc.) software.

Results

Patient characteristics

Twenty-three patients with IVCD referred for CRT implantation were included in this study. The patient characteristics are presented in Table 1.

Table 1. Patient characteristics (n=23)

Variable	Value
Men	16 (64)
Age	72±10
Ischemic aetiology	18 (72)
NYHA class	
II	15 (60)
III	9 (36)
IV	1 (4)
LVEF (%)	29±5
QRS duration (ms)	158±23

Values are in means ± standard deviations or numbers (percentage values) NYHA = New York Heart Association, LVEF = left ventricular ejection fraction

Results of electro-anatomical mapping

Coronary venous electro-anatomical mapping was accomplished without complications in all patients. A mean number of 2.8 ± 0.7 coronary sinus branches were mapped during the procedure, of which 1.9 ± 0.5 were located on the LV lateral wall. Three-dimensional electrical activation maps were generated from 79 ± 18 unique anatomic points. Mapping time was 18 ± 5 minutes, fluoroscopy time during the entire procedure 19 ± 4 minutes, and total radiation dosage 4031 ± 2064 cGy x cm².

Delayed LV lateral wall activation, defined as maximal LVLW-AT exceeding 75% of the total QRS duration, occurred in 12/23 (52%) patients. In Table 2, LVLW-AT data are presented for patients with and without delayed LV lateral wall activation. In patients with delayed LV lateral wall activation, maximal LVLW-AT was 133 ± 20 ms (83±5% of QRS duration) and ranged from 103 to 181ms (75%-93% of QRS duration). In patients without delayed LV lateral wall activation, maximal LVLW-AT was 100 ± 19 ms (64±9% of QRS duration) and ranged from 69 to 138ms (45-74% of QRS duration). The number of lateral veins that were mapped did not differ between patients with and without delayed LV lateral wall activation (p=0.92). Also, baseline characteristics did not differ between the two groups. In patients with delayed LV lateral wall activation, the most delayed lateral region was more frequently located on the 'basal' lateral wall than in patients without delayed LV lateral wall activation (p=0.03).

Table 2. LV lateral wall activation time and latest activated regions in patients with and without delayed LV lateral wall activation.

Variable	Delayed LV activation (n=12)	No delayed LV activation (n=11)	P
Maximal LVLW-AT(ms)	133 (± 20)	100 (± 19)	
Maximal LVLW-AT (% of QRS)	83 (± 5)	64 (± 9)	
Region of maximal LVLW-AT			
Basal anterolateral	7 (58.3)	2 (18.2)	0.09
Basal inferolateral	4 (33.3)	3 (27.3)	1.00
Mid anterolateral	1(8.3)	4 (36.4)	0.16
Mid inferolateral	0	2 (18.2)	0.22

Values are in means ± standard deviations or numbers (percentage values). LVLW-AT = left ventricular lateral wall activation time.

Figure. 1 shows examples of coronary venous electro-anatomical mapping of 2 patients with and without delayed LV lateral wall activation. In the example shown in panel A, the coronary sinus and three side branches located on the anterior, inferior and inferolateral wall were mapped. Delayed activation (139ms [80% of QRS duration]) was found in the basal region of the inferolateral vein. In the example shown in panel B, coronary veins on both the anterolateral and inferolateral wall were mapped, but delayed activation could not be measured in either vein.

Figure 1. Examples of coronary venous electro-anatomical mapping.

Coronary venous electro-anatomical mapping of a patient with (A) and without (B) delayed LV lateral wall activation together with the corresponding 12-lead ECGs (left). Local electrical activation time was measured in milliseconds from QRS onset and projected on the maps using colour coding. Earliest activation is presented in white and red and latest activation in blue and purple. Grey indicates regions mapped too sparsely to fill data. AT = electrical activation time, AIV = anterior interventricular vein, MCV = mid cardiac vein, ILV = inferolateral vein, ALV = anterolateral vein, CS = coronary sinus.

ECG parameters in patients with and without delayed LV lateral wall activation.

The ECG characteristics of patients with and without delayed LV lateral wall activation are presented in table 3. QRS duration did not differ between patients with and without delayed LV lateral wall activation. Neither was there a difference in the prevalence of left axis deviation, right axis deviation, left anterior fascicular block, left posterior fascicular block or QRS fragmentation between patients with and without delayed LV lateral wall activation. There was also no difference in the distribution of the regions with QRS fragmentation between the two groups.

Table 3. ECG parameters in patients with and without delayed activation of the LV lateral wall

Variable	Delayed LVLW activation (n=12)	No delayed LVLW activation (n=11)	P
QRS duration (ms)	159 ($\pm$ 19)	157 ($\pm$ 27)	0.46
LAD	5 (46)	6 (55)	1.00
RAD	1 (9)	0	1.00
LAFB	4 (36)	6 (55)	0.67
LPFB	1 (9)	0	1.00
QRS fragmentation	7 (64)	5 (46)	0.67
Region of QRS fragmentation			
Anterior	2 (18)	2 (17)	1.00
Inferior	4 (33)	3 (27)	1.00
Lateral	5 (42)	2 (18)	0.37

Values are expressed as means $\pm$ standard deviations or numbers (percentage values). LVLW = left ventricular lateral wall, LAD = left axis deviation, RAD = right axis deviation, LAFB = left anterior fascicular block, LPFB = left posterior fascicular block.

Discussion

Delayed activation of the LV lateral wall is considered the electrical substrate underlying LV dysfunction amenable to CRT, and may be present in patients without LBBB QRS morphology [6, 17]. The present study demonstrates that coronary venous electro-anatomical mapping can be used at the time of CRT implantation to determine the presence of delayed LV lateral wall activation and specify the latest activated region in CRT candidates with IVCD. Delayed LV lateral wall activation was found in approximately half of the patients. In patients with delayed activation, the location of the latest activated region was practically confined to the 'basal' lateral wall, whereas patients without delayed activation showed a more heterogeneous distribution of the latest activated region on the LV lateral wall. Baseline 12-lead ECG QRS characteristics were not able to identify the presence of delayed LV lateral wall activation as determined by coronary venous electro-anatomical mapping.

Delayed LV lateral wall activation in IVCD patients.

The present study demonstrates that coronary venous electro-anatomical mapping can be used at the time of CRT implantation to identify IVCD patients with delayed LV lateral wall activation. Detailed 3D LV mapping in patients with IVCD has so far been limited to a single case series recently published by Ploux et al [6]. The authors characterised LV epicardial electrical activation of 15 IVCD patients referred for CRT implantation using non-invasive

3D electrocardiographic imaging and found significant LV activation delay in 3 (20%) of these patients. Additionally, the presence of LV activation delay in IVCD patients was shown to be associated with clinical response to CRT. Several other studies have also suggested that CRT may be beneficial in a subset of non-LBBB patients with evidence of LV activation delay [9, 18, 19].

Latest activated region.

In patients with delayed LV lateral wall activation, the region of latest activation was similar to that observed in previous mapping studies of patients with LBBB [2, 3, 6, 20]. This observation suggests the presence of a conduction disturbance at a similar level of that observed in patients with LBBB despite the absence of a typical LBBB morphology on surface ECG. On the other hand, in patients without delayed LV lateral wall activation, the location of the latest activated region was more heterogeneous, which suggests that QRS widening in these patients may have a different underlying aetiology such as LV hypertrophy, LV enlargement, myocardial fibrosis or conduction disturbances located more distally than the usual sites at the bundle branches [3]. These findings correspond with the results of a recent study by Eschaliér et al. who characterised a subset of patients with IVCD that had ventricular conduction properties similar to that of LBBB patients, but did not display typical LBBB characteristics on the 12-lead ECG [21].

Diagnostic performance of ECG parameters for delayed LV lateral wall activation

Patient selection in CRT has been primarily based on a wide QRS complex [5]. Yet in the present study we found that a larger QRS duration was not associated with delayed LV lateral wall activation in patients with IVCD. This may be explained by the fact that QRS duration is merely a surface depiction of biventricular depolarisation time, sensitive to conduction delay in either the left or right ventricle.

With respect to the frontal QRS axis, neither left nor right axis deviation was associated with delayed LV lateral wall activation in the present study. Especially the lack of delayed LV lateral wall activation in patients with left axis deviation was remarkable, as this is considered a sign of LV involvement in conduction delay. A possible explanation for this finding is that in heart failure patients, axis deviation may often be the result of a change in the anatomical position of the heart due to, for instance LV dilatation, rather than an actual change in the vector of electrical conduction [22, 23]. Although even more specific for left ventricular conduction delay, in this study neither anterior nor posterior fascicular block was associated with the presence of delayed LV lateral wall activation.

Given the fact that the presence of myocardial scar and ischaemic cardiomyopathy in a more broader sense have been shown to reduce the likelihood of a favourable response to CRT [24-26], we hypothesised that ECG markers of myocardial scarring/fibrosis have an inverse relationship with delayed LV lateral wall activation. Various ECG parameters have been related to the presence or extent of myocardial scarring [27]. Yet the majority of these parameters have not been validated in patients with ventricular conduction disorders. QRS fragmentation has previously been shown to indicate the presence of myocardial scarring and to predict worse outcome in patients with conduction disorders [16, 28]. However, in the present study a significant relationship between QRS fragmentation and delayed LV lateral wall was not found. These results are in line with the findings of two earlier studies that found no relation between the presence of QRS fragmentation and echocardiographic response to CRT [29, 30].

Limitations

The present study demonstrates the presence of delayed LV lateral wall activation in approximately 50% of IVCD patients. Admittedly, the study lacks data on acute haemodynamic response and long-term clinical outcome. Whether delayed LV lateral wall activation is also associated with CRT response in this group of patients needs to be confirmed in subsequent, larger and long-term follow-up studies. The small sample size of this study precludes extrapolating the results in our cohort of IVCD patients to larger populations. Nevertheless, the study population was large enough to demonstrate the feasibility of coronary venous electro-anatomical mapping to determine the presence of delayed LV lateral wall activation in CRT candidates with IVCD.

Conclusion

Coronary venous electro-anatomical mapping can be used at the time of CRT implantation to identify IVCD patients with delayed LV lateral wall activation, who are more likely to benefit from CRT. Baseline QRS characteristics on the ECG seem unable to identify delayed LV lateral wall activation in this subgroup of patients.

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Editorial comment: To implant or not to implant? That is the unsolved question concerning heart failure patients with non-LBBB.

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Comment

With their article published in this issue of the Journal, Stipdonk and colleagues touch on a subject bearing significant clinical implications [1].

The inception of the concept of electrical cardiac resynchronization therapy (CRT) was followed by an unprecedented clinical success story for heart failure patients suffering from bundle branch block. Initially we embraced this concept for all patients with long QRS duration independent of the morphology of the bundle branch block [2, 3]. As in all therapies, there were some non-responders; however, for a highly invasive therapy this was unacceptably high at 30–40%. Therefore considerable efforts have been put into echocardiography to improve patient selection as well as optimise atrioventricular and interventricular stimulation patterns.

These echocardiographic studies revealed that also patients with smaller QRS durations might suffer from delayed left ventricular wall activation leading to another multicentre study feeding the aspiration to further expand the indication for CRT. However, the higher the rise, the greater the fall. Consecutive studies painstakingly showed that CRT therapy might not only be ineffective but actually detrimental for the patients [4].

In the present guidelines, echocardiographic parameters for left ventricular activation delay are irrelevant for the CRT indication. Meta-analysis of the landmark CRT studies displays a dependency of the responder rate on QRS duration and left bundle branch block (LBBB) morphology. Therefore, only LBBB morphology represents a class I indication for CRT, whereas non-LBBB morphology was downgraded to a class IIa (QRS > 150ms) and IIb indication (QRS 120–150ms), respectively [5].

This re-evaluation was backed up by the results of the long-term follow-up of the MADIT-CRT study which revealed an improved prognosis solely for patients with LBBB, whereas the prognosis for patients with non-LBBB was worsened [6]. Non-LBBB is associated with a conglomeration of diverse causes which might also show delay in left ventricular wall activation.

This dilemma is obvious: On the one hand there are many heart failure patients with non-LBBB who are at the end of the road for medical therapy and urgently need further treatment options. On the other hand, we need some certainty that we do not harm these patients by implanting a CRT-D system.

The guidelines concerning implantation of CRT-D in patients with non-LBBB are reflective of this dilemma. They advise us to implant these patients only after careful selection. However, they do not tell us how to select [4].

This represents the value of the article from the Maastricht Group. By demonstrating the feasibility of coronary venous electro-anatomical mapping, they break new ground in proposing an individualised method of screening patients with non-LBBB for eligibility for CRT implantation, which might one day be part of the selection process.

In their study they draw the conclusion that neither QRS duration nor morphology are adequate discriminators for the selection process, already hinting that this selection might not be an easy one.

Likewise they consistently demonstrate that the latest activation region was consistently at the basal lateral wall, which raises a couple of questions which need to be answered in further systematic studies:

1. Do we really have to target our stimulation at the latest point of activation? This question is so important as it influences the way we interpret an electrical mapping which often displays a rather homogenous spread of activation with the last 10 or 20% of the map being activated very slowly. This is also closely related to the question how epicardial and endocardial mapping correlate, which seems close according to our own experience. Basal stimulation at a point where the coronary venous anatomy is still rather broad would be challenging and implies a call for the more frequent use of quadripolar or mechanically fixable electrodes which, due to their special pre-specified form, would allow easier positioning of an electrode in this target region. Therefore, the question has to be answered as to whether stimulating at this point yields haemodynamic benefit or if it is not sufficient to target some point where 80 or 90 % homogenous activation has passed and is located less basally. This brings up the next question:
2. Does our electro-anatomical activation correlate to our haemodynamic activation? There are some promising studies showing a correlation when comparing electrode delays, but further substantiating the above study is a sine qua non for further use of this method and it brings up the final and all-dominant question:
3. Will heart failure patients with non-LBBB selected for and implanted according to individualised electro-anatomical mapping show clinical benefit in the furnace of a randomised clinical trial?

There is a lot of a fascinating and exciting but also sobering and disillusioning road ahead to be filled with studies like the above, to form the pieces of a puzzle which some day might yield the whole picture, allowing us to finally answer the question if and how to implant these patients.

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**QRS area is a strong determinant of
outcome in cardiac resynchronization
therapy**

The background of the slide features several thin, black lines that are mostly horizontal but have a slight downward slope from left to right. A single, thin red line is positioned lower on the page, sloping downwards from left to right, intersecting the black lines.

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ABSTRACT

Background The combination of left bundle branch block (LBBB) morphology and QRS duration is currently used to select patients for cardiac resynchronization therapy (CRT). These parameters, however have limitations. This study evaluates the value of QRS area compared to that of current parameters and its additional value, in the association with clinical and echocardiographic outcomes in a large cohort of CRT patients.

Methods and Results A retrospective multicentre study was conducted in 1,492 CRT patients with a baseline 12-lead ECG. LBBB morphology, QRS duration and QRS area were evaluated for their association the occurrence of the combined primary endpoint of all-cause mortality, cardiac transplantation and left ventricular assist device (LVAD) implantation. Secondary endpoints were heart failure hospitalization within the first year after implantation, and echocardiographic reduction in left ventricular end-systolic volume (LVESV). During a mean follow period of 3.4 years, 32% of patients reached the primary endpoint. The association of QRS area with all outcomes was stronger than that of LBBB morphology and QRS duration separately, and at least as strong as the combination. QRS area identified patients that did not experience the primary endpoint better than QRS morphology and QRS duration (AUC 0.61 vs. 0.55 and 0.51 respectively). Furthermore, QRS area identifies patients with echocardiographic remodelling in response to CRT better than QRS morphology and duration (AUC 0.69 vs. 0.58 and 0.58, respectively). QRS area was the only independent electrocardiographic determinant associated with the primary endpoint; HR 0.50 [0.35, 0.71]. Furthermore, QRS area showed significant association with all outcomes in patients without LBBB and QRS greater than 150ms.

Conclusion QRS area has a strong association to clinical and echocardiographic response to CRT, at least as strong as current patient selection parameters. Moreover QRS area is associated to response in patients without a wide LBBB.

Introduction

Cardiac resynchronization therapy (CRT) is an established treatment for patients with heart failure (HF) and ventricular conduction abnormalities. In these patients, CRT has been shown to improve exercise tolerance and quality of life, and to reduce HF hospitalizations and mortality [1, 2]. However, identification of patients that benefit from CRT remains a challenge [3]. Initial guidelines on patient selection suggested QRS duration as a marker of the degree of electrical dyssynchrony and suitability for CRT [4]. More recent subanalyses of randomized clinical trials showed that left bundle branch block (LBBB) morphology has a strong association with CRT response [5, 6]. Current guidelines therefore include QRS duration and LBBB morphology to classify patients referred for CRT to a level of recommendation for implantation, as illustrated by table 1 [7]. The lower level of evidence of the recommendation for patients not having LBBB and a QRS duration > 150ms (class I indication) illustrates the existence of uncertainties about a significant portion of patients. Uncertainties in using QRS duration and LBBB morphology to properly identify patients that will respond to CRT may lie in caveats of the individual parameters. QRS widening may be caused by many different pathophysiological processes [5, 8] and the value of the QRS duration depends on how it is measured, with up to 20ms variability [9]. A disadvantage of the use of LBBB is, that there are various LBBB definitions [10], many of which consist of criteria that are sensitive to subjective interpretation.

Vectorcardiography (VCG) has recently been introduced as an alternative way to assess suitability for CRT. In particular the area under the three-dimensional QRS complex, QRS area showed a strong association with CRT response [11-14]. The ratio behind this parameter is that it expresses non-opposed electrical forces and high values of these parameters may therefore indicate dyssynchronous electrical activation. This hypothesis was confirmed in a recent study that showed that a large QRS area corresponds with delayed activation of the left ventricular postero-lateral wall, independently of QRS morphology [13].

The present study was undertaken to evaluate the value of QRS area in a large patient cohort undergoing CRT implantation on clinical and echocardiographic outcome. Special attention was paid to the added value of the QRS area in patients who do not have a LBBB with QRS duration > 150ms (class I indication).

Methods

The Maastricht-Utrecht-Groningen (MUG) study cohort was used for retrospective analysis of consecutive patients implanted with a CRT-device in 3 university hospitals in the Netherlands, from January 2001 up to January 2015 (Maastricht University Medical Centre, January 2010 – December 2015; University Medical Centre Utrecht, January 2005 – December 2015; University Medical Centre Groningen, January 2001 – December 2015). No formal inclusion criteria on LVEF, NYHA or QRS duration were set in advance. Patients were included if a baseline digital 12-lead ECG was available and if CRT was continued until end of follow-up. Patient selection, device implantation, lead positioning, as well as device and patient follow-up was according to then prevailing guidelines and local protocols. No formal optimization protocol was conducted to the patient cohort from either hospital, but was up to the discretion of the patients' physician.

Patient population

The MUG cohort consisted of a total of 1,946 patients with baseline 12-lead ECG available and continued CRT during follow-up. For the present study, we considered patients selected for de novo CRT device implantation according to current guidelines [7]. Accordingly, patients were excluded when baseline ECG showed right ventricular pacing (340 patients; 17%) or QRS duration less than 120ms (114 patients; 6%). The patient selection process is shown in figure 1.

Baseline data were retrieved from the local hospital patient information systems. Patient characteristics like HF aetiology and classification, comorbidity and medication were retrieved from patient history and referral letters. HF aetiology was deemed ischemic when there was clear evidence of myocardial infarction or CABG in the medical history. Device data were retrieved from specific device databases. Left ventricular lead location was judged from the fluoroscopic images or chest X-ray. The Dutch Central Committee on Human-related Research (CCMO) allows the use of anonymous data without prior approval of an institutional review board provided that the data are acquired for routine patient care. All data used were handled anonymously. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. As ongoing research and analyses on these data prohibit the release of the findings.

Electro- and vectorcardiography

Recorded baseline 12-lead ECGs were stored digitally in the MUSE Cardiology Information system (GE Medical System) and were evaluated for QRS duration and baseline ECG parameters using the automated ECG readings. LBBB morphology was defined according to accepted criteria [15]. Including QRS duration ≥ 120 ms, QS or rS in lead V1, broad (frequently notched or slurred) R waves in leads I, aVL, V5, or V6, and absent Q waves in leads V5 and V6. Patients were grouped according to the level of indication for CRT according to current guideline recommendations (Supplementary Table 1A) [7].

QRS area was calculated as described previously [16, 17]. In brief, the original digital signals were extracted from the PDF files stored in the MUSE system. Subsequently, custom Matlab software (MathWorks Inc., Natick, Massachusetts) was used to convert the 12-lead ECG into the three orthogonal VCG leads (X, Y, and Z-) using the Kors conversion matrix (18). QRS area was calculated as the sum of the area under the QRS complex in the calculated vectorcardiographic X, Y and Z lead [QRS area = (QRSarea,x2 + QRSarea,y2 + QRSarea,z2)1/2]. Figure 2 shows two examples of 12-lead ECGs converted to QRS area.

Study Endpoints

Patients were followed for 3.4 ± 2.4 years. The primary endpoint was a combination of LV assist device implantation, cardiac transplantation and all-cause mortality. Information was obtained from hospital records, linked to municipal registries. Secondary endpoints were HF hospitalization within the first year after CRT device implantation. The cause of hospitalization was considered HF when described as such in discharge forms by responsible physicians. Data was considered missing when follow-up was not in the centre where the implantation was performed. Another secondary endpoint was the reduction in left ventricular end-systolic volume (LVESV) determined by echocardiography at 6 to 12 months after implantation. Left ventricular dimensions and ejection fraction measurements were calculated by Simpsons modified biplane method. Echocardiographic CRT response was defined as a reduction in LVESV $\geq 15\%$.

Statistical analysis

The statistical analysis was performed using IBM SPSS statistics software version 21 (SPSS Inc., Chicago, IL, USA). Continuous and discrete variables are presented as mean $\pm$ standard deviation (SD) and counts (percentages), respectively. Dichotomous variables were compared using a X2 test. Continuous variables were compared using a Student t-test. Overall differences were evaluated for ECG parameters and QRS area. Stratification of QRS area for presentation purposes and initial analyses was based on median values when dichotomous. QRS area was further stratified into quartiles for the purpose of evaluation of its distinctive value next to that of accepted 4 groups based on QRS duration and LBBB morphology. Furthermore, patients without a class I indication (LBBB morphology and QRS duration ≥ 150 ms) were evaluated separately in the same way.

Kaplan-Meier survival analyses and cumulative hazard analyses were used when appropriate to evaluate the association between electrical parameters and the primary outcome. The log-rank test was used to determine the difference in survival probabilities between groups. The diagnostic performance of the electrical parameters for identifying patients without clinical endpoints or with echocardiographic response to CRT was evaluated using unadjusted receiver operating characteristic curve (ROC) analysis.

Cox and Logistic regression analyses were used to assess univariable and multivariable adjusted effects of ECG parameters and QRS area, on the association with the primary outcome and secondary outcomes when appropriate. Hazard and Odds ratios were reported respectively. Multivariable regression analyses of ECG parameters included known parameters associated with outcome to CRT (gender, age at implantation, HF etiology, history of atrial fibrillation, device type, LV lead position, baseline NYHA, baseline EF, and use of a betablocker, ACE-inhibitor or angiotensin receptor blocker, and mineralocorticoid receptor antagonist). Additional adjustment was done for interaction-terms and proportional hazards assumption was tested graphically. Comparison of continuous echocardiographic values was performed using 1-way ANOVA. Follow-up paired comparisons were made using the Tukey test. A 2-sided P value < 0.05 was considered statistically significant.

Results

Baseline Characteristics

The 1,492 patients included in the current analysis represent a typical CRT population, with a mean age of 67 years and predominantly male (71%). An ischemic aetiology was present in 50% of patients and most were in NYHA functional class II or III (93%). (Table 2) Mean QRS duration was 160 ± 21 ms, LBBB morphology was present in 78% of patients and 15% of patients showed atrial fibrillation on the baseline ECG.

Vectorcardiographic analysis was not possible in 17 (1%) patients due to frequent extrasystolic beats. Mean QRS area was $116 \pm 54 \mu\text{Vs}$. 56% and 23% of patients showed LBBB with QRS duration ≥ 150 ms and < 150 ms, respectively, and 12% and 9% of patients showed non-LBBB in combination with QRS duration ≥ 150 ms and < 150 ms, respectively. (Table 1)

Table 1. Baseline characteristics.

	Total* n=1,492
Age (years)	67 ± 11
Female gender %	29
BMI (m/kg^2)	27 ± 5
Atrial fibrillation %	15
Ischemic CMP %	50
Diabetes Mellitus %	25
Hypertension %	42
LVEF %	25 ± 9
LVEDV (ml)	219 ± 88
LVESV (ml)	168 ± 78
NYHA I %	2
NYHA II %	39
NYHA III %	54
NYHA IV %	5
NTproBNP (pmol/l)	334 ± 591
CreatClear (ml/min)	71 ± 32
Beta-blocker %	82
ACEi/ARB %	90
MRA %	45
CRT-D %	93
LV lead position	
Anterior %	1
Anterolateral %	11
Lateral %	36
Posterolateral %	44
Posterior %	8

Table 1. Continued

	Total* n=1,492
QRS duration (ms)	160±21
QRS area (μVs)	116±54
LBBB morphology %	78
LBBB/QRS ≥150ms %	56
LBBB/QRS<150ms %	23
Non-LBBB/QRS ≥150ms %	12

*Total population including 17 patients without QRS area calculation available. ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CMP, cardiomyopathy; CRT-D, cardiac resynchronization therapy with defibrillator function; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; VCG, vectorcardiography.

Primary endpoint

Information on the primary endpoint of LVAD implantation, cardiac transplantation or all-cause mortality was available in 1,491 patients. One patient was lost to follow-up due to emigration. During the follow-up time of 3.4 ± 2.4 years, 472 patients (31.7%) reached the primary endpoint.

Survival free from the primary endpoint was significantly different in patient groups stratified to LBBB morphology ($p<0.001$), QRS duration ($p=0.009$), and QRS area ($p<0.001$) (figure 3). The association with the combined endpoint was stronger in patients with QRS area $\geq 109\mu\text{Vs}$ compared to patients with QRS area $< 109\mu\text{Vs}$ (HR 0.49 [0.41, 0.59]), than in patients with LBBB morphology compared to non-LBBB morphology, and patient with QRS duration $\geq 150\text{ms}$ compared to those with QRS duration $< 150\text{ms}$ (HR 0.54 [0.43, 0.68], and HR 0.76 [0.62, 0.94], respectively). (Figure 3)

Figure 3. Kaplan-Meier estimates of survival free of the primary endpoint (combination of LVAD, cardiac transplantation or all-cause mortality).

Patients are stratified to (A) LBBB morphology, (B) QRS duration ($\geq/\lt 150\text{ms}$) and (C) QRS area ($\geq/\lt 109\mu\text{V}$). LBBB, left bundle branch block; LVAD, left ventricular assist device.

ROC analysis showed that QRS area improved identification of patients that did not experience the primary endpoint, compared to QRS morphology and duration (AUC 0.61 vs. 0.55 and 0.51 respectively). (Supplementary figure 1). The occurrence of the primary endpoint was significantly different between patient groups when stratified according to the combination of QRS duration (120-150ms vs. ≥ 150 ms) and morphology (LBBB vs. non-LBBB) ($p < 0.001$). Figure 4A shows that these differences were most clear between the subgroup of patients with LBBB and QRS duration ≥ 150 ms (class I indication) and the other subgroups (HR 0.71 [0.56, 0.89]).

Figure 4. Kaplan-Meier estimates of survival free of the primary endpoint using comparing the QRS area and the combination of LBBB morphology and QRS duration.

(A) The combination of QRS duration and morphology divides patients into subgroups according to presence of LBBB and QRS duration $< \text{or} \geq 150$ ms (corresponding to current guideline recommendations). (B) Subgroups of QRS area are based on quartiles. (C) Patients without a guideline class I indication [10] (without LBBB and QRS duration ≥ 150 ms) are stratified to QRS area $< \text{or} \geq 109 \mu\text{Vs}$. (D) Patients with a guideline class I indication [10] (with LBBB and QRS duration ≥ 150 ms) are stratified to QRS area $< \text{or} \geq 109 \mu\text{Vs}$. LBBB, left bundle branch block; LVAD, left ventricular assist device.

Pairwise comparison showed that patients with LBBB and QRS duration < 150 ms have a significantly higher event free survival than patients with non-LBBB and QRS duration ≥ 150 ms ($p = 0.025$, HR 0.72 [0.54, 0.96]). QRS duration did not affect the association with the primary endpoint in the non-LBBB subgroups.

A clearer separation in the occurrence of the primary endpoint was achieved when stratifying patients to quartiles of QRS area. Figure 4B shows significant deviation of the Kaplan-Meier estimates of survival free of events between the quartiles. Pairwise comparison shows a significantly higher event free survival in patients with QRS area $\geq 150 \mu\text{Vs}$ compared to those with QRS area of 109-150 μVs ($p = 0.004$, HR 0.64 [0.47, 0.87]). Patients with QRS area between 109-150 μVs had a higher event free survival compared to patients with QRS area between 75-108 μVs ($p < 0.001$, HR 0.60 [0.46, 0.77]). The occurrence of the primary event did not significantly differ between patients with QRS area between 75-108 μVs and below 75 μVs . (Figure 4B) The analysis of QRS area in patients without a class I indication showed that patients with QRS area $\geq 109 \mu\text{Vs}$ had a significantly higher event free survival from

the primary endpoint than the patients with a QRS area <109 μ Vs, with a relative risk reduction of 49% ($p<0.001$, HR 0.51 [0.36, 0.73]). (Figure 4C) In the group of patients with a class I indication for CRT, patients with QRS area $\geq 109\mu$ Vs also showed a significantly higher event free survival than those with QRS area <109 μ Vs, with a relative risk reduction of 46% ($p<0.001$, HR 0.54 [0.41, 0.70]). (Figure 4D)

A multivariable regression model for the entire cohort, including the combination of LBBB and QRS duration and quartiles of QRS area showed that only QRS area remained significantly associated with the primary endpoint ($p<0.001$, HR 0.75 [0.69, 0.83]), whereas the combination of LBBB and QRS duration was not independently associated to the occurrence of events ($p=0.134$). (Table 2) Also in patients other than those with LBBB and QRS duration ≥ 150 ms the association with the primary endpoint was only significant for QRS area ($p<0.001$, HR 0.49 [0.34, 0.71]), and not for QRS duration or LBBB morphology ($p=0.094$ and $p=0.671$ respectively). (Table 2)

Table 2. Uni- and multivariable logistic regression for ECG parameters and the association with clinical outcomes and echocardiographic response to CRT.

		Univariable Regression		Multivariable Regression	
	Variable	p	OR/HR* [95% CI]	p	OR/HR* [95% CI]
LVAD, cardiac transplantation, all-cause mortality					
All	LBBB + QRSd	<0.001	0.80 [0.73, 0.86]	0.134	0.93 [0.69, 1.02]
	QRS area quartiles	<0.001	0.73 [0.67, 0.79]	<0.001	0.75 [0.69, 0.83]
Non-Class I	LBBB morphology	0.032	0.76 [0.59, 0.98]	0.671	0.93 [0.66, 1.30]
	QRSd	0.049	0.77 [0.59, 0.99]	0.094	0.74 [0.52, 1.05]
	QRS area	<0.001	0.51 [0.36, 0.73]	<0.001	0.49 [0.34, 0.71]
Class I	QRS area	<0.001	0.54 [0.41, 0.70]	-	-
HF hospitalization within 1 yr of implantation					
All	LBBB + QRSd	0.030	0.81 [0.67, 0.98]	0.711	0.96 [0.76, 1.21]
	QRS area quartiles	0.004	0.74 [0.61, 0.91]	0.019	0.76 [0.60, 0.96]
Non-Class I	LBBB morphology	0.483	0.81 [0.45, 1.46]	-	-
	QRSd	0.891	1.05 [0.55, 1.99]	-	-
	QRS area	0.085	0.44 [0.17, 1.12]	-	-
Class I	QRS area	0.001	0.43 [0.27, 0.70]	-	-
Echocardiographic responder					
All	LBBB + QRSd	<0.001	1.69 [1.47, 1.96]	0.002	1.29 [1.09, 1.52]
	QRS area quartiles	<0.001	1.82 [1.61, 2.07]	<0.001	1.65 [1.43, 1.90]
Non-Class I	LBBB morphology	0.004	1.85 [1.22, 2.80]	0.20	2.01 [1.12, 3.62]
	QRSd	0.324	0.79 [0.50, 1.26]	-	-
	QRS area	0.007	1.90 [1.19, 3.03]	0.031	1.70 [1.05, 2.76]
Class I	QRS area	<0.001	3.54 [2.38, 5.28]	-	-

*Odds and Hazard ratio are reported for Logistic and Cox regressions respectively, used when appropriate for the selected endpoint. HF, heart failure; LBBB, left bundle branch block; LVAD, left ventricular assist device; LVESV, left ventricular end-systolic volume, QRSd = QRS duration

Heart failure hospitalization

Data on HF hospitalization within 1-year after CRT implantation was available for 1,269 patients (85%). 85 (5.7%) patients had been hospitalized.

Patient groups stratified according to the combination of QRS duration and morphology did not significantly differ in the occurrence of HF hospitalization (Figure 5A). Patients stratified according to QRS area differed significantly with respect to the occurrence of HF hospitalization ($p=0.007$).

Figure 5. Kaplan-Meier estimates of survival free from HF hospitalization with the 1st year after implantation.

(A) The combination of QRS duration and morphology divides patients into subgroups according to presence of LBBB and QRS duration $<$ or $\geq$ 150ms (corresponding to current guideline recommendations). (B) Subgroups of QRS area are based on quartiles. (C) Patients without a guideline class I indication [10] (without LBBB and QRS duration $\geq$ 150ms) are stratified to QRS area $<$ or $\geq$ 109 μ Vs. (D) Patients with a guideline class I indication [10] (with LBBB and QRS duration $\geq$ 150ms) are stratified to QRS area $<$ or $\geq$ 109 μ Vs. HF, heart failure; LBBB, left bundle branch block; LVAD, left ventricular assist device.

In the ROC analysis the AUC was higher for QRS area than for QRS morphology or duration (0.62 vs. 0.54 and 0.56 respectively). (Supplementary figure 1) In a multivariable analysis, QRS area remained the only significant ECG parameter of HF hospitalization ($p=0.019$, HR 0.76 [0.60, 0.96]). (Table 2).

Echocardiographic outcome

Paired LVESV measurements at baseline and follow-up were available in 929 patients (62%). The average reduction in LVESV was $19\pm 32\%$. Echocardiographic response to CRT, defined as LVESV reduction $\geq 15\%$, occurred in 516 (56%) patients.

LVESV reduction was significantly larger in patients with LBBB with QRS duration $>$ 150ms compared to those with

QRS duration <150ms. (Figure 6A) Response rate ranged from 31% in non-LBBB with QRS duration <150ms to 60% in patients with LBBB and QRS duration $\geq$ 150ms.

QRS area provided significant separation in the extent of LVESV reduction between all subgroups, except between quartiles with QRS area between 75-108 μ Vs and <75 μ Vs ($p=0.223$). (figure 6B) Response rate ranged from 37% in patients with QRS area <75 μ Vs to 77% in patients with QRS area >150 μ Vs.

Stratification of patients without a class I indication according to QRS area ($\geq$ / $<$ 109 μ Vs) showed that mean reduction of LVESV was significantly larger in patients with QRS area $\geq$ 109 μ Vs than in those with QRS area <109 μ Vs (20 vs 7%), resulting in response rates of 54% and 38%, respectively ($p=0.009$, OR 1.90 [1.19, 3.03]). (Figure 6C) In patients with a class I indication, stratification to QRS area also resulted in significant separation of response rates ($p<0.001$, OR 3.54 [2.38, 5.28]) and mean reduction of LVESV (29 vs 12%). (Figure 6D)

Figure 6. Echocardiographic reduction in LVESV and response rate.

Echocardiographic LVESV reduction in percentage at follow-up echocardiography in patient groups stratified by (A) The combination of QRS duration and morphology divides patients into subgroups according to presence of LBBB and QRS duration < or $\geq$ 150ms (corresponding to current guideline recommendations). (B) QRS area stratified into quartiles. (C) Patient without a class I indication according to current guidelines [10] (LBBB and QRS duration $\geq$ 150ms) stratified to QRS area < or $\geq$ 109 μ Vs. (D) Patient with a class I indication according to current guidelines [10] stratified to QRS area < or $\geq$ 109 μ Vs. Mean and standard deviations are presented. The red reference line represents echocardiographic response, defined as $\geq$ 15% reduction of LVESV. In the bottom of the graph the % of response according to this definition is shown per patient group. LBBB, left bundle branch block; LVESV, Left Ventricular End-Systolic Volume.

Identification of echocardiographic responders was better with QRS area, than with QRS morphology or duration (AUC 0.69 vs. 0.58 and 0.58, respectively). (Supplementary figure 1) Logistic multivariable regression showed a significant independent association of QRS area to LVESV reduction $\geq$ 15% (HR 2.87 [1.91, 4.32], $p<0.001$). (Table 2) In patients without LBBB with QRS duration $\geq$ 150ms, LBBB morphology ($p=0.02$, HR 2.02 [1.12, 3.62]) and QRS area ($p=0.03$, HR 1.70 [1.05, 2.76]), but not QRS duration ($p=0.449$), were significantly associated to echocardiographic response in a multivariable adjusted model for the ECG parameters. (Table 2)

Discussion

The main findings of this study are that QRS area alone can stratify CRT patients at least as good as the combination of LBBB and QRS duration. In the present study QRS morphology and duration fail to differentiate CRT response in patients without a class I indication for CRT. However, QRS area proves to be an independent electrocardiographic determinant of clinical and echocardiographic outcomes to CRT in these patients.

Because QRS area is a simple and objective measurement, it may be a valuable alternative measure for selection of patients for CRT, especially in those patients that do not have a wide LBBB QRS complex on their baseline 12-lead ECG

Association of QRS area with CRT response

The results on the primary endpoint and on the secondary endpoint of heart failure hospitalization demonstrate that QRS area is stronger related to clinical outcome than QRS duration and LBBB separately. The finding of the strong association of QRS area with reverse remodelling in the present study is in line with previous studies [12, 14, 16, 11]. In a recent prospective study in 240 patients, Maass et al. showed that QRS area was the strongest VCG predictor of echocardiographic response to CRT that also outperformed QRS duration and LBBB morphology [14]. Besides the support of these findings from a considerably larger cohort, the present study compares the association of QRS area to the combination of LBBB morphology and QRS duration in the way it is used in current practice.

Moreover, the present study shows that QRS area is of particular value in the group of patients that is considered to have a class IIa or lower recommendation for CRT: those not having a LBBB and QRS duration >150 ms. Among 637 of these patients, 155 had a QRS area value above the median ($109\mu\text{Vs}$) of the entire cohort. In this subgroup of 155 patients clinical outcome was as good as that of patients with a class I (level of evidence A) indication (Figure 4 and 5) and echocardiographic response was close to that as well (60 vs. 54% responders; Figure 6). These observations are supported by uni- and multivariable regression analyses, showing that QRS area is the only ECG parameter, independent of the other ECG parameters, associated to clinical as well as echocardiographic response to CRT. The 50% reduction in relative risk of clinical events and over 90% increase in relative risk of significant echocardiographic response suggest important associations of QRS area with outcome. Although QRS area provides similar separation in the subgroup of patients with a class I indication for CRT (LBBB and QRS duration ≥ 150 ms), results in this group are less relevant to clinical practice, as CRT will be instituted in these patients in almost every case, despite the value of QRS area.

The strong association of QRS area with CRT response may be explained by several properties. First of all, QRS area is large in the presence of strong electrical forces pointing in a dominant direction. While QRS area depends on QRS duration, it is also larger in patients with LBBB than in those with other conduction abnormalities [12]. Moreover, a study using coronary venous electrical mapping demonstrated that a large QRS area is predictive of delayed LV activation, the most important electrical substrate of CRT [13]. In that study one patient with RBBB showed a large QRS area and in that particular patient the LV lateral wall was shown to be activated late. Moreover, QRS area is lower in patients with ischemic cardiomyopathy [12] and, more specifically in the presence of focal scar [19], conditions which are known to reduce the benefit of CRT. Therefore, it seems that QRS area is a comprehensive parameter, reflecting multiple factors that contribute to the benefit of CRT. Though, as reflected by the AUC values of the ROC curve analyses for identification of clinical and echocardiographic outcomes, QRS area is limited to identification of the electrical substrate and some properties of the myocardial disease. Clinical, and to less extent

echocardiographic outcomes to CRT are dependent on many more patient, disease and treatment properties than electrical substrate alone, however QRS area seems to improve contribution to the prediction of these outcomes compared to conventional ECG parameters.

Performance of conventional ECG parameters

Whereas many studies and meta-analyses have evaluated QRS duration and/or LBBB morphology and their association with outcome to CRT [5, 6, 20-22], not many have evaluated their combination in the way these markers are used in current practice.

Individual studies specifically evaluating the combination of QRS morphology and QRS duration have shown significant associations with outcome to CRT for QRS duration as a continuous parameter in QRS morphology subgroups. In a REVERSE study subanalysis, QRS duration as a continuous parameter was associated to echocardiographic LVESV reduction in LBBB and non-LBBB patient subgroups. This showed that in LBBB patients the reduction in LVESV was larger in patients with longer QRS duration, whereas there was no significant reduction in LVESV in non-LBBB patients, regardless of QRS duration [5]. Dichotomous evaluations of QRS duration fail to show any significant associations with outcomes. A recent evaluation by Khidir et al. in 973 patients confirmed the association of LBBB morphology with outcome to CRT, but showed no significant differences in QRS duration ($\geq$ / $<$ 150ms) subgroups within the LBBB and non-LBBB subgroups [23]. However, an evaluation of echocardiographic outcomes to CRT from the same groups in 1,467 patients, showed that, although different, there was a significant correlation between increasing QRS duration and echocardiographic reduction in LVESV and increase in LVEF both LBBB and non-LBBB patient subgroups [24].

A much larger evaluation of 24,169 Medicare beneficiaries in the National Cardiovascular Data Registry's ICD Registry between 2006 and 2009 who underwent CRT-D implantation, however did show significant associations of QRS duration with clinical outcomes in QRS morphology subgroups. Whereas in this analysis the subgroups of LBBB with QRS duration 120-149ms and non-LBBB with QRS duration $\geq$ 150ms failed to show significant differences. The stronger predictive effect of LBBB than of QRS duration, observed in all these studies seems in disagreement with the results from two meta-analyses. These studies failed to show an independent association of LBBB to outcome in a model including QRS duration [25, 26]. This discrepancy may be caused by the use of different definitions of LBBB in the trials included in these analysis, thus probably creating variability in the non-LBBB and LBBB subpopulations. These recent studies show the uncertainties in the way these ECG parameters are used for patient selection in CRT in current practice. Although QRS morphology and duration have proven valuable as individual markers of response, their combination has not. The results presented in this study add to this uncertainty. Moreover the conflicting results of previous studies may be the result of the caveats of the individual parameters. Which may be even greater when used in combination. Due to the heterogeneity of underlying causes of QRS broadening in patients other than broad LBBB [27], strict morphologic criteria may not be applicable. Furthermore, QRS duration may be prolonged because of excessive scarring or dilatation, as opposed to conduction delay in a narrow sense.

Clinical implications

The results from the present study provide important evidence that QRS area is a valuable additional electrocardiographic parameter that can be used to improve patient selection for CRT. Like QRS duration, it can be measured as a continuous variable, while the variability in its measurement is likely to be less than QRS duration.

After all, variability in indicating the beginning and end of the QRS complex greatly affect QRS duration, but hardly affect QRS area, since its value is largely determined by the amplitude of the QRS complex.

While some studies [11, 12] used digital ECG recordings, others, including the present study, extracted the original signals from PDF files stored in the ECG database using simple software. For future, wider application, it is possible to program current ECG equipment to automatically calculate QRS area in the way QRS duration is currently calculated. Automated QRS area calculation can be easily implemented in current ECG equipment because signal amplitudes are available and onset and end of QRS complex are already recognized by the software, and ECG equipment currently already convert the 12-lead ECG information into a vectorcardiogram, which however is currently not frequently used in clinical practice.

Limitations

Inherent limitations due to the studies' retrospective nature are selection, referral, and attrition biases. The retrospective design of our study prohibited the inclusion of a non-treated control group. Therefore, we do not know the absolute benefit of CRT compared to non-treated patients with respect to the primary clinical endpoint. However, the echocardiographic response is measured using each patient as his/her own control.

Conclusion

QRS area has a strong association with clinical and echocardiographic outcomes to CRT in this large population. Since the QRS area is a simple and objective measurement, it might be an alternative measure for selection of patients for CRT, especially in those patients that do not show a wide LBBB QRS complex on their baseline 12-lead ECG.

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Supplemental material

Supplementary table 1. Patient groups based on levels of indication for CRT implantation*.

ECG markers		Recommendation	(LOE)
QRS morphology	QRS duration		
LBBB	≥150ms	I	A
LBBB	<150ms	IIa	B
Non-LBBB	≥150ms	IIa	B
Non-LBBB	<150ms	IIb	B

LBBB, left bundle branch block; LOE, level of evidence

*Adapted from Epstein et al [7].

Part 2. Patient Management

Consensus of a Standardized Cardiac Resynchronization Therapy Care Pathway

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ABSTRACT

Aims: Cardiac resynchronization therapy (CRT) reduces mortality and morbidity in heart failure (HF) patients with conduction disturbances, a group of patients expected to grow substantially in the coming years. Currently a significant proportion of patients does not fully benefit from CRT. This seems partly caused by substantial heterogeneity of care. The objective of this design paper is to provide a uniform, multidisciplinary approach with structured aids for clinical CRT practice across Europe. This may reassure optimal benefit from CRT for HF patients, and reduce resource utilisation and healthcare costs.

Methods and results: Experienced electrophysiologists and HF cardiologists from 3 European expert centres (Maastricht University Medical Centre, the Netherlands; Liverpool Heart & Chest Hospital, England; and Rigshospitalet Copenhagen, Denmark) were invited to participate in discussion meetings focused on (1) identifying experienced problems in current clinical CRT care, (2) reviewing current evidence on these problems, and (3) providing simple and broadly applicable aids to solve these problems. This resulted in a consensus CRT care pathway, using a multidisciplinary approach, with concrete aids to provide effective and efficient CRT care.

Conclusion: This paper provides a concrete consensus CRT care pathway with structured aids to be used in daily clinical CRT care based on clinical experience and current evidence. Aiming to assure homogeneous CRT care in Europe, optimizing patient benefit and reducing resource utilisation and healthcare costs.

Introduction

Cardiac resynchronization therapy (CRT) is one of the most successful HF therapies that has emerged over the last few decades. Several randomized clinical trials have shown CRT to reduce symptoms of HF, improve exercise capacity and quality of life, as well as to reduce hospitalizations and mortality [1-4]. Furthermore, economic evaluations have shown it to be a cost-effective therapy in HF [5, 6]. Clinical guidelines of the European Society of Cardiology and the American College of Cardiology Foundation/American Heart Association endorse these results and promote utilisation of CRT in selected HF patients [3, 7-9].

Despite guidelines and experts' consensus, high variations in patient selection, implantation techniques, in-hospital management and follow-up are observed [10-12]. In part because of this, the percentage of patients experiencing limited benefit of CRT remains about 25-30%. This is, despite numerous efforts to improve the response to therapy over the last years. This emphasises the complex nature of CRT in HF and that it therefore requires thorough patient selection, deliberate device and LV lead implantation and a comprehensive follow-up [13-16]. Multiple studies have shown, that successful treatment of HF in general requires specialised (multidisciplinary) care [3, 15]. Therefore ideally, there should be a uniform, multidisciplinary approach to patient selection, therapy delivery and follow-up of patients post CRT device implantation [13].

In complex care pathways, checklists have shown to improve organisation structure, homogeneity in therapy and the ability to prevent complications. Moreover, checklists improve implementation of care pathways, especially in heart failure [17, 18]. Still, checklists are not typically used in CRT care.

Several major European hospitals, with great experience in CRT and organisation of CRT-care, have partnered in developing a structured CRT care pathway model using an integrated collaboration between the HF, electrophysiology (EP) and imaging departments. This best practice pathway model has been developed based on available clinical evidence and experts' consensus and has become part of the routine clinical care protocol in these centres. It aims at achieving 1) high quality, integrated care for the CRT patients 2) a proactive and structured approach to the improvement of the clinical response to CRT, and 3) control of the costs of providing care.

This paper is the first to provide a detailed format and structured aid for an optimised clinical CRT care pathway. The aim is to provide centres, whether implanting or following patients post- implantation, a framework to evaluate their current CRT care, identify opportunities for improvement and to provide standardized tools for CRT care management.

Methods

The CRT care pathway, and structured aids as described in this paper, are based on a series of discussions of current evidence with highly experienced physicians in CRT. The specialists involved were not appointed by any professional European or national association, but rather a group of experts experiencing the same clinical practice issues and recognizing the overall problem of heterogeneity of practice and related suboptimal treatment in CRT. Therefore there is no explicit endorsement of any professional organisation for the care pathway as described in this paper. The specialists involved were all experienced implanting and supervising CRT specialists, either primarily focussed on HF or EP, providing a multidisciplinary focus. Meetings based upon concerns about clinical CRT care as described in the introduction were initiated. Three expert centres (Maastricht University Medical Centre, the Netherlands; Liverpool Heart & Chest Hospital, England; and Rigshospitalet Copenhagen, Denmark) were invited to participate in these discussion meetings. First evaluating the 'current state' of CRT care in the hospitals involved, focussing on local issues related to the general problems in CRT care, and the processes involved. Hereafter, thorough analysis and literature review, with live and remote expert clinician-led consensus workshops were organised, involving both expert clinicians and external consultants. This methodology ensured that the consensus was driven by three imperatives: to deliver best clinical quality and safety outcomes for patients, to deliver the best possible patient experience and to optimise cost of care across the care continuum. The result was a "model CRT care pathway" with structured aids as described in this paper.

Results

CRT care pathway design

Figure 1 depicts an overview of the consensus CRT pathway. This model pathway was the result of the consensus meetings combining minimal medical content deemed necessary to guarantee adequate guidance of CRT patients and local experiences from CRT care processes. Individual steps in the model pathway will be described in detail.

Figure 1.

Figure 1. Continued

Consensus cardiac resynchronization therapy (CRT) pathway overview. Flow chart of CRT pathway steps a patient goes through in the pathway. Different steps (Referral review and pre-assessment clinic, implantation procedure, and follow-up management) are indicated with content of the assessments and structured aids available for the assessment.

Referral review

Patients referred for CRT should undergo careful evaluation. The referral letter should provide the patient characteristics consistent with a valid indication. The completeness of referral information and additional considerations are checked by a standardized checklist (figure 2).

Referral review checklist

Heart failure history	☐	Considerations
NYHA classification	☐	
CMP Etiology	☐	
OMT (≥ 6 months)	☐	
Antiplatelet therapy	☐	
Anticoagulation	☐	
Brady- and/or tachyarrhythmias	☐	
Upgrade	☐	
Pacemaker/Lead details	☐	
Additional evaluation	☐	Considerations
12-lead ECG (QRS ms, QRS morph)	☐	
Holter (VPB/SVT/NSVT)	☐	
Echocardiography (EF, RV function)	☐	
Ischemia detection	☐	
Add cardiac imaging (CMR, biopsy)	☐	
Co-morbidities	☐	Considerations
Thyroid disease	☐	
COPD	☐	
OSAS	☐	
Diabetes	☐	
Renal insufficiency (GFR/dialyses)	☐	
(treated) Malignancies	☐	
Cachexia or obesity	☐	
Anemia / Iron deficiency	☐	
Patient life-expectancy	☐	

Figure 2

Referral review. Considerations to be checked at referral review, to ascertain completeness of indication and possible complicating factors for the procedure, follow-up and probability of beneficial response to CRT. NYHA = New York Heart Association. CMP = cardiomyopathy. OMT = optimal medical treatment. QRS ms = QRS-duration in milliseconds. QRS morph = QRS-morphology. VPBs = ventricular premature beats. SVT = supraventricular tachycardias. NSVT = non-sustained ventricular tachycardias. EF = Ejection fraction. RV = right ventricle. CMR = cardiac magnetic resonance imaging. COPD = chronic obstructive pulmonary disease. OSAS = obstructive sleep apnoea syndrome. GFR = glomerular filtration rate.

Thorough information can be gathered during the pre-assessment outpatient clinic visit. We recommend assessing all referred patients as one of the major problems in CRT is identifying suitable patients, leading to a general underutilization of CRT [10-12]. Therefore, referring physicians should be encouraged to send their patients to the CRT clinic for pre-assessment. Ideally, the patient should have already been informed by the referring physician about CRT and should have given preliminary consent.

As the rationale behind the indications for CRT is extensively stated elsewhere [13, we will not go into this in depth. Rather, we will try to outline a standardized way of acquiring the minimum required information from referrals needed to be reviewed during assessment.

Pre-assessment clinical visit

If the reviewing CRT specialist considers the referred patient suitable for CRT, a single day pre- assessment visit at the outpatient cardiology clinic should be planned, as well as the actual implantation procedure date (figure 1). The objective of the pre-procedure appointment is to check referral information and add any missing details, to further educate the patient on CRT (and ICD if relevant), to assess the patient's 'fitness for surgery' and to obtain informed consent. This should be planned shortly before the implantation procedure (depending on the local waiting list). The patient invitation package to the outpatient pre-assessment cardiology clinic includes a letter detailing the pre-assessment visit, patient educational materials (booklet on implantation procedure, complications and therapy goals, follow-up and remote monitoring), the implantation procedure day details and contact information in case of questions or required change in bookings.

CRT specialist review

At pre-assessment, the CRT specialist first sees the patient. The CRT specialist evaluates HF history, complaints, current medication, comorbidities, and their influence on daily activities. The CRT specialist also explains CRT (and ICD therapy if relevant). The indication, implantation procedure, procedure related complications, benefit of CRT and the possibility of limited response, should be discussed. Also, CRT follow-up and future replacements or disabling of ICD therapies, are discussed with the patient. Any additional questions the patient may have are answered and patient consent is obtained.

The CRT specialist evaluates current antiplatelet and anticoagulation medication and determines the peri-procedural strategy [13, 19, 20]. Patient suitability for standard analgesic protocol and antibiotic strategy according to local protocols is assessed [21]. Suitability for single day case procedures is determined at this stage.

General review

A general review, focussed on CRT and ICD therapy, assessing patient's understanding of CRT (and ICD therapy if relevant) is done. The pre-procedure, procedure and post-procedure processes are explained to the patient in simple non-medical and non-technical language. The impact of device implantation on daily life is discussed, i.e. wound care, driving restrictions, other surgical interventions, device follow-up requirements including remote monitoring, medical follow-up, HF rehabilitation and shock management. The patient is also informed about related patient-association groups.

As the aim in the CRT care pathway is a short admission for the implantation procedure, 'fitness for surgery' (complicating issues or contra-indications for procedure) is assessed in advance, to minimize the chance of implantation procedure cancelation at admission. Furthermore, periprocedural medication recommendations related to co-morbidities are reviewed. Discharge planning is already discussed with the patient.

Finally the pre-assessment checklist (figure 3) is completed and final approval is given for the procedure. Questionnaires may be used to assess baseline quality of life [22, 23] and psychological status [24, 25]. If necessary, the patient may be referred for further evaluation and treatment.

Pre-assessment checklist

Procedural considerations	Check	Action
• Allergies	☐	
• Diabetes (oral/insulin)	☐	
• Anticoagulation	☐	
• Antiplatelet agents	☐	
• Antibiotics	☐	
• Sedation protocol	☐	
• Discharge planning	☐	
• Informed consent	☐	
Contra-indications/complications	Check	Action
• Complaints	☐	
• Physical (pocket side)	☐	
• Laboratory	☐	
• Chest X-ray (lead positions)	☐	
Information and follow-up	Check	Action
• Restrictions arm movement	☐	
• Drivers license	☐	
• Follow-up procedure	☐	
• Cardiac rehabilitation	☐	
• Remote monitoring	☐	

Figure 3
Pre-assessment checklist. Designed to ascertain thorough procedural planning and therefore eliminating unpredictable situations during and after implantation for physician as well as patient.

Implantation Procedure

Pre-assessment

On admission, a short re-assessment should be performed ruling out current infections or decompensation by evaluating complaints and a clinical exam including blood pressure, pulse and temperature. Also, discharge planning can be adjusted if any unforeseen (at pre-assessment) circumstances should emerge at re-assessment. If the patient is on anticoagulation that has been intentionally continued, an INR value is obtained upon admission; with a target INR of 2.0-2.5 during the implantation procedure. In case of use of NOACs the patient is asked whether the medication was stopped as recommended at pre- assessment. The patient is prepared for implantation and prophylactic antibiotics are administered.

Device Implantation

Before the implantation, the WHO surgical safety checklist is used to ascertain safe surgical care [26]. The physician checks patient data, planned procedure and its requirements, allergies and operation site with the patient in a standardized order. Compliance with fasting, preoperative medication strategy (anticoagulation), preoperative antibiotics and proposed sedation strategy are checked. Next, the CRT device implantation takes place. General recommendations for equipment, environment and staffing are reported elsewhere in detail [13]. This is also the case for recommendations about which side to implant the device, venous access, and order of lead implantation [7, 13].

As LV lead positioning plays an important role in CRT optimization, careful consideration of positioning is critical [27-29]. Once access to the coronary sinus (CS) has been obtained, we recommend performing a retrograde angiography of the coronary venous anatomy, preferably in two orthogonal views for optimal visualization of the target vein.

LV lead implantation should target the basal infero-lateral wall outside regions of scar. [28, 30, 31] There is increasing evidence that LV lead placement in a location on the free wall with delayed LV activation (determined either by echocardiography [27, 32] or specific electrical measurements [33-36]) improves benefit from CRT. A specific way to measure the extent of electrical delay during procedure, is to measure the Q-LV sense delay; defined by the time interval from the first deflection on the surface ECG to the local intrinsic activation at the LV stimulation site [35, 37]. To provide pacing vector options (in case of phrenic nerve stimulation or an apical position of the lead tip), and to ensure lead stability (by distal positioning) and still being able to pace at a mid or basal electrode, a multi-electrode LV lead is preferred [38-42]. The final position of all leads should be registered fluoroscopically in two orthogonal views to provide a reference for re-assessing lead-position in the future.

We believe optimization should begin at implantation. The implanting specialist should explicitly recommend protocols for medication cessation, continuation or up-titration of HF medication in the procedure report. This is also the case with respect to advice about treatment of existing atrial fibrillation and optimizing rate or rhythm control.

Post-procedure

The post-procedure check-up should take place at least 2 hours after the implantation and includes a chest X-ray, wound check, 12-lead ECG and a device check-up. These checks are performed to ensure successful CRT system implantation, appropriate CRT device function and absence of complications before discharge.

As there currently is no convincing evidence for device optimization, we suggest a pragmatic approach. Optimization can be performed at the discretion of the CRT specialist by either echocardiographic or ECG methods [43-46]. Whether or not optimization is performed, appropriate CRT with contribution from LV pacing should be confirmed on the ECG before discharge [47, 48].

A discharge checklist (figure 4) is used to ensure patient education (reminders, dos and don'ts), remote monitoring enrolment, and verification of medication (and device optimization plan, if applicable) at discharge. Also standardized follow-up appointments are planned.

Pre-discharge checklist		
CRT device and implant check	Check	Action
• Device check-up	☐	
• Chest X-ray	☐	
• 12-lead ECG	☐	
• Pocket wound check up	☐	
Follow-up advice and planning	Check	Action
• Medication advice CRT specialist	☐	
• Anticoagulation strategy	☐	
• Patient education (do's and don'ts)	☐	
• Drivers license	☐	
• Remote monitoring start up	☐	
• Follow-up appointments planned	☐	

Figure 4

Pre-discharge checklist. Completing this check-up makes sure short-term complications have been ruled out and patient has been educated and will be followed to minimize the chance of mid- to long-term complications. CRT = cardiac resynchronization therapy.

CRT follow-up management

Follow-up management should ensure adequate patient recovery from surgery and provide visit timelines and pathways to assess therapy effectiveness and to optimize CRT. Moreover, follow-up should strive to provide structured HF care and minimize hospital resource utilization.

138

4-6 weeks follow-up

The first outpatient clinical visit, is scheduled 4-6 weeks after discharge. At this visit the pocket wound and pain, as well as patient general well-being are assessed, with specific attention to signs of device-related complications. A device check-up includes standard device tests, diaphragm stimulation test, measurement of percentage of biventricular pacing, checking for the presence of arrhythmias and evaluation of the device HF diagnostics (patient activity, thoracic impedance measurements, heart rate variability, etc.). Also, enrolment in remote patient monitoring is checked. If there are no complications and no signs of suboptimal CRT are present, the patient will continue with (already planned) regular follow-up schedule.

3 months (remote) follow-up

At three months a remote device transmission and remote clinical response evaluation is performed. This remote device transmission is evaluated for device function, percentage of biventricular pacing, presence of arrhythmias, and HF diagnostics.

For the remote clinical evaluation the patient is assessed by phone; the patient general well-being is evaluated, HF medication is reviewed, and dietary restrictions and compliance are discussed.

6 month follow-up

At 6 months, patients are evaluated during a single visit at the outpatient clinic. The follow-up plan at six months contains a 12-lead ECG, full device check-up and re-evaluation of clinical response. Finally, patient satisfaction is evaluated.

At this time general outcome measures will be evaluated. Different outcome measures have been used to get a more objective view of response to CRT. Commonly used measures are the 6 minute hall walk test (6MWT), patient activity (using device diagnostics) and echocardiographic parameters (LVEF, LVESV). Also, assessments of quality of life and psychological status can be (re-) evaluated to measure subjective patient health outcomes.

As an optimization-tool, independent of clinical response or outcome measures, the 'Mullens check-list' is used consistently at each follow-up moment to evaluate the need for possible further optimization of CRT [49]. This check-list consists of various potential reasons for suboptimal benefit of CRT and should therefore be evaluated step-by-step (figure 5).

Optimization checklist

Heart failure evaluation

Decompensated HF

OMT

Compliance evaluation
(fluid restriction/diet/intox/meds)

Reasons deterioration HF

☐

☐

☐

☐

Electrocardiographic/device evaluation

Underlying narrow QRS complex

< 95% biventricular pacing

Arrhythmias (VPB/SVT/NSVT)

☐

☐

☐

Echocardiographic evaluation

Structural worsening of disease

Increased filling pressures

Suboptimal AV timing

Primary RV dysfunction

☐

☐

☐

☐

LV-lead position evaluation

Chest X-ray lead position

scar region evaluation

☐

☐

Co-morbidities

Anemia / Iron deficiency

Renal dysfunction

Deconditioning

Psychological status

Others*

☐

☐

☐

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Considerations

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Figure 5
*Optimization checklist. Structured check-up for optimization of heart failure patients with CRT. Incorporating previously identified factors contributing to suboptimal benefit from therapy. HF = heart failure. OMT = optimal medical therapy. Intox = intoxications. VPBs = ventricular premature beats. SVT = supraventricular tachycardias. NSVT = non-sustained ventricular tachycardias. AV = atrioventricular. RV = right ventricular. LV = left ventricular. * = other comorbidities identified at referral review (figure 2). Adapted with permission from Mullens et al. [49].*

139

In order to identify reasons for suboptimal benefit of CRT, the checklist focusses on (1) general HF treatment, (2) device related issues, and (3) comorbidities. Additional resources (echo- cardiography, Holter monitoring, etc.) should be used accordingly.

General HF treatment includes checking clinical status, compliance to salt and fluid restriction, diet, HF medication, and cessation of substance abuse (smoking, alcohol, drugs). Underlying reasons for HF deterioration (ischemia, hypertension, right ventricular (RV) dysfunction etc.) should be excluded [3]. Furthermore HF medication should be further titrated post-implantation [50, 51].

With regard to device related issues; contribution from left ventricular (LV) pacing should be present on the 12-lead ECG [52, 53]. Also optimal atrioventricular (AV)-timing should be determined using available optimization (invasive-, echocardiographic- or ECG-) techniques [53-55] and underlying conduction disturbances re-evaluated using LV lead delay-measurements performed either intra-procedurally or at device interrogations during follow-up. As a high percentage of biventricular pacing (>95%) is required, any arrhythmias should be addressed aggressively by either rate or rhythm control strategies [7, 56, 57]. Appropriate LV lead position on the infero-lateral LV wall, outside regions of scar and at a site of delayed LV activation should be (re-) assured using pre-implantation imaging and LV lead delay-measurements [27-29, 31, 58, 59].

Co-morbidities (kidney function disturbances, anaemia, iron-deficiency, thyroid dysfunction, etc.) should be treated adequately [60, 61]. Furthermore, as stated before, special attention should be given to signs of anxiety or depression, as these are common complications of HF as well as device therapy [62].

Finally, all patients should be considered for and encouraged to join a HF rehabilitation program, regardless of previous participation in such a program. Any deconditioning that could have been caused by catabolic metabolism before implantation can perhaps now be redeemed with a more profitable metabolic situation after implantation [63].

Regular (non-intensive) follow-up

From the 6-month follow-up on, the patient will return to the regular HF outpatient clinic. CRT follow-up will consist of biannual check-ups of device function, including general device parameters, battery status, and HF diagnostics. In practice, this will come down to a once-a-year remote device transmission, checking for general device function, with special attention to percentage of biventricular pacing, presence of arrhythmias, and HF diagnostics. The 6 month remote transmission is alternated with a 6 month visit in the outpatient clinic for full device check-up, followed by HF assessment. This regular follow-up could eventually entail further optimization whenever possible, decisions about replacement of device (battery) or, in some cases, ending of therapy as demanded by the patient.

If, during regular follow-up, there is any indication of failure of CRT or complications of therapy, the patient will be evaluated on an ad hoc basis until a satisfactory situation has returned and the patient can be put back on the regular follow-up plan.

Ad hoc intensive follow-up plan

When warranted by complaints or device information at remote check-up, the patient will be evaluated in the outpatient clinic, within 1-2 weeks. The general assessment will be the same as the regular follow-up assessments, with access to CRT and HF specialist consultation, and any additional diagnostic resources needed.

For the intensive follow-up, a full device check-up is performed and patient complaints are evaluated. Physical examination and, if needed, additional resources i.e. ECG, echocardiogram, chest X-ray, laboratory investigations and an exercise test are used to exclude device-related complications and verify adequate device functioning. The "Mullens-checklist" is used to systematically evaluate possible reasons for suboptimal benefit from CRT. If indicated, the patient is evaluated on an ad hoc basis, until a stable condition has returned. Once intensive follow-up is no longer applicable, the patient will return to the regular (non-intensive) follow-up plan.

Discussion

CRT is a proven, evidence-based therapy for HF. With continued extensive research, the indications are tending to expand and the health care burden will likely increase. Apart from HF being a comprehensive and complex disease, CRT remains a complex treatment for HF, the mechanisms of which we still do not fully understand. In addition, a substantial portion of patients treated in large trials and registries have limited benefit of CRT. Therefore it is essential for CRT care, in combination with general HF care, to be structured and above all multidisciplinary, with specialised nurses, electrophysiologists, HF-specialists and imaging-specialist working as part of a single care pathway, to optimize delivered care and minimize healthcare burden.

Even though guidelines and expert consensus papers extensively describe what to do in terms of CRT indications, implantation, follow-up and optimization, they do not provide a comprehensive protocol for routine clinical practice. With this paper, we propose a protocol-based, best practice, CRT care-pathway. This model allows for adjustments due to local practices and resources, while still providing uniform care for all CRT recipients by making use of standardized forms and algorithms.

Although guidelines provide clear recommendations for the indications for CRT, multiple studies have shown considerable heterogeneity in utilisation of this therapy, with both under- utilisation in appropriate patients and over-utilization in inappropriate patients [49, 62]. To address heterogeneity issues and suboptimal care in HF, recent studies have investigated the role of structured checklists and other aids in clinical practice. The IMPROVE HF study, as the OPTIMIZE HF study earlier, showed that structured CRT care (with the help of structured aids) helped in guideline adherence for an outpatient population [17, 18].

The best practice CRT care pathway described in this manuscript does not prescribe the indication for CRT as that may change with time. However, through the use of the checklists for screening of referrals, we expect referring physicians to feel more confident about referring appropriate patients for CRT. By using this care pathway implanters acquire more insight into the completeness of the indications and contra-indications for CRT in the referred case.

One of the major issues in CRT is uncoordinated care and fragmentation of care across different specialities. While most studies on CRT have been focused on inclusion criteria and implantation techniques for CRT, little attention has been paid to follow-up care.

A few studies have focused on a structured, multidisciplinary approach to optimize outcomes in CRT. Mullens et al. [49] was the first to show that an algorithm with standard equipment and testing, reproducible in any outpatient cardiology clinic, could identify suboptimal medical treatment, LV lead position, and uncontrolled arrhythmias that were associated with a suboptimal response to CRT. Furthermore, they showed that if this protocol-driven CRT approach was started immediately after implantation it was associated with improved response to CRT. Importantly, these favourable effects appeared to be driven not only by appropriate device and arrhythmia management but also by improved HF care, by HF education and optimization of HF medication [50]. More recently, a larger

multidisciplinary CRT care program was evaluated and compared to a retrospective conventional care group of patients. This study has confirmed that a multidisciplinary approach in CRT was associated with improved outcomes [64].

Another objective of the CRT care pathway is to address the issue of resource utilisation and healthcare costs in CRT care. In many hospitals, patients suitable for CRT have to go through multiple visits with a variety of doctors and departments [11]. In this CRT care pathway, the patient assessments for CRT, as well as follow-up visits after implantation, are structured and effective. The office visits are planned to have device follow-up before medical follow-up to make sure device information on general HF status (heart rate and rhythm), and HF diagnostics (patient activity and thoracic impedance measurement), as well as CRT specific data (percentage of biventricular pacing, arrhythmias) are available to incorporate into the general heart failure management and CRT optimization. Device measured parameters have proven to be helpful in the assessment of HF status and the ability to detect possible deterioration [64-67]. Moreover standard incorporation of remote monitoring can reduce outpatient visits and have been shown to result in a significant improvement in the prediction of heart failure deterioration and improved outcomes resulting in a reduction of HF hospitalizations [68-72].

It is key for the success of any standardized process that roles and responsibilities are clearly defined, described and implemented. In addition, different local rules may require different timings for follow-up and patient contact. The roles and visit types and timings described in this paper may not align with the roles and responsibilities and requirements in other clinics. They are intended to give guidance in identifying appropriate functions and disciplines that should be involved and suggest visit timing when setting up/improving a CRT care pathway in any type of clinic. Adjustments to fit local rules and requirements are expected.

Conclusion

As the HF population eligible for CRT is rapidly expanding, there is a need to implement a structured and integrated pathway in order to optimize costs, improve efficiency and, most important, improve clinical outcomes. By introducing this consensus CRT care pathway, using a multidisciplinary approach, we aim to deliver effective and efficient therapy for CRT indicated HF patients and ensure early detection and management of suboptimal benefit from CRT.

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Implementation of a Structured Cardiac Resynchronization Therapy Care Pathway

The background of the slide features a series of thin, dark diagonal lines that create a sense of movement and structure. A single, thin red line is also present, intersecting the other lines and adding a subtle contrast to the overall design.

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ABSTRACT

Aims Cardiac resynchronization therapy (CRT) reduces mortality and morbidity in selected heart failure (HF) patients. Selection, implantation procedure and follow-up care of patients treated with CRT is complex and puts a significant burden on health care resources. As a result, a significant proportion of patients does not derive maximum benefit from CRT. The objectives of this study are to implement a structured clinical care pathway, reassuring structured referral and management of CRT patients, with the goal to derive maximal benefit for HF patients, as well as reducing health care resource burden.

Methods and results Leveraging the European Pathway Associations' (EPA) care pathway methodology and the Lean Six Sigma methodology, the creation of the care pathway consisted of 3 phases. The first phase aimed at designing a "model best practice care pathway" by evaluating current practices, reviewing the literature and reaching consensus amongst multiple European CRT centres. In a second phase, the model pathway was translated into an "operational pathway" fitting with the specific needs and environment of the Maastricht University Medical Centre, after a thorough assessment of the current state of the care process and the local contributors' input. In a final phase, the gaps between current state and the defined "operational pathway" were prioritised and improvements to the current care process were implemented in a continuous improvement process.

Conclusion This paper introduces a structured care pathway for HF patients treated with CRT and shows its implementation in a referral centre in the Netherlands.

Introduction

Cardiac resynchronization therapy (CRT) is one of the most successful heart failure (HF) therapies that has emerged over the last few decades. The therapy entails the implantation of a biventricular pacemaker or ICD in order to restore electrical synchrony. Several randomized clinical trials have shown CRT to reduce symptoms of HF, improve exercise capacity and quality of life, as well as to reduce hospitalizations and mortality in selected HF patients [1-4]. Furthermore, economic evaluations have shown it to be a cost-effective therapy in HF [5, 6]. Clinical guidelines of the European Society of Cardiology and the American College of Cardiology Foundation/American Heart Association endorse these results and promote utilisation of CRT [3, 7-9].

Despite guidelines and experts' consensus, high variations in patient referral and pre-assessment, implantation procedure and follow-up management are observed [10-12]. Partly because of this heterogeneity in the care process as well as the complexity of HF care, with patients suffering from numerous co-morbidities affecting the outcomes of CRT, it is estimated that 30% of patients do not derive maximal benefit. Indeed, CRT is a complex therapy, involving more than just electrical therapy for an electrical problem. Instead, it is an electrical therapy for a combination of electrical, mechanical and haemodynamic problems, of different origins, requiring thorough patient selection, skilled implanting physicians and a comprehensive follow-up [13-16]. Moreover, multiple recent studies have shown, that successful treatment of HF requires specialised (multidisciplinary) care [3, 15]. Ideally, there should be a uniform, multidisciplinary approach incorporating all aspects of HF care in patients referred for CRT implantation [13].

Care pathways are increasingly used to structure complex interventions in health care [17]. Care pathways have goals and key elements based on Evidence Based Medicine, best practice and patient expectations by facilitating the communication, coordinating roles and sequencing the activities of the multidisciplinary care team and patients by documenting, monitoring and evaluating variances and by providing the necessary resources and outcomes [18]. In addition to the support of evidence based medicine in complex interventions, care pathways have been proposed as a strategy to optimise resource utilisation [17, 19].

The objectives of our study were (1) to develop a care pathway for CRT-care and (2) to implement it into current practice in a CRT referral centre in the Netherlands. Aiming at achieving a high quality, integrated care, tailored to the needs of every CRT treated HF patient, and a proactive and structured approach to the improvement of clinical response to CRT, as well as improvement of organisation and control of resource utilisation.

Methods

Starting from December 2012, three European hospitals that are experienced in delivering CRT care, participated in the development of a model CRT-care pathway (The Liverpool Heart and Chest Hospital in the UK, The Copenhagen Rigshospitalet in Denmark, and The Maastricht University Medical Centre in the Netherlands). These centres are large referral centres (averaging 150 to 300 CRT device implantations a year), experiencing difficulties in structuring their care for CRT patients. They were selected based on their experience in CRT and their willingness to evaluate and reorganise their current CRT practice.

To evaluate and redesign current CRT practice in these centres both the European Pathway Association (EPA) Care Pathway methodology [20] and the Lean Six Sigma methodology [21] were used. The EPA Care pathway methodology defines 4 levels of care pathways products. Using this methodology we aimed for a stepwise design of an evidence-based 'model care pathway' to a locally applicable 'operational pathway', and individual 'assigned pathway' (figure 1).

Figure 1. EPA Care pathway methodology: the 4 levels of a care pathway

EPA Care pathway methodology: the 4 levels of a care pathway. The model pathway being based on international and national evidence and not being organisation specific. The operational pathway is an organization specific pathway based on the model pathway taking into account local processes and resources. The assigned pathway is the operational pathway that is used for a specific patient. The completed pathway shows the compliance with the interventions embedded in the pathway and provides information for improvement of the pathway. Reprinted with permission from Oxford University Press [20].

The Lean Six Sigma methodology is a highly structured methodology that uses a set of management and statistical methods to optimise processes and reduce waste in business processes, which has previously been used to design pathways in health care [22]. The general sequence of managing a project with this methodology consists of three phases (Assess, Improve and Sustain), aiming at implementing a locally applicable ‘lean’ structured care pathway (figure 2). Combined together, these methodologies provide a highly structured approach to ideal pathway definition and practical implementation.

Results

1. Definition of the "Model care pathway"

Medical specialists and device technologists involved in CRT care from the three participating hospitals were involved in defining the model pathway. Participants had several meetings to discuss current guidelines [7, 13] and literature, and to compare with local experience in CRT care in order to benchmark the CRT care process. To enable an effective sharing and identification of differences in CRT care practices, expert consultants (Medtronic Integrated Health Solutions), on care pathway design and Lean Six Sigma methodology conducted an evaluation (observations, interviews and measurements) of the current practices in each hospital prior to the consensus meetings. Combining the evaluation of current practice and consensus benchmark CRT care resulted in a detailed "Model care pathway" (Chapter 8), including aides (checklists) to use in evaluating current local CRT care and implementation of the consensus CRT care pathway. This exercise required two face to face consensus meetings and 4 conference calls and was completed in 4 months. The preparation of this phase required 10 consulting days per hospital.

2. Translation into an "Operational pathway" for the Maastricht University Medical Centre.

To customize the model care pathway into a locally applicable operational pathway, the expert consultants first conducted a more detailed evaluation of the baseline processes involved in current CRT care in the Maastricht University Medical Centre (MUMC). First, mapping of the processes (including systems and communications) involved in current CRT care was performed through observations, interviews and a workshop involving all personnel contributing to CRT care. Subsequently, a random measurement survey was conducted in 30 CRT patients implanted between 2010 and 2012 (first 10 new CRT implantations each year, excluding any patient involved in a clinical study). This survey included detailed observations of predefined operational outcomes such as activities, use of resources, personnel and time, as well as patient-based outcomes such as procedure-related complications and hospitalisation

or death during follow-up. All measurements were mapped for each step of the pathway. The analysis was structured so that similarities and disparities between the current practice CRT care and the “**model care pathway**” could be mapped and measured when possible. Conclusions drawn from this analysis are presented in table 1.

Table 1. Current process bottlenecks, per process stage

Referral and Pre-assessment	Implantation procedure	Follow-up management
Heterogeneous referral No structural case identification Many contacts pre-implant Long referral-to-treatment time	Long length of stay	Heterogeneous follow-up Many contacts post-implant No structural CRT optimization No integration of HF/device care Long referral time in non-response

Finally, a workshop with all stakeholders was conducted to define the “Maastricht Operational pathway”, based on both the “**Model care pathway**” and the detailed assessment of the current local practices and processes. The local multidisciplinary team was challenged to evaluate the newly designed pathway for feasibility in practice and to control whether any identified ‘waste’ (according to the assessment) could indeed be removed. This phase lasted 4 months and required 30 consulting days, as well as 2 workshops for local stakeholders. A high level view of the “Operational pathway” for MUMC is shown in figure 3.

Figure 3. High level “Operational pathway” in MUMC.

Figure 3. Continued

Figure 3. Continued

Flow chart of CRT pathway steps a patient goes through in the operational pathway in the MUMC. Different steps (Referral review and pre-assessment clinic, implantation procedure, and follow-up management) are indicated with content of the assessments and structured aids available for the assessment.

3. Step-wise implementation of the "Operational pathway" in MUMC

To introduce the "Operational pathway", a step-wise implementation design was used. This encompasses an introduction of the new processes in each subsequent step in the process; (1) Referral and Pre-assessment clinic, (2) Implantation Procedure and (3) Follow-up management as shown in figure 3. Depending on medical content, contributors to the process and anticipated time needed to introduce and implement the process, the process steps were implemented into current practice. As such the 'Implantation Procedure' step was the first to be implemented; as a 'stand-alone' process, not depending on implementations of the other two, this could more easily be implemented without interfering with care processes in the other steps. Subsequently, the 'Referral and Pre-assessment clinic' and the 'Follow-up Management' steps were introduced.

Referral and Pre-assessment clinic

From January 2014 to July 2014 the new referral and pre-assessment pathway was implemented into practice. Contributors to this part of the pathway were HF cardiologists and electrophysiologists, specialised nurses and administration/planning office.

Major changes in pre-assessment were the introduction of a multidisciplinary (HF cardiologists and electrophysiologists) evaluation of the referred patient; identifying possible caveats in the work-up, discussing the need for additional tests and if possible deciding on whether CRT is indicated. A referral review checklist (see Chapter 8) was introduced to reassure consideration of every possible confounder in delivery of CRT.

In order to reduce patient and recourse burden, single-day visits were introduced. The planning office invites the patient for a standardized series of consultations with the implanting cardiologist and subsequently the specialised nurse. No specific training was involved in implementing this evaluation. During these consultations general medical and pre-implantation assessment are conducted. Also a thorough discharge planning is prepared. Informed consent is obtained in this pre-assessment phase. Planning of the pre-assessment visit and the date of implantation happens simultaneously as a standardised sequence of events. A specifically designed patient invitation package includes a letter detailing the pre-assessment visit, patient educational materials (booklet on implantation procedure, complications and therapy goals, follow-up and remote monitoring), the implantation procedure day details and contact information in case of questions or required change in bookings. Implementation into the planning system took 4 consultant day and 2 hours of additional training of contributors.

Implantation procedure

From September 2013 to December 2013 the use of a specific pre-assessment checklist (see Chapter 8), as well as a pre-discharge checklist (see Chapter 8) guiding patient pre- and post- implantation assessment by a specialised nurse was implemented, within the single-day admission protocol. The implementation of the checklist did not involve any additional training of the contributors.

Follow-up management

The improvements to the continuous follow-up post-implantation process were introduced from August 2014 to January 2015. Implementation involved training of both device technician as well as specialised (HF) nurses to use a standardized way of interdisciplinary transfer of contributing information (device HF diagnostics, arrhythmias and biventricular pacing percentage) and the use of a CRT optimization checklist (see Chapter 8) to be used at every patient contact to ensure optimal benefit from CRT. In addition, systematic enrolment on remote device monitoring was introduced to reduce patient and resource burden. The implementation of this part of the pathway was facilitated through designing standardized templates of reports and providing training for the interpretation of findings by the specialized nurses. This took 6 hours (3 times 2 hours) of dedicated training of HF nurses by an implanting cardiologist. To ascertain optimal follow-up care and improve implementation, specialized nurses outpatient clinic consultations were supervised by an electrophysiologist (1 part-time day every week) during the implementation period.

Discussion

In this paper, we describe the development and implementation of a protocol-based, structured clinical CRT care-pathway. The objective of this care pathway is to provide standardized care for all HF patients treated with CRT by providing protocolled care by using forms and algorithms, while allowing for adjustments to local practices and resources.

As demonstrated during the baseline assessment of current practice care in the referral hospital in this report, one of the major issues in CRT is uncoordinated care. This results in diminished quality of patient selection, reduced benefit of therapy, more complications and unnecessary resource utilisation. Studies and registries have shown this to be a general issue in CRT care [24-27]. Although guidelines and extensive practice documents are available to guide clinical CRT care [3, 7, 13], adherence to recommendations is heterogeneous [11, 28-30]. As shown in HF care in general, treatment of this disease requires structured, multi-disciplinary care. Structured multidisciplinary HF care is currently widely recommended [3], but has yet to be implemented in many practices. This is even more important when patients are indicated and treated with CRT. Often consultations for these patients focus on the electrical part of the treatment, rather than the underlying condition and general HF treatment. Whereas further optimization of HF treatment seems mandatory to obtain maximal benefit from CRT [31, 32]. On the other hand, when patients are on the scope for their HF, these frail patients are requested to visit the outpatient clinic for many consultations and additional investigations which often are redundant when care would be structured and coordinated.

A few studies have focused on this problem, introducing a structured, multidisciplinary approach to optimize outcomes in HF, and more specifically CRT care. Single and multicentre, randomised trials have focused on the introduction of (in hospital) care pathways in the treatment of HF. Overall the outcomes of these trials show positive results on mortality and length of stay during admission [33, 34]. Mullens et al. were the first to show that an algorithm with standard equipment and testing, reproducible in any outpatient cardiology clinic, could identify suboptimal HF and CRT care. If adjusted accordingly, this could improve response to CRT [35]. Furthermore, improvement in response to CRT appeared to be driven not only by appropriate device and arrhythmia management but also by improved HF care, by HF education and optimization of HF medication [31]. More recently, a larger multidisciplinary CRT care program was evaluated and compared to a retrospective conventional care group of patients. This study confirmed that a multidisciplinary approach in CRT was associated with improved outcomes [36].

As a structured aid in complex care pathways, checklists have shown to improve organisation structure, homogeneity in therapy and the ability to prevent complications and therefore improve implementation of care pathways, especially in HF [37, 38]. However, checklists are not typically used in CRT care. Recent studies have investigated the role of structured checklists and other aids in clinical practice. The IMPROVE HF study, as the OPTIMIZE HF study earlier, showed that structured HF care (with the help of structured aids) improved guideline adherence in an outpatient HF population [37, 38].

Another objective of the CRT care pathway is to address the issue of resource utilisation and healthcare costs in CRT care. In many hospitals, patients suitable for CRT have to go through multiple visits with a variety of doctors and departments [11]. In this CRT care pathway design, patient assessments for CRT, as well as follow-up visits after implantation, are structured and effective. The office visits are organized to have device follow-up before medical follow-up to make sure device information on general HF status (heart rate and rhythm), HF diagnostics (patient activity and thoracic impedance measurement), as well as CRT specific data (percentage of biventricular pacing, arrhythmias) are available to be incorporated into the general HF management and CRT optimization program. Device measured parameters have proven to be helpful in the assessment of HF status and the ability to detect possible deterioration [39-41]. Moreover, standard incorporation of remote monitoring can further reduce outpatient visits [42-45] and has been shown to result in a significant improvement in the prediction of HF deterioration, therefore reducing the number of HF hospitalizations [45-47].

Conclusion

As care for HF patients treated with CRT is complex, multifactorial and puts a high burden on health care utilisation, there is a need to implement a structured and integrated pathway in order to optimize costs, improve efficiency and, most important, improve clinical outcomes. By introducing this international, expert based structured CRT care pathway, using a multidisciplinary approach, and by implementing it into actual practice using a structured, comprehensive and practical methodology, we aim first to deliver effective and efficient therapy for CRT indicated patients and ensure early detection and management of suboptimal benefit from CRT, and second to promote the feasibility of optimising CRT care across all CRT centres.

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General Discussion

The background of the slide is white and features a series of thin, dark grey diagonal lines that run from the top-left towards the bottom-right. These lines are spaced out and vary slightly in their starting and ending points, creating a sense of movement and depth. A single, thin red line is also visible, running diagonally across the middle of the slide, intersecting with the other lines.

This thesis evaluates patient selection and management in cardiac resynchronization therapy (CRT), in order to maximize the benefit for heart failure (HF) patients treated with CRT. This chapter will discuss the findings of the studies presented in this thesis with respect to their scientific and clinical relevance, limitations and will give an outlook towards the future. The work in this thesis can be divided in parts related to selection of patients for CRT (part I) and improving management of patients treated with CRT (part II)

Part I. Patient selection

The research, presented in **part I** of this thesis, evaluates criteria for defining left bundle branch (LBBB) QRS morphology on the 12-lead ECG, used for patient selection in CRT. Since several years guidelines dictate that LBBB morphology is the most important electrocardiographic selection criterion for patient selection for CRT [REF]. However, the studies presented in this thesis, show that LBBB morphology is not as straight forward as it seems, and propose a new selection criterion to overcome these limitations.

Variability in classification of LBBB

Chapter 2 summarizes the available evidence for the currently recommended ECG markers for patient selection in CRT. From this summary it becomes clear that the use of QRS duration, and especially QRS (LBBB) morphology comes with uncertainties that need further evaluation. The fact that meta-analyses of the studies evaluating the value of LBBB as a predictor of outcome in CRT show no association with clinical outcome, while individual randomized studies do, gives room for thought about how different study-groups defined LBBB and whether this issue could play a significant role in clinical decision-making as well.

In **chapter 3** of this thesis we show that indeed there is a profound difference in the subjective identification of LBBB between implanting cardiologists, and the interpretation of the LBBB definitions in the various clinical guidelines and landmark CRT trials. In this study we showed that rigorous application of the exact definitions, used in the guidelines and landmark papers, yielded significantly different "LBBB patient" populations, compared to those established through routine clinical observation by experienced CRT-device implanting physicians. This is reflected by the large differences in the probabilities to be classified as LBBB, (ranging from 0.20 to 0.76) and in phi-coefficients of correlation between LBBB definitions ranging from 0.10 to 0.68. In addition, inter-observer variability in clinical diagnosis compared to application of the exact LBBB definition led to re-classification in one in five patients. Assuming that the implanting cardiologists, who acted as observers in this investigation, are a good representation of clinical practice, patient selection in practice may differ markedly from that in the landmark trials and between landmark trials.

The level of evidence of the recommendations in current guidelines suggests a sound scientific basis for the use of LBBB in patients selection [1, 2]. Two large meta-analyses, including the large randomized controlled trials in CRT, however show no independent association of LBBB morphology with outcome in CRT. While one analysis clearly states the lack of an independent association of LBBB morphology to outcome in CRT as its' conclusion [3], the other analysis included it in the final model even though it did not increase the 'goodness of fit' [4]. An important consideration is that these meta-analyses did not consider how the included trials classified LBBB. Both studies acknowledged the lack of detailed ECG pattern information as a limitation to their conclusions. Yet, this might be the

very reason for LBBB not showing up as independent predictor of CRT response. Unfortunately, meta-analyses may thus be misleading and should be disregarded in clinical guidelines if essential mechanistic or clinical information is lacking from the studies the meta-analysis is based upon.

When reviewing the methods of classifying ECGs as LBBB in the various trials, it becomes clear that there has been appallingly little attention for this topic. The early landmark trials MIRACLE [5], MUSTIC [6] and CARE-HF [7], and the more recent REVERSE trial [8] do not mention LBBB morphology at all. The COMPANION [9], MADIT-CRT [10] and RAFT [11] trials mention the use of LBBB morphology, but failed to define it. Only subanalyses of some of these trials, specifically addressing the issue of LBBB morphology, accurately define LBBB. However, all these subanalyses (REVERSE [12], MADIT-CRT [13] and RAFT [14] trials) classified LBBB morphology differently. This also becomes apparent from the percentage of patients classified as LBBB, ranging from 60 to 79 percent in these trials. These differences support the results from the analyses in this thesis. While the percentage of patients classified as LBBB according to landmark trial definitions ranged between 75 and 78%, larger variations were found with guideline (ESC and AHA/ACC/HRS) recommended definitions (18 and 75%) and the newly introduced Strauss definition (69%).

The analysis in a large multicentre CRT cohort in the Netherlands in **chapter 5** further shows that in each of the four analysed LBBB definitions there is at least one redundant ECG feature that does not have any association with outcome in CRT. Moreover, only three of the eleven ECG features included in any of the LBBB definitions together are independently associated with outcome. This may be of importance as we show in **chapter 3** that inter-observer variability was largest in the most complex definition (AHA/ACC/HRS), which was attributed to features that are more sensitive to subjective interpretation, i.e. notching/slurring of the R wave in different leads.

An important consideration in this observation, is that most of the definitions of LBBB have never been developed to predict outcome in CRT, but to merely describe a conduction abnormality. The results in **chapter 5**, show that only a few ECG features suffice to predict CRT response. It may be worthwhile to investigate the development of a 'CRT-outcome' specific marker from the 12-lead ECG. In this regard, modern machine learning techniques may be useful.

In general the conclusions from **chapter 3** and **chapter 5** stress the need for uniformity and '**simplicity**' in the definition of LBBB in clinical practice. However even when guidelines and trials would recommend and use a uniform definition of LBBB, it remains a collection of morphological patterns on the 12-lead ECG sensitive to subjective interpretation in clinical practice. Future research should therefore focus on finding a simpler, objective marker for patient selection in CRT.

Predicting outcome in CRT with LBBB

This thesis presents two retrospective studies that investigate the value of LBBB as predictor of CRT response. In **chapter 4** of this thesis we show that in a multicentre, international cohort of 316 CRT patients, only the ESC 2009 and 2013 definitions were significantly associated with clinical outcome. In contrast, in **chapter 5**, analysis in the aforementioned 'MUG' cohort consisting of 1492 patients, all LBBB definitions used were associated with the combined clinical endpoint. Although this study confirmed the major differences in populations classified as LBBB by different definitions, it showed that a patient classified as LBBB has a significantly better outcome in CRT than patients classified as non-LBBB, irrespective of the definition used. The difference in final conclusion between the

analyses in **chapter 4** and **5** as to whether all proposed LBBB definitions are associated with outcomes to CRT, can be explained by the differences in number of patients included ('statistical power'). For instance, in **chapter 4** only 90 patients classified as LBBB according to the AHA/ACC/HRS LBBB definition, with only 19 events occurring during follow-up. In **chapter 5** 213 patients were classified as LBBB according to the AHA/ACC/HRS definition, experiencing 49 events.

Another explanation for the different results may be the use of different observers in the two analyses. This may, as mentioned in **chapter 3**, induce significant inter-observer variability. Although in both studies the AHA/ACC/HRS definition provided the highest specificity, there was a considerable difference in specificity between the two studies. In the analysis in **chapter 4** 29.0%, and in the analysis in **chapter 5**, 18.5% of patients were classified as LBBB according to AHA/ACC/HRS definition.

If inter-observer variability would indeed be the cause of the difference in specificity, this would add to the concern about heterogeneity of LBBB classification. A secondary analysis in the MADIT-CRT trial strengthens this hypothesis by showing that when 'LBBB-like IVCD patterns' (n=191, 62% of IVCDs) were added to the 'LBBB group', association with the primary endpoint remained significant with odds ratio increasing only from 0.47 to 0.55 [13]. In contrast, overall results in the IVCD patient group (n=308) treated with CRT showed a trend towards worsening outcomes as compared to the ICD treated group.

The studies in **chapters 4** and **5** have a limitation which precludes extrapolation of their results in an absolute way to all patients referred for CRT. The retrospective nature results in bias of excluding patients deemed not suitable by treating physicians. This has probably lead to a lower overall proportion of non-LBBB patients (as it seems less likely that CRT is denied to an LBBB patient). Furthermore, the absence of a non-CRT treated "control group" does not allow to completely contribute the association of outcomes to the effect of therapy, as this may be an effect of the presence of LBBB or associated patient characteristics itself. The logical next step would be to analyse the different LBBB definitions in a landmark CRT-trial and evaluate whether outcome of CRT differs between LBBB definitions.

In conclusion, the results from **chapter 4** and **chapter 5** reassure the value of LBBB as a positive predictor of CRT benefit, regardless of the definition of LBBB. However, considering that in the CRT patient cohort the event rate of all-cause mortality, cardiac transplantation, or LVAD implantation was the same (33.3%) in non-LBBB patients according to AHA/ACC/HRS definition and in LBBB patients according to the MADIT definition, one should give considerable thought to the preferred definition. When applying the numbers found in the real life cohort presented in this thesis; using AHA/ACC/HRS definition in 100 CRT patients would lead to 47 (out of 71) non-LBBB patients with good clinical outcome in CRT being denied therapy. On the other hand, using MADIT definition in the same 100 CRT patients would lead to 25 (out of 75) LBBB patients) being treated although clinical outcome is not good. Using AHA/ACC/HRS definition a likely responder is denied appropriate therapy, possibly increasing health care costs as well, since CRT has been shown to be cost-effective, certainly in responders. In the latter case the patient is inadvertently exposed to the risk of procedure related complication and possibly even to adverse effects of CRT, as shown by the Echo-CRT trial [15]. The device implantation without clinical benefit will definitely increase health care costs.

One major limitation in the patient data used in this thesis and therefore, the abovementioned translation into practice, is the absence of a untreated control group (no CRT device implanted or CRT-off) in the studies. Because of this lack of controls, we cannot attribute worse outcome to the absence of effect of CRT. The bad outcome could be caused by baseline worse HF condition, in which an untreated patients would have reached the endpoint even sooner.

CRT and non-LBBB

In **chapter 6**, we show that in 50% of patients with IVCD delayed activation of the LV lateral wall is present, as measured invasively by electro-anatomical mapping (EAM). 12-lead ECG assessment using QRS duration and other well-established indices were not able to identify the IVCD patients that harbour the electrical substrate amenable to CRT.

These results are important because studies up to now, do not agree on the level of benefit for non-LBBB patients [12-14]. In a substudy of the RAFT trial, Birnie et al. [14] showed no significant benefit of CRT with respect to death or HF hospitalization in 60 RBBB and 83 IVCD patients treated with CRT, compared to similar patients not treated with CRT. Event rate in these small subgroups of patients was low and therefore the analysis was not powered to prove significance. However, using improvement in a composite clinical score, which provides significantly more power to the analysis, did not result in significant improvement in the non-LBBB subgroup of the REVERSE trial (n=238) either [12]. Furthermore, echocardiographic endpoints like improvement in end-systolic volume and LVEF were all non-significant in this study. The largest number of non-LBBB patients (n=327), analysed in the MADIT-CRT substudy by Zareba et al. [13] once again showed no benefit in clinical outcomes when these patients were treated with CRT-D versus ICD. Echocardiographic outcomes however did improve significantly in the non-LBBB groups treated with CRT-D versus ICD. These reductions in end-systolic volume and increase in LVEF were present in both RBBB (n=136) and IVCD (n=183) subgroups.

The results from **chapter 6** demonstrate that while on average non-LBBB patients may not benefit from CRT, there may be an important subgroup of responders. This diversity within non-LBBB patients fits with the results from previous studies that showed that non-LBBB patients, especially IVCD patients, are a heterogeneous group of patients with multiple causes of conduction delay among which some can be corrected with CRT and consequently show benefit from therapy [12-14, 16, 17].

As some non-LBBB patients may have the electrical substrate amenable to CRT, they might benefit from therapy. Though it should be noted that although these patients harbour the electrical properties (delayed activation of the LV lateral wall), they might not fulfil LBBB criteria because of the presence of scar or other known factors decreasing the chance of benefit from CRT. As IVCD is common among patients currently being referred for CRT, the search for an ECG marker differentiating those IVCD patients with the electrical substrate present deserves to be intensified.

QRS area in patient selection for CRT

In **chapter 7** we try to contribute to the quest for a better 12-lead ECG marker for the substrate amenable to CRT by evaluating the association of QRS area with outcomes in CRT. In the abovementioned MUG cohort, QRS area was associated with echocardiographic as well as clinical outcome in CRT. Furthermore it proved to be associated with both clinical and echocardiographic response to CRT, whereas the combination of QRS duration and LBBB morphology, currently used in patient selection for CRT, was not.

The data adds considerably to the already available data in small single centre studies [18, 19] on the value of vectorcardiographic QRS area in identifying patients able to benefit from CRT. Moreover, Mafi Rad et al. [20] have shown that QRS area has a stronger association with the presence of delayed activation of the left ventricular lateral wall than various LBBB definitions and QRS duration. The recent multicentre prospective Markers of Response

to CRT (MARC) observational study in the Netherlands investigated a large range of potential biomarkers of CRT response in a group of 230 patients. This study found that QRS area was the strongest marker of echocardiographic response to CRT, out of all tested predictors [21].

The analysis in **chapter 7** shows that QRS area has added value in differentiating between responders and non-responders in the category of patients with an LBBB morphology and a QRS duration above 150ms (class I indication), although this category is already recommended for CRT by current guidelines. An even larger additive value of QRS area is achieved in the non-class I patients. **Chapter 7** shows that non-class I patients with a QRS area $\geq 109 \mu\text{Vs}$ have a similar clinical and echocardiographic outcome in CRT as class I patients. Moreover, in multivariable analysis of the ECG markers, QRS area proved to be the only marker independently associated with clinical outcome.

While the strength of this study is the large number of (real-world) patients included, the true “CRT benefit” can only be quantified by analysis in a randomized trial. This is currently being performed for data from the RAFT study [14]. Furthermore, while class I patients are already recommended for CRT implantation, adding QRS area to the selection for CRT would reduce the number of non-responders. However, use of QRS area in non-class I patients could uncover potential responders who are currently not selected for CRT. For the latter purpose, our group is currently starting a prospective observational multimarker study (MARC-2 study), like the aforementioned MARC-study, now focussing on non-LBBB patients.

For the analyses presented in this thesis, QRS area was calculated using custom-made software to converge vectorcardiographic data and the QRS area algorithm from the original digital 12-lead ECG signals. An important step towards a wider clinical use of QRS area is to program the algorithm for its calculation into ECG machines. When, indeed QRS area can be calculated automatically and its value will be further established in substudies of randomized trials, it may be possible that QRS area replaces LBBB morphology and QRS duration as ECG markers for patient selection in CRT. Such use would avoid the subjectivity and variability involved in defining LBBB morphology, **‘simplifying’** patient selection and increasing prediction of outcomes to CRT.

Patient management

The aim of the research presented in **part II** of this thesis is to introduce a solution for the complex care for HF patients treated with CRT. As the reasons for non-response or diminished benefit from CRT are numerous, complexity of management of these patients is high, needing both HF and electrophysiological evaluation and treatment. This often leads to a large burden on the outpatient clinic, with many consultations and additive investigations. Moreover, as these patients are by definition limited because of their disease and frequent comorbidities, the burden of visits and examinations for these patients is high.

In this part of the thesis we show how we benchmark and implement a structured CRT patient management program, including evidence and experience-based process and medical management recommendations for care of HF patients treated with CRT. The consensus CRT care pathway paper presented in **chapter 8** differs from guidelines [2, 22] and consensus papers [23] already available in such a way that it offers the reader an ready-to-use blueprint including tools (checklists) to compare and improve their current practice. Guidelines scanty address the topic of management of the HF patient with CRT, apart from the patient selection and implantation phase. Moreover, most of the recommendations on patient management have a level of evidence C (expert consensus) and are of little help to introduce and implement a CRT patient management program in clinical practice [1, 2].

Reorganization of outpatient HF care has been introduced and broadly accepted in the last decades. In order to cope with the already vast burden on the healthcare system, studies have shown outcomes in HF patient nurse-lead care to be at least as good as, if not better than usual care [24, 25]. To maintain high quality in care for CRT patients and to be able to cope with increasing demands, implementation of CRT care into the already broadly implemented nurse-led HF outpatient clinics seems inevitable.

While checklists have been used before in HF treatment, they have not been used in CRT practice yet. The IMPROVE-HF prospective multicentre registry included over 30.000 patients from over 160 US clinics. In this study the introduction of clinical decision support tools and algorithms provided significant improvement of adherence to guideline recommended treatment on 5 to 7 performance indicators among which medication adherence, ICD and CRT implantation and HF education [26]. These results prove the value of the translation of extensive guidelines into practical tools for the implementation of evidence-based medicine. Altman et al. [27] specifically addressed the CRT patient population and recognized the complexity of the combination of HF and device care in this population. The effect of a structured multidisciplinary care program was compared to a retrospective usual care cohort at the same site. They constructed a care pathway for CRT patients in which a structured evaluation of CRT patients was performed by both HF specialist and electrophysiologist at predetermined times of follow-up until discharge into normal care at 6 months post-implantation. Compared to usual care, they found a significant improvement in event-free (hospitalization, transplantation and death) survival after 2 years follow-up. Mullens et al. [28] also investigated a protocol-driven approach to CRT patient management. Focussing on finding reasons for suboptimal response in CRT patients referred for optimization, a designated nurse and cardiologist evaluated CRT patients in a structured follow-up program. The intervention group showed a significantly lower event-rate (all-cause mortality, cardiac transplantation, LVAD implantation and first HF hospitalization) within 6 months of follow-up [28, 29].

Whereas these studies support the idea of a structured, protocol driven optimization pathway, interventions rely on time and extensive material resources or highly specialized personnel available for the process. The aim of the benchmark CRT care pathway presented in this thesis is to reassure structured, evidence-based CRT care, without relying on specialized personnel or increasing local health care burden. In contrast, by including detailed information on 'minimal' resources needed we offer a chance to cut away 'waste' from the process in order to reduce unnecessary resource use, in a way '**simplifying**' the CRT care process without losing quality of care.

Pathway development and implementation strategies have only recently been introduced to optimize processes in HF care management [30]. Reviewing reports on care pathway introduction into HF care, this exclusively concerned in-hospital treatment of HF patients. The introduced interventions led to a decrease of mortality rates and length of hospital stay, but did not have any effect on readmission rates or hospital costs [30]. Though, in-hospital treatment of HF patients seems difficult to manage in a care pathway because of high variability of patient presentation. As outpatient HF care generally addresses patients in the stable phase of the disease, this would perhaps be a more suitable phase of the disease to be managed in a structured way.

In **chapter 9** we describe the implementation of the aforementioned care pathway into the Maastricht University Medical Centre (MUMC) outpatient HF care program. In order to implement the care pathway and reorganize outpatient management processes, lean six sigma methodology was used. This methodology has been used in the outpatient clinic previously for the introduction of an outpatient syncope pathway in 5 European hospitals [31]. The

introduction of the care pathway showed to result in a significant reduction of time-to-diagnosis, and a significant increase in diagnostic yield. Furthermore, it resulted in a significant reduction of resource utilisation.

Currently, we are awaiting results on medical and organizational outcomes of the introduced CRT care pathway. However, when comparing 64 patients (2015-jun 2016) included in the care pathway to 41 patients that received a CRT device in the year (2012) before implementation of the care pathway significant advantages become apparent. With respect to care-related outcomes there is a significant reduction in referral to treatment (implantation) time (65 to 46 days), in-hospital stay for implantation of the device (2.1 to 1.1 days), and a significant reduction in follow-up consultation in the first six months of follow-up (3.8 to 2.6 consultations). Medical and patient related outcomes generally take more time and numbers to show significant improvement and hence echocardiographic response to CRT does not show any significant increase. Intermediate quality of care endpoints do show clear improvements, as the CRT care pathway lead to significantly better identification of possible reasons for non-response to CRT in patients. For instance, increased use of guideline recommended HF medication, increased recognition and treatment of comorbidities, and identification and reprogramming of ineffective delivery of CRT, and consideration of baseline electrical dyssynchrony and expectations of therapy. These preliminary results provide high hopes for improved echocardiographic and eventually clinical outcomes on the long term. Importantly, from the individual patient and health care providers perspective, satisfaction with CRT management seems to be greatly improved.

Results from the introduction of the CRT care pathway into our local clinic will be presented in the near future. As this prospective study has been conducted in a non-randomized fashion its results, if as anticipated, will have to be replicated in a RCT to definitively establish the value of this reorganization of CRT care.

Conclusions

The main conclusions of the present thesis are that regarding patient selection for CRT our current ECG parameters have considerable caveats which need to be overcome. The analysis in the MUG database strongly suggests that selection can be improved AND **'simplified'** when QRS area instead of standard ECG markers QRS duration and morphology are used. Improvements in patient selection can be expected both with the sole use of QRS area, or in combination with the established ECG makers, improving selection in patients with a current class I indication and even more so in those without a class I indication for CRT implantation.

With respect to care for the patient treated with CRT the thesis provides an evidence and experience based consensus blueprint for a structured CRT care pathway. Which aims to help in reducing (unnecessary) resource use while maintaining quality of care for these patients. Preliminary results show that reorganizing local CRT care using this blueprint CRT care pathway may help establishing these goals.

In conclusion this thesis shows that **'simplifying'** CRT patient selection and patient management may be **'the key to CRT'**.

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Summary

Valorization

Samenvatting

Dankwoord

List of publications

Curriculum Vitae

Summary

Heart failure (HF) is a clinical syndrome entailing symptoms like shortness of breath, decreased exercise tolerance, fatigue and ankle swelling. Despite huge progress in the treatment of HF in the last couple of decades annual mortality is 1 in 10 and hospitalization 1 in 3 patients. Furthermore, quality of life of these patients remains low. One of the abnormalities that contribute to development of HF is abnormal, slow conduction of the electrical impulse within the heart, which leads to ineffective cardiac contraction.

When electrical conduction is normal, the specialized conduction tissue in the heart ensures a rapid and synchronous electrical activation of the myocardial cells and an coordinated contraction of the ventricles. In about one in three HF patients a defect in the electrical conduction is present.

A specific therapy is available to treat the electrical dyssynchrony: cardiac resynchronization therapy (CRT). To this purpose, a biventricular pacemaker; with electrodes in the right and left ventricle, is implanted. Large, randomized trials have shown that CRT improves the electrical synchrony and cardiac contractility. As a consequence symptoms decrease and prognosis improves. However, the benefit of a patient from CRT varies considerably, ranging from complete resolution of HF to worsening of the disease.

This thesis describes research aiming to improve the outcome of CRT through two approaches:

1. Improve the selection of patients that should receive CRT
2. Improve the clinical management of patients that receive CRT

Part I: Patient selection

The most common tool for patient selection in CRT is the electrocardiogram (ECG). The presence of a conduction disorder results in an increase in the total activation time of the ventricles, expressed as a longer duration of the QRS-complex on the ECG. Indeed, QRS duration was the first ECG marker for selection of CRT patients. However, not all QRS prolongation indicates dyssynchrony amenable to CRT, for example delayed activation in the right, rather than the left ventricle, or prolongation caused by non-conductive scar. Around ten years ago the morphology of the QRS complex was shown to be associated to response in CRT. Multiple studies showed that in patients with left bundle branch block (LBBB), response to CRT was significantly better than in non-LBBB patients. Ever since, prevailing guidelines have adopted LBBB as the leading criterion for patient selection in CRT. However, like QRS duration, LBBB QRS morphology has its limitations. Importantly, there are several definitions of LBBB. Moreover, qualification of LBBB is rather subjective.

In the first part of this thesis we have evaluated LBBB as a patient selection criterion in CRT. For this purpose, we have evaluated four currently used LBBB definitions. Four researchers assessed one hundred baseline ECGs of patients who underwent CRT implantation, applying the exact LBBB definitions. Next to this, four experienced cardiologists assessed the same ECGs for LBBB based on their clinical judgement. Finally, two researchers and two cardiologists assessed the ECGs twice for intra-observer variability. When two different reviewers assessed the same ECG, there was a one in five chance of discordance. When comparing the use of exact definitions to assessment by experienced

cardiologists, 2 in 5 judgements were discordant. Assessment of the same ECGs twice by one reviewer showed a discordant assessment of 1 in 10 ECGs. Translating these results to clinical practice, this means that assessment of LBBB is subject to large variability either when using exact definitions or clinical assessment. Moreover clinical assessment shows a large discordance with the assessment according to definitions used in trials, which puts major concerns at the translatability of trial results to current clinical practice.

When major differences exist in the qualification of LBBB, it is of major importance that every available definition has the same significance in CRT. In collaboration with Cardiocentro Ticino, Lugano, we evaluated the effect of the presence of LBBB on the baseline ECG according to different ECG definitions, on outcome in a group of over 300 CRT patients. Outcomes were time to death, time to HF hospitalization and echocardiographic reverse remodelling. Results from this study showed that the presence of LBBB according to some definitions did, and according to others did not relate to prognosis in CRT. This finding may be of major importance to clinical practice, excluding commonly used LBBB definitions from a role of importance in CRT.

We sought to confirm this result in a larger population. In order to get access to a large population of CRT patients we collaborated with the university medical centres of Utrecht and Groningen to create a retrospective CRT database ('MUG': Maastricht-Utrecht-Groningen) including every CRT treated patient in the past 15 years, including almost 2.000 patients. In an analyses of 1.500 of these patients, we found that, in contrast to the earlier mentioned study, the presence of LBBB according to any definition identified patients with better prognosis than the respective non-LBBB CRT patients. On average the LBBB patients had a 40% increased chance of being alive without a cardiac assist devices or transplantation, after 3 years of follow-up. When the individual criteria composing the LBBB definitions were evaluated, it appeared that every LBBB definition contained criteria without any association to outcome. Moreover only 3 criteria were independently associated to outcome. Combining these criteria however, did not improve diagnostic performance of LBBB. These findings support the use of LBBB, what ever the definition.

Despite the evidence for the superior prognosis of CRT patients with LBBB at baseline compared to non-LBBB CRT patients, patients without LBBB can certainly experience benefit from CRT. Earlier studies have shown that amongst non-LBBB patients, there are patients profiting considerably from CRT, but also patients experiencing significant harm from CRT. Prevailing guidelines, therefore are not clear on how to treat this patient group. The heterogeneous response to CRT may be explained by the existence of true left ventricular dyssynchrony in part of these patients, but the absence of dyssynchrony in others. In the latter, CRT may introduce dyssynchrony rather than cure it. In order to further investigate this hypothesis, we conducted a study in 23 patients without LBBB QRS morphology present on their baseline ECG, eligible for CRT. During implantation of the CRT-device in these patients, we assessed the duration of the very first start of the electrical activation of the ventricles until the local activation at the left ventricular lateral wall (measured in any possible CS tributary vein available). After all, in LBBB patients it has been shown that the left ventricular lateral wall is the area of latest activation, and the presence of late activation of the left ventricular lateral wall is associated to the effectiveness of CRT (independently from the presence of LBBB). Our study showed that in one in two patients without LBBB, there is significantly delayed activation of the left ventricular lateral wall. However, none of the tested ECG parameters were able to identify those patients with delayed activation present. Up until this point this thesis has focussed on the limitations of the major criterion for patient selection in CRT, concluding that although various available LBBB definitions all seem associated to prognosis in CRT patients, variability in assessment seems (too) large. Moreover, it does not seem that the 12-lead ECG is able to further refine

the identification of patients able to benefit from CRT. Therefore in this thesis we assessed an alternative for the currently recommended ECG criteria.

Even though 12-lead ECG markers have their limitations, the ECG is a real time display of the electrical activation of the heart, and available to every physician involved in CRT. The derived marker(s) need to take into account the direction of the electrical activation more than QRS duration, and need to be less sensitive to subjectivity and variability than LBBB QRS morphology.

Vectorcardiographic analyses display the heart's electrical activation in three main directions as a 'vectorloop', earlier studies have shown this instrument to be useful in assessing eligibility for CRT. Our group has shown that a vectorloop can reliably be constructed from the standard 12-lead ECG, and that a simple parameter, QRS area, can be calculated using the area under the QRS complex in these three directions. Smaller studies have shown that baseline large QRS area is associated to a good prognosis in CRT patients.

In the earlier mentioned MUG database, we have analysed the association of QRS area to the occurrence of events in CRT treated patients. In this cohort, it appeared that QRS area significantly improved identification of patients with good and bad outcome to CRT compared to the recommended combination of QRS duration and LBBB. QRS area provided additive diagnostic value combined with classic ECG criteria. Moreover, QRS area appeared to be equally effective in the subgroup of patient with non-LBBB QRS morphology. From these results we concluded that QRS area could be a valuable addition, or even better, alternative to currently used criteria in prevailing guidelines for CRT. To further establish the value of QRS area in patient selection for CRT, our group will conduct an analyses of QRS area in one of the large randomized CRT-trial data, including CRT-treated and non-treated patients. Therefore QRS area can truly be established as a marker of amenability to CRT. Moreover, if the results presented in this thesis prove to be reproducible, QRS area will be established on the same level of evidence as the classic criteria, justifying consideration for guideline recommendation. Another future step will be the evaluation of fully automated calculation of QRS area, to increase availability up to the level of QRS duration and morphology.

Part II: Patient management

Care for HF patients treated with CRT is complex. It demands knowledge of HF disease management and device management of the treating physician. In clinical practice, however, these are subspecialties of different cardiologists. Therefore, in order to deliver optimal medical care, the fragile HF patient needs many consultations with different physicians and allied professionals. Some studies have shown that intensive and multidisciplinary follow-up care for CRT patients results in superior response to therapy, with better long term outcomes. However, taking into account the already vast burden on (local) health care systems, introducing such elaborate care processes does not seem sustainable on the long term. In order to tackle the issue of increasing health care burden, in general HF patient management, solutions have been suggested some time ago. Research has shown that substitution of specialist care by HF nurses is non-inferior. Thereafter, worldwide general HF clinics introduced nurse-lead HF clinics. Furthermore, checklists have proven to improve adherence with guidelines in HF care, subsequently leading to improved quality of care. None of the abovementioned interventions, have however found their way to present CRT practice.

In this thesis we describe the design and implementation of a care system which aims to optimize management of CRT patients in the sense of quality of care and governability in the future. Optimal quality of care is achieved by combining HF- and device knowledge into standardized checklists. Simultaneously making care for CRT patients efficient by standardizing and combining consultations and specialist-lead care. In order to achieve this, an international panel of physicians with extensive experience in CRT, and backgrounds in HF and device management, put together a consensus document. This document summarizes the minimal medical content of care system for CRT patients, to guarantee quality of care. This medical content is subscribed to different steps in CRT management; from patient selection to implantation of the device and follow-up thereafter. Quality of care is ensured by providing checklists relevant to each process step. Moreover efficient care was ensured by combining consultations and minimizing loss of information in the process. After designing a blueprint of the optimal care process, in 2014 we started implementing the CRT care pathway in the Maastricht University Medical Centre + (MUMC+). As process management in health care is relatively new, the implementation was supervised by consultants specialized in lean process management, ensuring minimization of waste in the new process.. First step was the description of the current care process. Next to the evaluation of the minimal requirement for high quality of CRT care, determinants of efficient health care were evaluated. This showed that the CRT care process in the MUMC+ was high in quality, but inefficient, with a high burden for CRT patients, as well as the local health care system. In multiple phases the blueprint CRT care pathway was implemented to replace the old care process. This entailed reorganisation of planning and logistics, making recourses available and training of the healthcare professionals involved in the process. Unfortunately the final evaluation of the introduced CRT care pathway was not finished at the time this thesis was finished. However, for (inter)national symposia we have conducted multiple preliminary evaluations in small numbers of patients included up till then. These evaluations show important improvements in determinants of efficiency, including a clear reduction in consultations, referral-to-treatment times, and in-hospital days for implantation. Clinical outcomes like echocardiographic remodelling, patient reported HF complaints and HF hospitalization are non-inferior to the previous care process. However positive results on the identification of determinants of response to CRT and optimization of general HF treatment compared to the baseline assessment are encouraging for future evaluations of clinical outcomes in a larger group of patients. Moreover, individual patient and health care professional's comments over the years since implementation have been very positive.

In conclusion, the research presented in this thesis has shown that currently recommended aids in patient selection for CRT show low reproducibility and therefore add to the large diversity in patient response to CRT in clinical practice. Importantly, in this thesis we have shown that a large part of the patients that have a questionable indication for CRT according to current selection criteria, do show evidence of dyssynchrony amenable to CRT. The limitations laid bare for complex and subjective QRS morphology in this thesis, do not apply to the simple, quantitative QRS area. This new marker in CRT was shown to be strongly associated to outcome in CRT with better association than the currently recommended markers. The research in this thesis focussing on patient management in CRT presents a blueprint for efficient, multidisciplinary care that can be implemented in any HF clinic dealing with these patients, aiming for sustainable high quality of CRT care.

Valorization

About 1-2% of the adult population in developed countries suffers from heart failure (HF). (1) Of these patients 36% has a significantly reduced ejection fraction ($\leq 35\%$). (2) Despite advances in therapy, HF has a poor prognosis. One-year all-cause-mortality in patients with HF is 7%, and reaches 17% in patients hospitalized for HF. Hospitalization rate is 32% per year (3), and patients experience a significantly reduced quality of life. Cardiac resynchronization therapy (CRT) has been shown to be able to reduce mortality and HF-hospitalizations significantly (by approximately 25% and 40%, respectively), and to significantly improve quality of life of the patients. (4)

CRT aims at treating HF patients in which electrical conduction disorders contribute to, or cause HF with a reduced ejection fraction. When applying current guidelines (HF with reduced ejection fraction, wide QRS complex) approximately 10% of all HF patients could be considered for CRT. (5)

Although CRT provides great reductions in HF burden on a population level, the benefit at the level of the individual patient varies significantly. Studies show a great benefit from therapy in 50-70% of patients but worsening in up to 22%. (6, 7) As CRT entails the implantation of a costly biventricular pacemaker or ICD device, the risk of procedural complications, and the need of intensive follow-up and future invasive procedures, patient selection and management in CRT are of great importance.

Patient selection

In **part I** of this thesis we have shown that the most important recommended 12-lead ECG parameter used in patient selection for CRT, left bundle branch block (LBBB), has important limitations. Guidelines embrace this marker with high levels of evidence, based on several substudies of large randomized trials. However, guidelines neglect to take into account the existence of multiple LBBB definitions, and the overall subjectivity in judgement of the QRS morphology. We have demonstrated that the interpretation of LBBB-patterns on the 12-lead entails great inter-observer and inter-definition variability and has a poor (no more than moderate) association with clinical interpretation by experienced implanters. These findings question the applicability of the results of the aforementioned clinical trials on clinical practice.

Because of the great variability found in aforementioned analysis, we have investigated the associations of each of the available LBBB definitions' associations to outcome in CRT patients. We confirm that patients, qualified as LBBB according to any definition have significantly better outcomes to CRT, compared to those qualified as non-LBBB patients. However, the analyses in this thesis also show that the available LBBB definitions entail morphological criteria not relevant to patient selection in CRT. Therefore, LBBB definitions may be unnecessarily complex, perhaps leading to the abovementioned variability. In a quest to improve the prediction of benefit from CRT in patients, we have designed a novel outcome based LBBB definition, consisting of the morphological criteria that proved to be independently associated with CRT outcome in our retrospective cohort analysis. However, this outcome-based definition did not improve diagnostic yield. Therefore, it appears that the morphological features of ventricular activation, displayed on the 12-lead ECG, are not able to further improve patient selection.

In order to help improve patient selection, we have explored a novel ECG-derived marker of dyssynchrony. After synthesis of the vectorcardiogram from the 12-lead ECG, the QRS area was calculated and, in a large patient cohort, evaluated for its association with outcome to CRT. Our findings greatly support earlier small studies showing a strong association of QRS area with clinical and echocardiographic outcome to CRT. In the analysis presented, QRS area improved prediction of outcome over the currently recommended combination of LBBB and QRS duration. Furthermore, QRS area is especially of value as it provides significant separation in patients with better and worse outcome in the subgroup of non-LBBB QRS morphology, a group in which the application of CRT is currently debated (Guideline IIa and b recommendations). (1)

Application of QRS area in clinical practice and recommendation of its use in the prevailing guidelines would require the prospective evaluation of QRS area appended or replacing current patient selection parameters. However, as the value of current markers has been shown in subanalyses of the landmark randomized controlled trials, it seems realistic to evaluate QRS area in the same way. This is currently being performed in data from the RAFT study. (8) Furthermore, while LBBB patients already have a class I recommendation for CRT implantation, adding QRS area to the selection for CRT could improve specificity, denying non-responders CRT. However, use of QRS area in the currently disputed indications in non-LBBB patients could uncover potential responders who are currently not selected for CRT. For the latter purpose, our group is currently starting a prospective observational multimarker study (MARC-2 study) focussing on non-LBBB patients.

For the analyses presented in this thesis, QRS area was calculated using custom-made software to converge vectorcardiographic data and the QRS area algorithm from the original digital 12-lead ECG signals. An important step towards a wider clinical use of QRS area is to program the algorithm for its calculation into ECG machines. When, indeed QRS area can be calculated automatically and its value will be further established, it may be possible that QRS area replaces LBBB morphology and QRS duration as ECG markers for patient selection in CRT. Such use would avoid the subjectivity and variability involved in defining LBBB morphology, '**simplifying**' patient selection and increasing prediction of outcomes to CRT.

Patient management

Apart from selecting the patient able to benefit from CRT, implantation of the biventricular pacemaker or ICD device, follow-up, and general patient management in all steps involved in CRT for HF is of great importance. The patient will be followed for both HF disease management and resynchronization therapy or device management. These properties are generally specialties of several different health care providers. Furthermore, studies have shown a wide range of device- and HF-related factors related to suboptimal benefit from CRT. (9-11) CRT patient management therefore is comprehensive and complex, and often entails many health care providers' contacts and additional investigations. In this thesis we presented a blue print 'CRT care pathway', combining the knowledge of experienced health care providers into a streamlined process. This blueprint allows clinics involved in care for HF patients treated with CRT to compare their current patient management process and add steps or checks essential, or instead cut 'waste', for optimal patient management, with minimal health care and patient burden. Furthermore, we shown the process of implementation into the Maastricht University Medical Centre + and the reorganization involved in introducing the CRT care pathway into the existing CRT patient care. All together **part II** of this thesis provides the tools to introduce a structured care pathway in any CRT follow-up clinic, and implement it into current care. Although

the evaluation of these changes has not yet finished, and therefore the benefit for both patients and clinic have not been proven, patients and health care providers' feedback are encouraging. Multidisciplinary CRT programs have been studied and found effective before. (9, 12) The average clinic does not have the resources available to change their CRT follow-up practice into the programs evaluated in these studies as they entail the addition of expertise or resources. The presented CRT care pathway, however aims to increase patient benefit from CRT, as well as decrease patient and health care burden. When evaluation of the care pathway proves to increase patient benefit and/or reduce patient and health care burden, the research presented here will allow for easy implementation into any clinic interested in improvement of their care for heart failure patients treated with CRT.

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Samenvatting

Hartfalen is een verzameling van klachten, zoals kortademigheid, verminderd inspanningsvermogen, vermoeidheid en vocht in de benen. Ondanks veel vooruitgang in de behandeling van hartfalen sterft jaarlijks 1/10 van de patiënten en wordt meer dan 1/3 van de patiënten jaarlijks opgenomen in het ziekenhuis. Daarnaast is de kwaliteit van leven van patiënten met hartfalen nog altijd erg slecht. Bij een deel van de patiënten met hartfalen is er sprake van een afwijking in de elektrische aansturing van het hart. De pompfunctie van het hart wordt begeleidt door een elektrische prikkel die over het hart trekt. Normaal zorgt een speciaal geleidingssysteem in de hartkamers voor een snelle, synchrone elektrische activatie, waardoor een efficiënt leegknijpen volgt. Bij ongeveer 1/3 van de hartfalen patiënt is er sprake van een geleidingsstoornis, die een snelle en synchrone activatie van de kamers onmogelijk kan maken. Dit kan leiden tot een minder efficiënt samentrekken van het hart met (verergering van) hartfalen als gevolg. Voor de correctie van dyssynchrone elektrische activatie van de linker hartkamer is een specifieke behandeling beschikbaar: cardiale re-synchronisatie therapie (CRT). Hiervoor wordt een pacemaker gebruikt met elektroden in de rechter en linker kamer. Grote, gerandomiseerde onderzoeken hebben laten zien dat CRT de elektrische activatie en daarmee de pompfunctie van het hart verbetert. Dit zorgt zo voor vermindering van klachten van hartfalen en een betere prognose. Het effect van CRT verschilt echter enorm tussen verschillende patiënten, variërend van volledig verdwijnen van hartfalen tot verslechtering van de ziekte.

Het onderzoek gepresenteerd in dit proefschrift heeft als doel de resultaten van CRT te verbeteren via 2 wegen:

1. Het verbeteren van de selectie van patiënten voor CRT
2. Het verbeteren van de behandeling van patiënten die CRT krijgen.

Deel I: Patiënten selectie

Het hartfilmpje (ECG) is bij uitstek het instrument dat gebruikt kan worden bij de patiënten selectie voor CRT. Dit makkelijk beschikbare hulpmiddel geeft immers de elektrische activatie van het hart weer. Dat (een deel van) de linker kamer later geactiveerd wordt dan de rest betekent dat de totale activatie van de kamers, weergegeven door het 'QRS-complex' op het ECG langer duurt, en dus de 'QRS duur' groter wordt. Sinds het begin van CRT voor de behandeling van hartfalen is de QRS duur op het ECG al gebruikt om patiënten te selecteren. Echter kan de QRS duur verlengd worden door vertraging van de activatie van (delen van) zowel de rechter als de linker kamer van het hart. Bovendien kan de activatieduur van de kamers door bijvoorbeeld littekens lokaal vertraagd zijn. Gezien het de linker hartkamer is die behandeld kan worden middels CRT, moet de dyssynchrone elektrische activatie wel ook de (gehele) linker kamer betreffen. Naast de duur van het QRS is sinds ongeveer 10 jaar bekend dat specifieke patronen van het QRS-complex, behorende bij geleidingsstoornissen van het speciale geleidingsweefsel van de linker (linker bundeltak blok) kamer, een beter effect van CRT voorspellen. Sindsdien hebben de richtlijnen voor de behandeling van hartfalen behoudens QRS duur ook linker bundeltak blok (LBTB) als leidend criterium aangenomen om patiënten voor CRT te selecteren. Echter evenals QRS duur, heeft LBTB haar beperkingen. De belangrijkste beperking is dat er meerdere definities beschikbaar zijn die naast elkaar gebruikt worden. Bovendien zijn de beschrijvingen van deze definities gevoelig voor verschillende interpretaties.

Het eerste deel van dit proefschrift neemt het gebruik van LBTB als selectiecriteria onder de loep. Er werden vier verschillende LBTB definities vergeleken die recent onderzocht zijn en aanbevolen worden door beschikbare richtlijnen. Vier onderzoekers beoordeelden honderd ECG's van patiënten die CRT kregen en pasten de definities exact toe. Daarnaast beoordeelden vier in CRT ervaren cardiologen de ECG's naar eigen inzicht van LBTB (zoals ze dat in de dagelijkse praktijk zouden doen). Tevens beoordeelden enkelen van hen dezelfde ECG's twee maal. Hieruit bleek dat wanneer dezelfde persoon twee maal hetzelfde ECG beoordeelt, één op de tien ECG's de tweede keer anders beoordeeld wordt. Daarnaast is er een kans van een op vijf dat een beoordeling verschilt als twee verschillende personen hetzelfde ECG beoordelen. Wanneer we de in studies onderzochte definities vergeleken met de beoordeling door de cardiologen in de praktijk, bleek dat voor slechts maximaal 60% overeen te komen. Dit betekent dat er in de dagelijkse praktijk waarschijnlijk grote verschillen in patiënten selectie bestaan en het onduidelijk is of we dezelfde effecten van CRT in de praktijk mogen verwachten als aangetoond is in de studies.

Omdat er grote verschillen bestaan tussen verschillende LBTB definities, is het belangrijk dat de elke definitie eenzelfde betekenis heeft voor de prognose van de patiënt behandeld met CRT. Daarom werd er in samenwerking met het Cardiocentro Ticino in Lugano, in een groep van meer dan driehonderd CRT patiënten gekeken of de aanwezigheid van LBTB volgens diverse definities geassocieerd was met de prognose. Uit de studie bleek dat de aanwezigheid van LBTB volgens enkele definities wel, en andere definities niet helpt bij het herkennen van patiënten met een gunstige prognose (uitblijven van overlijden, opname vanwege hartfalen en verbetering van de pompfunctie van het hart). Deze bevinding kan van groot belang zijn voor de klinische praktijk, gezien dit veel gebruikte LBTB definities zou uitsluiten voor gebruik voor de selectie van patiënten voor CRT.

Om dit verder te onderzoeken, is er in samenwerking met de universitaire ziekenhuizen in Utrecht en Groningen naar het gezamenlijke aantal patiënten behandeld met CRT over de afgelopen vijftien jaar gekeken in de 'MUG' database (Maastricht, Utrecht, Groningen). Dit betrof een totaal aantal van bijna 2.000 patiënten. In 1.500 van deze patiënten bleek, in tegenstelling tot de eerdere studie, dat de aanwezigheid van LBTB bij patiënten volgens alle van de hier vergeleken definities hielp bij het herkennen van hen die een betere prognose hadden na CRT. Hierbij hadden de LBTB patiënten over een periode van drie jaar gemiddeld een 40% lagere kans op overlijden, een steunhart of een harttransplantatie dan patiënten die geen LBTB op hun ECG hadden. Wanneer de LBTB definities, die bestaan uit diverse karakteristieken van het hartfilmpje, opgesplitst werden tot deze individuele karakteristieken, bleek dat deze niet allen bijdragen aan het herkennen van de patiënten met een goede prognose. Deze karakteristieken leiden dus mogelijk onnodig tot grotere variatie in de beoordeling van LBTB. In een poging om tot een superieure definitie voor LBTB te komen, gericht op het voorspellen van uitkomst bij CRT, werden de individuele karakteristieken die bijdroegen aan het herkennen van patiënten met een gunstige prognose gecombineerd tot een nieuwe definitie. Deze definitie leidde echter niet tot een verbetering van de herkenning van de CRT patiënten met een gunstige prognose.

Ondanks dat de studies in dit proefschrift de waarde van de aanwezigheid van LBTB voor de herkenning van een patiënt die baat heeft bij CRT bevestigen, betekent dit niet dat patiënten zonder LBTB geen enkel voordeel van CRT zouden kunnen hebben. Eerdere studies hebben laten zien dat er in de groep patiënten met geleidingsstoornissen anders dan LBTB, patiënten bij zijn die profiteren, maar ook die nadeel ondervinden van CRT. De huidige richtlijnen zijn dan ook niet duidelijk voor deze patiënten groep. Daarom hebben we in een studie met 23 patiënten zonder aanwezigheid van LBTB, tijdens de implantatie procedure van een CRT apparaat, de daadwerkelijke duur van het allereerste begin van de elektrische activatie van de kamers tot aan de lokale activatie van alle mogelijke punten aan

de van de linker kamer gemeten. In patiënten met LBTB is namelijk aangetoond dat dit het gebied van laatste activatie is, en bovendien is een late activatie in dit gebied (los van de aanwezigheid van LBTB) een voorspeller van een gunstig effect van CRT. Bij 50% van de patiënten zonder LBTB bleek er in onze studie toch sprake van een dergelijke late activatie van de vrije wand van de linker kamer. Helaas konden we bij deze kleine groep patiënten geen kenmerken van het ECG vinden die duiden op aanwezigheid van die late activatie.

Tot dusver hebben wij in dit proefschrift laten zien dat het klassieke LBTB een teken is voor een gunstige prognose bij patiënten die overwogen worden voor CRT. Echter, de verschillende LBTB definities zorgen voor een grote diversiteit van geselecteerde patiënten. . Bovendien lijken de meegenomen karakteristieken niet te combineren tot één superieure LBTB definitie.

Derhalve zijn we in dit proefschrift op zoek gegaan naar een alternatief selectie criterium. Hoewel het ECG tot op heden nog niet de gewenste specificiteit heeft om nabij 100% voordeel voor patiënten te komen, lijkt het gezien de directe weergave van de elektrische activiteit van het hart en de grote beschikbaarheid van het ECG voor iedere cardioloog wel het ideale instrument voor patiënten selectie. Een maat die meer rekening houdt met de richting van activatie dan de QRS duur en simpeler is dan LBTB lijkt nodig. Hiervoor is uit de ECG signalen het vectorcardiogram gereconstrueerd, dat de activatie van het hart in de drie hoofdrichtingen weerspiegelt. Uit eerdere, kleine studies was al bekend dat de grootte van het uit het vectorcardiogram berekende QRS area, geassocieerd is met de kans dat een patiënt baat heeft bij CRT.

In de eerder genoemde MUG database is gekeken hoe goed QRS area de prognose van CRT patiënten voorspelt. Het bleek dat QRS area meer onderscheidt maakt tussen CRT patiënten die een goede en slechte prognose hebben, dan (de combinatie van) de klassieke ECG criteria QRS duur en LBTB. Bovendien was dit onderscheidend vermogen ook aanwezig in de groep van patiënten die geen LBTB hebben. Ook wanneer QRS area als maat toegevoegd wordt aan de klassieke criteria lijkt dit een verbetering te geven van het onderscheid tussen patiënten die voordeel hebben en zij die dat niet hebben. Om de waarde van QRS area voor de patiënten selectie voor CRT werkelijk te bewijzen zullen wij in de nabije toekomst een analyse in één van de grote CRT-studies presenteren. In deze studies zijn patiënten behandeld met CRT en niet behandeld met CRT bestudeerd om het effect van CRT te bewijzen. Doordat ook onbehandelde patiënten beschikbaar zijn, is het mogelijk in deze studies de waarde van QRS area als voorspeller van het effect van CRT te bewijzen. Daarnaast dient voor de implementatie van QRS area in de klinische praktijk de bepaling volledig geautomatiseerd plaats te vinden. Met enkel het updaten van de software van huidige ECG-apparatuur met de simpele formule voor het berekenen van QRS area, kan in de toekomst deze maat voor iedere cardioloog en niet-cardioloog direct beschikbaar zijn bij het verrichten van het klassieke 12-kanaals ECG.

Deel II: Patiëntenzorg

De zorg voor patiënten met hartfalen behandeld met CRT verdient aandacht in dit proefschrift vanwege 2 belangrijke problemen. Ten eerste heeft 1 tot 2% van de volwassen populatie hartfalen. Dit betreffen met name ouderen. Hartfalen brengt een forse ziektelast voor de patiënt en veel zorgbelasting en kosten voor de maatschappij met zich mee. Bovendien wordt verwacht dat met de vergrijzing, het voorkomen van hartfalen en dus de zorgbelasting fors zal toenemen over de komende jaren. Ten tweede is de zorg voor hartfalen patiënten behandeld met CRT complex. Het vereist van de behandelend cardioloog dat deze kennis van zowel hartfalen als elektrofysiologie bezit. In de

praktijk zijn dit echter subspecialisaties binnen de cardiologie die niet vaak gecombineerd voorkomen. Dit betekent dat voor optimale zorg deze fragiele en laag-belastbare patiënten een veelheid aan consultaties bij de cardioloog nodig zijn. Hoewel enkele studies inderdaad hebben laten zien dat een intensieve en multidisciplinaire nazorg bij CRT patiënten een superieur resultaat oplevert op gebied van klachten en prognose, lijkt dit geen houdbare oplossing voor de lange termijn. Om het eerste probleem, de zorgbelasting, aan te pakken is bij de algemene hartfalen populatie reeds gezocht naar oplossingen. Hieruit is duidelijk gebleken dat verplaatsing van zorg naar gespecialiseerd opgeleid verpleegkundigen ten minste gelijkwaardig is aan zorg door de hartfalen-cardioloog zelf. Tevens is gebleken dat het werken met checklists in hartfalen zorg leidt tot een verbetering van het volgen van geldende richtlijnen, en dus kwaliteit van zorg.

In dit proefschrift beschrijven wij het ontwerp en de implementatie van een zorgsysteem waarin beoogd wordt optimale kwaliteit van zorg te leveren door het combineren van hartfalen- en elektrofysiologische kennis. Tegelijkertijd wordt de zorg efficiënter gemaakt met minder contacten of specialistische zorg. Hiertoe is door een internationaal panel van cardiologen met een hartfalen- en/of elektrofysiologie achtergrond een consensus document samengesteld van wat de minimale medische inhoud van een zorgsysteem voor hartfalen patiënten behandeld met CRT zou moeten zijn. De kwaliteit van de medische zorg werd door het ontwerp van checklists voor iedere afzonderlijke stap binnen het proces gewaarborgd. Na het ontwerp van een blauwdruk voor het proces, werd in 2014 begonnen met implementeren van het CRT zorgpad in het Maastricht Universitair Medisch Centrum + (MUMC+). Proces verander strategieën zijn relatief nieuw in de zorg. Om het zorgproces rondom de CRT patiënten te veranderen hebben we met hulp van gespecialiseerde consultants het bestaande zorgproces in kaart gebracht. Daarnaast hebben we determinanten van efficiënte zorg geëvalueerd. Hieruit bleek dat het proces inefficiënt was, met een hoge belasting voor patiënt en zorgsysteem. In fases hebben we daarna het nieuwe zorgproces geïmplementeerd. Dit omvatte het reorganiseren van plannings- en logistieke structuren, het beschikbaar stellen van de in het proces benodigde hulpmiddelen, en training van verantwoordelijke zorgprofessionals. Helaas is de definitieve evaluatie van het resultaat van de implementatie van dit nieuwe CRT zorgproces nog niet afgerond ten tijde van het afronden van dit proefschrift. Ten behoeve van presentaties op (inter)nationale congressen hebben voorlopige evaluaties in kleine aantallen patiënten echter laten zien dat er belangrijke verbeteringen van proces parameters zijn opgetreden, met een duidelijke vermindering van het aantal patiënten bezoeken, wachttijden en opnameduur rondom implantatie. Daarbij zijn medische uitkomsten, als echocardiografische verbetering, hartfalen opnames en patiënt gerapporteerd welbevinden gelijk gebleven. Positieve intermediaire uitkomsten als het aantal geïdentificeerde factoren dat bijdraagt aan het niet profiteren van CRT en algemene hartfalen behandeling geven echter goede hoop op verbeterde medische uitkomsten voor de toekomstige evaluatie bij een grotere groep patiënten. Daarnaast werd sinds implementatie van het zorgpad uit commentaar van individuele patiënten en betrokken zorgprofessionals duidelijk dat de verandering als zeer positief ervaren wordt.

Concluderend heeft het onderzoek gepresenteerd in dit proefschrift laten zien dat de huidige hulpmiddelen voor patiënten selectie voor CRT, hoewel bruikbaar, slecht reproduceerbaar zijn en bijdragen aan de grote diversiteit in patiënten selectie voor CRT in de klinische praktijk. Bovendien heeft een groot deel van de patiënten die volgens deze maten niet zo evident voordeel van CRT zullen hebben, wel degelijk dezelfde onderliggende elektrische vertraging als de patiënten die wel aan deze criteria voldoen. QRS area daarentegen blijkt een simpele, goed reproduceerbare maat met een betere voorspelling van een goede uitkomst in CRT. Verder beschrijft het onderzoek in dit proefschrift een blauwdruk voor een efficiënt zorgproces dat kwalitatieve, multidisciplinaire zorg voor CRT patiënten waarborgt met een gelijktijdige vermindering van de zorglast voor patiënt en zorgsysteem.

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Curriculum Vitae

Twan (Antonius) Martinus Wilhelmus van Stipdonk was born August 17th 1983 in Nuenen, the Netherlands. After attending high school at the Lorentz-Casimir Lyceum in Eindhoven in 2002 he started his medical training at the Faculty of Health, Medicine, and Life Sciences at the Maastricht University (UM). His interest in Cardiology developed during the 3rd year of medical training. This resulted in assisting in research with emeritus professor in transmural cardiology Ton Gorgels and dr. Miguel Lemmert. Following internships in cardiology were all attended at the Cardiology department of the Maastricht University Medical Centre (MUMC+). After obtaining his Medical Degree in July 2008, he was able to start as a physician at the same MUMC+ Cardiology department. After a short period of clinical work, an opportunity to join the PAAHR-project (Psychische en Arbeidsgerelateerde Aspecten van HartRevalidatie); a revision of the outdated Dutch cardiac rehabilitation guideline presented. Working together with dr. Petra Kuijpers (Cardiology Department, MUMC+) and professor Angelique de Rijk (Social Medicine Department, UM) he gave rise to the 2011 NVVC guideline of cardiac rehabilitation. During these 2 years, for 1 day a week, he remained doing clinical work at the Cardiology department in the MUMC+. After finishing this project in 2011 he resumed his clinical Cardiology training. After his 4th year of training, at the Zuyderland Medical Centre, Heerlen, mainly focussing on invasive procedural training, he became interested in the field of cardiac devices. Upon arriving back at the MUMC for his 5th year of cardiology training in 2015, this was noticed by current co-promotor, dr. Kevin Vernooij. He was offered the opportunity to put his cardiology training on hold for 2 years to start up research, mainly focussing on health care process management and development, with the CRT care pathway-project presented in this thesis. During this period a care pathway for CRT patient was developed and introduced into the MUMC with success. The intensive collaboration with heart failure cardiologists in this project attenuated his interest for devices to the overall (electrical) management of heart failure patients. Furthermore, during the research period he started a collaboration with the University Medical Centres of Utrecht and Groningen on a joint CRT patient database, leading to many of the papers presented in this thesis. Since the start of his PhD-track, he has presented his work at many national and international congresses, leading to the first prize in the EHRA young investigator award in 2017. After 2 years of dedicated research he went back to his clinical training keeping his focus on CRT and general heart failure management, getting his EHRA pacing and ICD certificate at the 2018 EHRA congress. Eventually he finalized his training in Cardiology Oktober 17th 2018. Currently he is working as a fellow in Electrical Management of Heart Failure in the MUMC+.