Mapping and prevention of cardiac dyssynchrony

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Mapping and prevention of cardiac dyssynchrony

**Towards better substrate identification and lead
implantation**

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 16 september 2016 om 10:00 uur**

door

Masih Mafi Rad

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Promotores:

Prof. Dr. H.J.G.M. Crijns

Prof. Dr. F.W. Prinzen

Copromotor:

Dr. K. Vernooy

Beoordelingscommissie:

Prof. Dr. J.C.A. Hoorntje (voorzitter)

Prof. Dr. T. Delhaas

Dr. M. Meine (Universitair Medisch Centrum Utrecht)

Prof. Dr. U. Schotten

Prof. Dr. J.L.R.M. Smeets (Radboud Universitair Medisch Centrum Nijmegen)

Voor mijn kleine wooshies Elyse en Ryan

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General introduction:
Background and general
aims of the thesis

Chapter

Introduction

In a normal heart, electrical activation starts in the sinus node, the physiological pacemaker of the heart which is located in the right atrium, and from there spreads through the atria. After reaching the atrio-ventricular node, the electrical activation is rapidly conducted toward the right (RV) and left ventricle (LV) through the specialized ventricular conduction system consisting of the His bundle, the right and left bundle-branches and the Purkinje fibers. Because conduction through the Purkinje fibers is much faster than myocyte-to-myocyte conduction, physiological depolarization of the RV and LV occurs fast and synchronously (Figure 1a). A fast and synchronous ventricular activation is considered of utmost importance for maintaining coordinate ventricular contraction and optimal cardiac pump function.

Dyssynchronous ventricular activation

In patients with left bundle-branch block (LBBB) or patients that receive RV pacing because of symptomatic bradycardia, the LV is no longer rapidly activated through the fast conducting left bundle-branch. Instead, activation starts from the RV side of the septum and travels from the right- to the left side of the heart by relatively slow myocyte-to-myocyte conduction, which results in a delayed and dyssynchronous activation and contraction of the LV (Figure 1B and 1C).¹⁻³ The dyssynchronous LV electrical activation and contraction resulting from LBBB or RV pacing impairs LV pump function and, on the long run, is associated with adverse structural changes and increased risk of heart failure and cardiac mortality.⁴⁻¹⁰ Intrinsic or pacing-induced dyssynchrony are pathophysiological conditions that should be prevented or treated to maintain or improve cardiac pump function.

Treatment of dyssynchrony

Cardiac resynchronization therapy (CRT) aims to restore synchronous ventricular electrical activation and contraction by paced pre-excitation of the delayed activated LV (Figure 1D). CRT is most commonly applied by simultaneous electrical stimulation of the RV and LV. The RV

Figure 1. Reconstruction of the electrical activation in the ventricles based on contact mapping at the epicardium and non-contact mapping of the LV endocardium of a canine heart during normal conduction (A), LBBB (B), right ventricular apex pacing (C), and after CRT (D). During normal conduction fast and synchronous activation of the RV and LV are observed. During LBBB and RV apex pacing, the RV wall is activated earliest, followed by slow progression of the electrical wave front to the LV septum (green colors) and then the LV basal lateral wall (blue colors). Simultaneous pacing at the RV apex and the epicardium of the mid lateral LV wall during CRT results in a faster and more synchronous electrical ventricular activation. (Adapted from Gorscan et al., Strik et al., and Mills et al.¹⁷⁻¹⁹)

Figure 2. Comparison of outcome after CRT implantation among different studies according to outcome criteria used. (Reproduced from Daubert et al.¹⁶)

pacing electrode is usually positioned in the RV apex and the LV pacing electrode is inserted into the coronary sinus and positioned in one of its side branches running on the LV epicardium. In the last decade and a half, CRT has emerged as a successful treatment for symptomatic heart failure patients with impaired LV systolic function and electrocardiographic evidence of electrical dyssynchrony manifesting itself by a wide QRS complex. Several large clinical trials have shown that CRT reduces morbidity and mortality, improves cardiac pump function and clinical status and reverses LV remodeling in this group of patients.¹¹⁻¹⁵ However, despite its obvious benefits, a substantial proportion of apparently suitable patients fail to show clinical and / or echocardiographic signs of response.¹⁶ Depending on the outcome measure used in clinical studies, the non-response rate varies from 15% to almost 50% (Figure 2).¹⁶ Such lack of response is not desirable for a treatment which involves a relatively expensive therapy and requires essentially irreversible implantation of a device and leads. Efforts to increase the response rate have mainly been focused on improving patient selection and optimizing therapy delivery by better lead positioning and device programming.

Patient selection for CRT

Major efforts have been focused on finding echocardiography-based indices of mechanical dyssynchrony that can predict CRT response. However, such measures of mechanical dyssynchrony have yet failed to provide additive predictive value for CRT response in prospective trials.²⁰⁻²² This has refocused interest in the electrical substrate. Sub-analyses of large CRT trials

Figure 3. Cumulative probability of heart failure (HF) or death (left) and of death (right) according to QRS morphology in the cardiac resynchronization therapy with defibrillator (CRT-D) arm of the Multi-Centre Automatic Defibrillator Implantation trial-Cardiac Resynchronization Therapy (MADIT-CRT). (Adapted from Gold et al.²³)

have revealed that patients with LBBB are most likely to respond favorably to CRT (Figure 3), whereas the effect of CRT in patients with right bundle-branch block (RBBB) is indifferent and even tends to be deleterious in patients with intraventricular conduction delay (IVCD) (Figure 4).²³⁻²⁹ On the other hand, several studies have suggested that CRT may be beneficial in a subset of non-LBBB patients with evidence of LV activation delay.³⁰⁻³³ The clinical importance of LV activation delay is further evidenced by efficacy of CRT in animal models of isolated LBBB and by studies that have shown 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 benefit from CRT (Figure 5).³⁴⁻³⁷ Taken together, these observations indicate the importance of LV activation delay as an electrical substrate for CRT.

The key clinical investigation to detect and evaluate the extent of LV activation delay remains the surface ECG. Yet, the conventional electrocardiographic markers for delayed ventricular electrical activation, QRS duration and LBBB morphology, remain insufficient in accurately identifying patients likely to benefit from CRT. To improve patient selection, tools are required that provide more accurate identification of patients with an electrical substrate for CRT.

LV lead placement

With regard to LV lead positioning, increasing evidence supports the practice of placing the LV lead in the latest activated region as a means of maximizing CRT response.³⁶⁻⁴³ Conventional LV lead placement strategy targets a lateral or posterolateral vein, which is based on the contention that most patients eligible for CRT have LBBB, where the lateral or posterolateral wall is typically the latest activated region.¹⁶ However, studies have shown that the LV activation pattern varies considerably between patients, even in patients with LBBB, resulting in inter-individual variability in the region of latest activation.^{30, 44-47} Also, a significant percentage of CRT candidates do not have the typical LBBB morphology or have an indeterminate ventricular conduction defect indicating a more heterogeneous activation sequence making the latest activated site less predictable. These observations imply that a one size-fits-all strategy may not provide optimal therapy delivery on the individual level and emphasize the need for a patient-tailored approach to optimize LV lead positioning. Yet, the best method to guide LV lead placement to the latest activated region still needs to be established. Echocardiography

Figure 4. Cumulative probability of heart failure (HF) event or death according to treatment (cardiac resynchronization therapy with defibrillator [CRT-D] vs. implantable cardioverter defibrillator [ICD] only) in patients with LBBB, non-LBBB, RBBB and IVCD) in Multi-Centre Automatic Defibrillator Implantation trial–Cardiac Resynchronization Therapy (MADIT-CRT) patients. (Reproduced from Gold et al.²³)

and other imaging modalities have been proposed as methods to assess the LV mechanical activation pattern and guide LV lead placement,^{39,48-51} but these techniques are challenging to apply during CRT implantation and often require a separate pre-operative assessment. In order to assess the electrical activation pattern some investigators used complicated invasive electrical mapping techniques that are time-consuming and not without risk.^{2,44-46,52} Others simply measured the electrical delay at the LV pacing site using the intra-cardiac electrogram recorded from the LV lead, which provides only limited information on LV electrical activation.^{38,40} More detailed, yet practical techniques are thus required to optimize LV lead targeting in clinical practice.

Controversies in LV lead targeting to the latest activated region

Current strategies of targeted LV lead placement are based on targeting either the region of latest electrical activation³⁸ or the segment of latest peak contraction assessed by speckle-tracking echocardiography.⁴² The choice between targeting the region of latest electrical activation or the segment of latest peak contraction is currently a matter of debate. On the one hand, pre-clinical studies have shown that electrical and mechanical activation of the heart are closely coupled. On the other hand, several recent clinical studies, like the PROSPECT and EchoCRT trials, showed the inability of time-to-peak measures of mechanical dyssynchrony to predict CRT response.^{21,22} Two recent small-scale studies compared LV electrical and mechanical activation in patients with dyssynchronous heart failure, but showed conflicting results.^{53,54} More research on LV electromechanical coupling is therefore required to determine whether current LV lead targeting strategies are comparable.

Figure 5. Comparisons of the changes in LV end-systolic volume (LVESV), end-diastolic volume (LVEDV), ejection fraction (LVEF), and quality of life (QOL) from CRT implantation to 6 months follow-up for Q-LV quartiles. ("Reproduced from Gold et al.³⁶)

The latest activated region is typically assessed during intrinsic ventricular activation. Yet, in daily clinical practice, CRT is most commonly applied by (almost) simultaneous RV and LV pacing, i.e. biventricular pacing, which bypasses contribution from intrinsic conduction. Although LBBB and RV apex pacing have similar QRS morphologies, suggesting that the conditions are electrically equivalent, their activation patterns may be quite different.⁵⁵ Whether this has implications for the choice of the optimal pacing site needs to be investigated.

Prevention of pacing-induced dyssynchrony

While in patients with LBBB, CRT pacing can be used to reduce dyssynchrony, in patients with symptomatic bradycardia, cardiac pacing often creates dyssynchrony, even though bradycardia is prevented. Especially pacing at the RV apex seems to be hemodynamically unfavorable.^{56,57} Yet, the RV apex has become the most commonly applied site for ventricular pacing because it is easily accessible and yields chronically stable lead positions and stimulation thresholds. In patients with unreliable or absent AV conduction, continuous ventricular pacing is unavoidable. In these patients, pacing at alternative ventricular sites may produce less ventricular dyssynchrony and preserve LV pump function.^{17,57-63} Yet, most alternative sites investigated so far have either shown inconsistent results,^{58,64} or are technically too challenging for widespread application in clinical practice.⁶⁵ Studies in canine hearts suggested that pacing at the LV septum yields LV pump function closely approximating that during normal ventricular conduction.^{17,63}

Figure 6. Electrical and mechanical activation during LV septal pacing as compared to RV apex pacing and normal conduction in a canine heart. Upper panels, electrical activation maps. During RV apical pacing, the RV wall is activated first, followed by slow progression of activation to the LV septum (green colors) and then the LV lateral wall (blue colors). In contrast, LV septal pacing leads to rapid activation around the LV endocardium, resulting in a pattern that resembles the pattern during normal conduction, although activation of the RV wall is now moderately delayed. Lower panels, bull's eye plots showing distribution of systolic shortening in the LV wall, as determined in 160 regions (5 short-axis slices, 32 regions per slice). LV septal pacing results in a more homogeneous distribution of systolic shortening compared with RV apex pacing, resembling that during normal conduction. (Adapted from Mills et al.¹⁷)

The hemodynamic benefit of LV septal pacing has been related to a more physiological sequence of LV electrical activation and contraction (Figure 6), resulting in less LV electrical and mechanical dyssynchrony.¹⁷ In the canine experiments, permanent and stable implantation of an LV septal lead was achieved by introducing a custom pacing lead with extended helix transvenously into the RV and driving it from the RV side through the interventricular septum to the LV septum.¹⁷ Whether permanent placement of a pacing lead in the LV septum using a transvenous approach through the interventricular septum is also feasible and safe in patients has not been investigated yet.

Aim of the thesis

The aims of this thesis are:

1. To develop a useful method for patient-tailored LV lead placement focused on targeting the latest activated region.
2. To investigate the difference in LV electrical activation sequence between intrinsic LBBB and RV apex pacing in candidates for CRT.

3. To determine the relationship between the timing of LV electrical and mechanical activation in candidates for CRT.
4. To improve identification of patients with an appropriate electrical substrate for CRT.
5. To perform a first-in man study investigating the feasibility of a novel method of ventricular lead placement for anti-bradycardia pacing therapy that targets the LV septum, which may reduce the extent of pacing-induced dyssynchrony and the adverse effects associated with this condition.

Outline of the thesis

In **chapter 2** of the thesis we describe a novel method of epicardial electroanatomic mapping via the coronary veins that can be used during the procedure of CRT implantation to assess the LV electrical activation sequence and guide LV lead placement to the latest activated region. This coronary venous electroanatomic mapping technique does not increase the invasiveness of the procedure and causes only minor prolongation of procedure time.

In **chapter 3** we investigated differences in LV electrical activation between intrinsic LBBB and RV apex pacing and the potential implications thereof for LV lead placement. For this purpose, we assessed the LV electrical activation pattern of CRT candidates during both intrinsic LBBB and RV apex pacing using the coronary venous electroanatomic mapping technique described in **chapter 2**.

In the study described in **chapter 4** we investigated whether current LV lead targeting strategies, which are based on targeting either the region of latest electrical activation or the segment of latest peak contraction, are comparable. For this purpose we performed a within-patient comparison of the timing of LV electrical activation obtained from coronary venous electroanatomic mapping and the timing of LV peak contraction derived from speckle-tracking echocardiography in CRT candidates.

In **chapter 5 and 6** we investigated whether coronary venous electroanatomic mapping can be used at the time of CRT implantation to determine the presence of delayed LV lateral wall activation, an electrical substrate amenable to CRT.

Ideally, characterization of the electrical substrate is performed in advance so that this information can be used to guide the decision on whether or not to implant a CRT device. In this regard, QRS characteristics other than QRS duration and morphology may provide valuable additional information. Therefore, in **chapter 5** we also investigated whether such alternative QRS characteristics can identify delayed LV lateral wall activation in a cohort of IVCD patients by comparing ECG measurements with data from coronary venous electroanatomic mapping. We also hypothesized in **chapter 6** that the vectorcardiogram (VCG), which contains three-dimensional information of electrical forces within the heart, can provide markers that identify delayed LV lateral wall activation better than the conventional electrical markers QRS duration and LBBB morphology. To investigate this we compared VCG measurement with data from coronary venous electroanatomic mapping in a cohort of LBBB and non-LBBB patients.

In **chapter 7** we aimed to translate the results of previous canine experiments into clinical practice by performing a first-in-man study in which we investigated the feasibility of permanently implanting an LV septal lead in patients using a transvenous approach through the interventricular septum. At first instance, this novel pacing mode is meant to prevent the development of pacing-induced dyssynchrony in patients requiring pacing because of bradycardia.

Besides the abovementioned studies, the thesis also contains a case report (**chapter 8**) and an editorial (**chapter 9**) on the value of measurements of acute hemodynamic response to CRT for improving patient selection and optimizing CRT delivery by systematic hemodynamic evaluation of potential LV pacing sites and atrio-ventricular and inter-ventricular stimulation intervals. The thesis ends with a general discussion (**chapter 10**) where the findings of the abovementioned studies are put in a broader perspective with special emphasis on clinical implications and future studies.

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Left ventricular lead placement in the latest activated region guided by coronary venous electroanatomic mapping

Chapter

Masih Mafi Rad, Yuri Blaauw, Trang Dinh, Laurent Pison,
Harry J. Crijns, Frits W. Prinzen, Kevin Vernooy

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Abstract

Aim: Left ventricular (LV) lead placement in the latest activated region is an important determinant of response to cardiac resynchronization therapy (CRT). We investigated the feasibility of coronary venous electroanatomic mapping (EAM) to guide LV lead placement to the latest activated region.

Methods: Twenty-five consecutive CRT candidates with left bundle-branch block underwent intra-procedural coronary venous EAM using EnSite NavX. A guidewire was used to map the coronary veins during intrinsic activation, and to test for phrenic nerve stimulation (PNS).

Results: The latest activated region, defined as the region with an electrical delay >75% of total QRS duration, was located anterolaterally in 18 (basal, $n = 10$; mid, $n = 8$) and inferolaterally in 6 (basal, $n = 3$; mid, $n = 3$). In 1 patient, identification of the latest activated region was impeded by limited coronary venous anatomy. In patients with >1 target vein ($n = 12$), the anatomically targeted inferolateral vein was rarely the vein with maximal electrical delay ($n = 3$). A concordant LV lead position was achieved in 18 of 25 patients. In 6 patients, this was hampered by PNS ($n = 4$), lead instability ($n = 1$) and coronary vein stenosis ($n = 1$).

Conclusion: Coronary venous EAM can be used intraprocedurally to guide LV lead placement to the latest activated region free of PNS. This approach especially contributes to optimization of LV lead electrical delay in patients with multiple target veins. Conventional anatomical LV lead placement strategy does not target the vein with maximal electrical delay in many of these patients.

Introduction

Cardiac resynchronization therapy (CRT) reduces morbidity and mortality and reverses left ventricular (LV) remodeling in heart failure patients with LV systolic impairment and electrical dyssynchrony.¹⁻³ Despite the striking effectiveness of CRT, a substantial proportion of apparently eligible patients fail to benefit.⁴ Part of this reduced benefit has been attributed to a suboptimal LV lead position.⁴ There is increasing evidence to suggest that positioning of the LV lead in the region of latest electrical activation provides superior clinical outcome.^{5,6} The conventional LV lead placement strategy involves an anatomical approach, targeting a coronary venous branch situated on the posterolateral wall. This strategy is based on the contention that the posterolateral wall is typically the latest activated site of the ventricle in patients with left bundle-branch block (LBBB). However, studies have shown a considerable variability in the ventricular activation pattern in LBBB, resulting in inter-individual variability in the optimal pacing site.⁸⁻¹⁰ Therefore, a more patient-specific physiological approach focused on achieving maximal LV lead electrical delay may improve CRT response. Electroanatomic mapping (EAM) is typically used in the electrophysiology lab to guide diagnostic or ablation procedures of cardiac arrhythmias. Recently, the technique has also been applied during CRT implantation to determine the electrical activation pattern of the coronary venous system.^{11,12} Final LV lead position, however, depends on several factors such as cardiac venous anatomy, performance and stability of the lead and the absence of phrenic nerve stimulation (PNS). The feasibility of coronary venous EAM to guide LV lead placement to the latest activated region during CRT implantation remains to be assessed. The aim of the present study was to assess the feasibility of positioning the LV lead in the latest activated region guided by coronary venous EAM in patients undergoing CRT implantation.

Methods

Population

From December 2012 to May 2013, consecutive patients referred for CRT device implantation, with LV ejection fraction (LVEF) <35%, New York Heart Association (NYHA) functional class 2, 3 or ambulatory 4, and LBBB according to ESC guidelines,¹³ were prospectively enrolled. The study complied with the declaration of Helsinki. Our locally appointed ethics committee approved the study protocol and waived the need for informed consent.

Electroanatomic mapping and LV lead placement

All patients underwent intraprocedural coronary venous three-dimensional (3D) EAM using EnSite NavX (St. Jude Medical). Prior to LV lead placement, an occlusive coronary venogram was recorded under fluoroscopy in right anterior oblique (RAO) and left anterior oblique (LAO) view for optimal visualization of the coronary veins. Subsequently a 0.014 inch guidewire (Vision Wire, Biotronik SE & Co.KG) was inserted into the coronary sinus (CS) and connected to EnSite NavX along with the surface electrocardiogram (ECG). This guidewire has complete polyethylene isolation except for 15 mm at the distal "J"-shaped tip and 30 mm at the proximal end permitting unipolar sensing and pacing.¹⁴ The guidewire was used to map all target veins located on the anterolateral or inferolateral LV wall as defined by the American Heart Association (AHA) 17-segment heart model.¹⁵ A 3D electrical activation map was constructed during intrinsic ventricular activation. Electrical delay was measured in milliseconds (ms) from QRS onset on the surface ECG to the peak negative slope on the unipolar intra-cardiac electrogram (EGM) and expressed as a percentage of total QRS duration. All measurements were performed in EnSite NavX at a screen speed of 400 mm/s. The latest activated region of the LV was defined

as the region with an electrical delay comprising >75% of 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 anatomic region to its timepoint within the QRS complex. Candidate pacing sites were tested for PNS by 10 V unipolar pacing on the tip of the guidewire and regions with PNS or absence thereof were annotated on the EAM using EnSite NavX. After the mapping procedure, the LV lead was connected to EnSite NavX for real-time

Figure 1. (A) Coronary venous EAM of a patient during intrinsic ventricular activation together with the corresponding unipolar EGMs collected from the regions of earliest and latest activation. The CS and all side branches have been mapped and the anterolateral vein has been tested for PNS. Connecting the LV lead to EnSite NavX allowed real-time visualization and navigation of the lead to the latest activated region in the electroanatomic map. (B) Corresponding coronary venogram. (C) X-ray of final LV lead placement. AIV, anterior inter-ventricular vein; ALV, anterolateral vein; CS, coronary sinus; IIV, inferior inter-ventricular vein; ILV, inferolateral vein; RV, right ventricular; RA, right atrial; Red dot, PNS; Green dot, no PNS.

Figure 2. Angiographic classification of the latest activated region and final LV lead position. (A) The AHA standardized 17-segment heart model, adapted from Cerqueira et al.¹⁵ (B) Coronary venogram in RAO. This view, representative of the long axis of the heart, was used to classify the latest activated region and final LV lead position into basal, mid-ventricular, and apical segments. (C) Coronary venogram in LAO. This view, comparable to the short axis of the heart, was used to divide the LV wall into four equal parts; anterior, anterolateral, inferolateral and inferior. AIV, anterior inter-ventricular vein; ALV, anterolateral vein; IIV, inferior inter-ventricular vein; ILV, inferolateral vein.

visualization and navigation of the lead to the latest activated region free of PNS in the created EAM. Standard bipolar leads of various vendors were used. Figure 1 shows an example of a coronary venous EAM together with the results of PNS testing and the final LV lead position. The latest activated region and final LV lead position were classified according to the AHA 17-segments heart model by detailed evaluation of pre-implantation venograms and post-implantation LV lead fluoroscopy images (Figure 2). The final LV lead position was described as concordant if the lead was located in the same myocardial segment as the latest activated region.

Statistical analysis

Continuous variables are expressed as mean $\pm$ SD. Categorical variables are expressed as observed number and percentage values. Continuous variables were compared using Mann-Whitney U test. Statistical significance was accepted at the 95% confidence interval ($P < 0.05$). Statistical analysis was performed using SPSS version 20.0 (SPSS Inc.) software.

Results

Patient characteristics

Twenty-five consecutive patients with LBBB referred for CRT device implantation were included in this study. The patient characteristics are described in Table 1.

CRT implantation

In 21 patients a *de novo* CRT defibrillator was implanted. Two patients were upgraded from an Implantable cardioverter-defibrillator to a CRT defibrillator and 2 patients received a CRT pacemaker. LV lead implantation was successful in all patients. There were no procedural complications.

Coronary venous electroanatomic mapping

In all patients, occlusive coronary venography revealed at least one target vein on the anterolateral or inferolateral LV wall. In 12 of 25 patients, 2 target veins were available. All target veins were successfully mapped. Three-dimensional electrical activation maps were generated from an

Table 1. Patient characteristics (n = 25)

Age, years	72 ± 6
Male gender (n, %)	14 (56)
Ischemic heart disease (n, %)	8 (32)
NYHA functional class (n, %)	
II	11 (44)
III	14 (56)
Echocardiography characteristics	
LV ejection fraction (%)	27 ± 5
LV end-diastolic diameter (mm)	59 ± 4
LV end-systolic diameter (mm)	55 ± 5
LV end-diastolic volume (mL)	146 ± 30
LV end-systolic volume (mL)	107 ± 24
ECG characteristics	
LBBB (n, %)	25 (100)
QRS duration (ms)	154 ± 15
Intrinsic rhythm (n, %)	
Sinus rhythm	22 (88)
Atrial fibrillation	3 (12)
Treatment (n, %)	
Diuretics	17 (68)
ACE-i/ARB	24 (96)
Beta-blockers	22 (88)
Spironolactone	15 (60)
Digoxin	1 (4)
Amiodarone	3 (12)

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

average of 46 ± 28 unique anatomic points. Mapping time was 19 ± 6 min and fluoroscopy time during the entire procedure 20 ± 6 min. Figure 3 shows the distribution of the latest activated regions in all patients. The latest activated region was located anterolaterally in 18 (basal, $n = 10$; mid, $n = 8$) and inferolaterally in 6 (basal, $n = 3$; mid, $n = 3$). In 1 patient (No. 7), identification of the latest activated region was impeded by limited coronary venous anatomy.

LV lead placement

Figure 4 shows the distribution of the final LV lead position in all patients. The LV lead was positioned anterolaterally in 16 (basal, $n = 9$; mid, $n = 7$) and inferolaterally in 9 (basal, $n = 4$; mid, $n = 5$). The final LV lead position was concordant with the latest activated region in 18 of 25 patients. In 6 patients, concordant LV lead placement was hampered by PNS ($n = 4$, one of

them depicted in Figure 5), lead instability ($n = 1$) and coronary vein stenosis ($n = 1$). In the patient in whom the latest activated region could not be identified (No. 7), the LV lead was positioned at the site where maximal electrical delay was measured with coronary venous EAM. An overview of the latest activated regions and final LV lead positions of all patients together with the corresponding electrical delays at these sites is provided in Table 2. In patients with a concordant LV lead position, electrical delay was 132 ± 15 ms ($85 \pm 6\%$ of QRS duration) at the latest activated region and 128 ± 13 ms ($83 \pm 5\%$ of QRS duration) at the final lead position ($P = 0.17$). In patients with a discordant LV lead position, electrical delay was 125 ± 10 ms ($84 \pm 3\%$ of QRS duration) at the latest activated region and 94 ± 15 ms ($63 \pm 7\%$ of QRS duration) at the final lead position ($P = 0.002$). LV lead electrical delay was significantly longer in patients with a concordant compared to patients with a discordant LV lead position ($P < 0.001$).

In 9 of 12 patients with 2 available target veins (Nos. 1, 11, 12, 13, 14, 15, 18, 23, and 24), the latest activated region was located in a different vein than the anatomically targeted inferolateral vein (Table 2). In these patients, maximal electrical delay was 89 ± 14 ms ($58 \pm 6\%$ of QRS duration) in the anatomically targeted vein vs. 133 ± 15 ms ($87 \pm 5\%$ of QRS duration) at the latest activated region ($P < 0.001$). The LV lead was positioned in the latest activated region in 7 of 9 patients (Nos. 1, 11, 12, 14, 15, 23, and 24). In these patients, maximal electrical delay was 89 ± 16 ms ($57 \pm 7\%$ of QRS duration) in the anatomically targeted vein vs. 131 ± 14 ms ($85 \pm 4\%$ of QRS duration) at the final LV lead position ($P = 0.001$). In the other 2 patients (Nos. 13 and 18), coronary vein stenosis and PNS hampered concordant LV lead placement. Figure 6 illustrates the additional value of mapping-guided LV lead placement as compared with the conventional anatomical LV lead placement approach. In this example, the coronary venous EAM of patient no. 24 is shown where a pure anatomical

Figure 3. Distribution of the latest activated region. Each circled number represents a patient. Numbers refer to the order of inclusion. The latest activated region was mainly located on the anterolateral LV wall. In one patient (No. 7), the latest activated region could not be identified by coronary venous EAM due to limited coronary venous anatomy. A, anterior; AL, anterolateral; AS, antero-septal; I, inferior; IL, inferolateral; IS, infero-septal; L, lateral; S, septal.

Figure 4. Distribution of the final LV lead position. Each circled number represents a patient. Numbers refer to the order of inclusion and correspond with the numbers in Figure 3. A, anterior; AL, anterolateral; AS, antero-septal; I, inferior; IL, inferolateral; IS, infero-septal; L, lateral; S, septal.

approach would have resulted in a suboptimal LV lead position in the inferolateral vein with a maximal electrical delay of only 90 ms. However, additional mapping of the small anterolateral vein resulted in a potentially far better LV lead position with an electrical delay close to 140ms.

Figure 5. (A) Coronary venous 3D electrical activation map during intrinsic ventricular activation of a patient in whom PNS hampered placement of the LV lead in the latest activated region. Mapping of the anterolateral and inferolateral vein revealed the latest activated region at the mid-anterolateral LV wall. Unfortunately this was also a region with PNS. The LV lead was eventually placed as close as possible to the latest activated region and pacing was performed at the ring of the LV lead, which in contrast to the tip still offered some space between ventricular capture and PNS. (B) Corresponding coronary venogram. (C) X-ray of final LV lead placement. Red dot, PNS; Green dot, no PNS; R, LV lead ring; T, LV lead tip. AIV, anterior inter-ventricular vein; ALV, anterolateral vein; ILV, inferior inter-ventricular vein; ILV, inferolateral vein; RV, right ventricular.

Table 2. Overview of the latest activated regions, final LV lead positions and empirical target veins of all patients together with the corresponding electrical delays

Patient No.	No. of target veins	Latest activated region	Electrical delay	Final LV lead position	Electrical delay	Reason for discordance	Empirical target vein for LV lead	Maximal electrical delay
1	2	B-AL	139 (93%)	B-AL	131 (87%)	-	IL vein	90 (60%)
2	1	B-AL	136 (86%)	B-AL	126 (80%)	-	-	-
3	1	M-IL	122 (79%)	M-IL	122 (79%)	-	-	-
4	1	M-AL	131 (84%)	M-AL	128 (82%)	-	-	-
5	1	B-IL	131 (85%)	B-IL	128 (83%)	-	-	-
6	1	M-AL	110 (85%)	M-IL	72 (56%)	PNS	-	-
7	1	Not identified	-	M-IL	103 (63%)	-	-	-
8	2	M-AL	126 (87%)	M-AL	126 (87%)	-	AL vein	-
9	1	B-AL	137 (84%)	M-AL	103 (63%)	Lead instability	-	-
10	1	B-AL	156 (96%)	B-AL	149 (92%)	-	-	-
11	2	B-AL	130 (85%)	B-AL	128 (83%)	-	IL vein	70 (45%)
12	2	B-AL	119 (91%)	B-AL	119 (91%)	-	IL vein	72 (55%)
13	2	M-AL	124 (86%)	B-IL	94 (65%)	Coronary vein stenosis	IL vein	94 (65%)
14	2	B-AL	149 (93%)	B-AL	138 (86%)	-	IL vein	106 (66%)
15	2	M-AL	116 (91%)	M-AL	111 (87%)	-	IL vein	80 (63%)
16	1	M-IL	131 (78%)	M-IL	131 (78%)	-	-	-
17	1	M-AL	111 (76%)	M-AL	111 (78%)	-	-	-
18	2	M-AL	118 (79%)	M-IL	94 (63%)	PNS	IL vein	94 (63%)
19	2	M-IL	130 (83%)	B-AL	116 (74%)	PNS	IL vein	-
20	1	B-AL	128 (83%)	B-AL	127 (82%)	-	-	-
21	1	B-IL	143 (80%)	B-IL	141 (79%)	-	-	-
22	1	B-AL	128 (85%)	M-AL	87 (57%)	PNS	-	-
23	2	M-AL	160 (84%)	M-AL	155 (81%)	-	IL vein	113 (59%)
24	2	B-AL	140 (83%)	B-AL	133 (79%)	-	IL vein	90 (54%)
25	2	B-IL	103 (80%)	B-IL	101 (78%)	-	IL vein	-

Legend on next page.

Legend of Table 2: Patient numbers correspond with the numbers provided in Figure 3 and 4. Electrical delay is reported in ms (percentage of total QRS duration). In patient No. 6, the anterolateral vein anastomosed with the inferior inter-ventricular vein, which made it possible to position the LV lead inferolaterally (via the anastomosis) despite the patient having only one target vein on the anterolateral LV wall. In patient No. 7, identification of the latest activated region was impeded by limited coronary venous anatomy. Patient No. 8 had 2 target veins on the anterolateral wall. For patients with 2 target veins, the second column from the right reports the target vein for the LV lead if the conventional anatomical lead placement approach would be used. The right-most column provides the maximal electrical delay measured within that vein. B, basal; M, mid; AL, anterolateral; IL, inferolateral; PNS, phrenic nerve stimulation.

Discussion

Pacing at the latest activated region of the LV appears to improve the outcome of CRT. The present study demonstrates that coronary venous EAM using EnSite NavX in combination with a mapping guidewire can be used intraprocedurally to guide LV lead placement to the region of latest electrical activation. In addition, the potential of this mapping approach to facilitate comprehensive identification of regions free of PNS is demonstrated.

Targeted LV lead placement at the latest activated LV region

Several studies have investigated the relationship between pacing in the region of latest activation and the response to CRT. Studies on mechanical activation suggest superior CRT outcome when the LV lead position coincides with the region of latest mechanical contraction compared with discordant positions.¹⁶⁻²¹ Two recent prospective single-center trials randomized a total of 407 patients to speckle-tracking echocardiography-guided LV lead placement targeting the site of latest mechanical activation or to standard unguided LV lead placement. In both trials, patients with an LV lead position concordant with the site of latest activation had a higher echocardiographic response rate, more clinical responders, and a reduced risk of mortality and heart failure hospitalization.^{22,23} Studies focusing on the electrical activation pattern have demonstrated that a greater delay in time from onset of the QRS complex to the local sensed LV lead EGM (Q-LV) is also associated with a greater likelihood of benefit from CRT.^{24,25} Recently, Zanon et al. measured the Q-LV interval of various pacing sites within patients, and evaluated the hemodynamic effect of pacing at the different sites by invasive measurement of LVdP/dtmax. Pacing the LV at the latest activated site resulted in greatest hemodynamic improvement.⁶ The choice between targeting the region of latest electrical or latest mechanical activation is still a matter of debate and definitive randomized trials that support the use of either approach to reliably select an optimal LV pacing site are lacking. Accordingly, current ESC guidelines have assigned a class 2b indication to targeted LV lead placement at the latest activated LV segment.⁷ A slightly stronger recommendation (class 2a) has been assigned to avoiding an apical LV lead position⁷ despite conflicting results in the literature.²⁶⁻²⁹ Therefore, larger prospective studies are required to settle the issue of whether pacing the latest activated LV region provides the best outcome of CRT.

While the position of the LV lead with respect to the site of latest activation is a factor that can influence CRT response, several studies have shown that the proximity of the LV lead to an area with myocardial scar is an important factor as well.³⁰⁻³⁴ Assessment of scar tissue should therefore be considered before CRT, especially in the population with ischemic heart disease. Integrating information obtained from scar imaging with measurements of electrical and mechanical delay may further optimize LV lead positioning and the clinical response rate.

Figure 6. Coronary venous EAM of patient No. 24, illustrating the additional value of LV lead placement guided by coronary venous mapping. Pre-implantation coronary venograms in LAO (A) and RAO (B) view revealed a large inferolateral and a small anterolateral vein. The conventional anatomical LV lead placement approach would target the inferolateral vein. However, coronary venous mapping during intrinsic ventricular activation (C) revealed a maximal electrical delay of only 90 ms in the basal inferolateral vein, which further decreased in the more distal segments, whereas a maximal electrical delay of 140 ms could be measured in the anterolateral vein. Based on the outcome of coronary venous mapping, the LV lead was positioned in the anterolateral vein, thereby achieving a clear benefit in LV lead electrical delay. (D) X-ray of final LV lead position in LAO view. (E) X-ray of final LV lead position in RAO view. AIV, anterior inter-ventricular vein; ALV, anterolateral vein; IIV, inferior inter-ventricular vein; ILV, inferolateral vein.

Feasibility of coronary venous EAM to guide LV lead placement to the latest activated region

Our observation that the location of the latest activated region varies between patients agrees with previous EAM studies in patients with heart failure and LBBB,⁸⁻¹⁰ and emphasizes the need for a patient-tailored approach to optimize LV lead positioning. The present study demonstrates that coronary venous EAM using EnSite NavX in combination with a mapping guidewire is a feasible method to tailor LV lead placement to the individual patient at the time of implantation. Using this approach, we were able to position the LV lead in the latest activated region in >70% of our patients. Conventional LV lead placement strategy involves an anatomical approach, targeting a coronary vein situated on the posterolateral wall. Approximately half the patients in our study cohort had more than one target vein available on the lateral LV free wall. In most

of these patients, the empirically targeted posterolateral vein was not the vein with maximal electrical delay, which is consistent with the findings of a previous study that also used coronary venous EAM to assess LV epicardial activation.³⁵ In the present study, coronary venous EAM resulted in targeting of an alternative vein in many of these patients, significantly increasing LV lead electrical delay from an average of 57% to 85% of total QRS duration. In addition, in patients with a single target vein, coronary venous EAM enabled targeting of the vein segment with maximal electrical delay. These results demonstrate the additional value of coronary venous EAM-guided LV lead placement as compared with the conventional anatomical LV lead placement approach for optimization of LV lead electrical delay.

The use of EnSite NavX to create an EAM of the coronary veins at the time of CRT implantation has previously been described by Ryu et al.¹¹ In addition, Del Greco et al. demonstrated that lead placement guided by the 3D navigation system of EnSite NavX is beneficial in terms of reducing X-ray exposure during CRT implantation.¹² Recently, Fujiwara et al. compared electrical and mechanical dyssynchrony using coronary venous EAM and speckle-tracking echocardiography.³⁵ However, sample sizes of these studies were small, LV lead placement was not targeted at the latest activated region, and constraints imposed by coronary venous anatomy for identifying the latest activated LV region were not taken into account. Therefore, the present study is the first to demonstrate, in a larger and representative CRT population, the feasibility of positioning the LV lead in the latest activated region guided by coronary venous EAM.

Unfortunately, concordant LV lead placement was still hampered in one-quarter of patients due to PNS, lead instability and unfavourable coronary venous anatomy. The use of additional technologies may increase the success rate of targeted LV lead placement on the basis of electrical delay. Venous angioplasty, for example, may have benefited one of our patients in whom coronary venous stenosis hampered LV lead placement in the latest activated region. In addition, the use of new lead technologies, such as active-fixation leads and multipolar leads could overcome the problem of lead instability and avoid PNS, which hindered concordant LV lead positioning in several other patients in our study. When confronted with PNS, also alternative pacing strategies such as thoracoscopic epicardial or LV endocardial pacing may be considered to stimulate the site of optimal electrical delay.

Our mapping approach was easy to implement intraprocedurally using a commercially available EAM system in combination with a guidewire that allows mapping and pacing of the coronary veins, making the approach applicable in any catheter laboratory that has access to the relevant instruments. In addition, the same wire used to guide the LV lead was also used to map the coronary veins which obviated the need for inserting additional electrophysiology mapping catheters during implantation. Echocardiography and other imaging modalities have also been proposed as methods to assess the LV activation pattern and guide LV lead placement,^{16-18, 20, 21, 36} but these techniques are challenging to apply in the catheter laboratory and often require a separate pre-operative assessment.

In current clinical practice, most implanters that tend to target LV lead placement to a region with significant electrical delay do not perform full EAM in favor of a simpler approach where electrical mapping of the anatomically targeted region is performed using the LV lead to test if electrical delay is sufficiently late. However, using this approach the latest activated region may be missed because other potential LV pacing sites are generally not tested when electrical delay at the empirically targeted LV region is considered late enough. Previous reports suggest that a Q-LV >95 ms or >50% of total QRS duration is sufficient to increase the odds of a favorable response.^{5, 37} However, further increase of the Q-LV to >120 ms has been shown to considerably improve these odds,⁵ suggesting that implanters should aim to optimize LV lead electrical delay

in order to maximize the chance of a positive CRT outcome. Besides, with simple electrical mapping, measurements are generally performed after final LV lead implantation. If the measured electrical delay is judged unsatisfactory, the implanter may have to relocate the LV lead to an alternative target vein, thus extending procedure and fluoroscopy time. Compared with simple electrical mapping using the LV lead, our 3D EAM approach has important advantages that can significantly contribute to LV lead placement optimization. The EnSite NavX system can be used to create an anatomic geometry of the coronary veins while electrical delay and PNS are assessed for any anatomic region accessible with the mapping guide wire. The small and flexible mapping guidewire allows for more detailed data collection by easy and quick mapping of multiple coronary veins and multiple points per vein which provides information on electrical activation timing and PNS of all potential LV pacing sites. Thus, all information about coronary venous anatomy, LV electrical activation and PNS can be readily obtained prior to LV lead placement. The LV lead can then be targeted to the latest activated region free of PNS in a single approach, thus reducing placement attempts at unsuitable sites. Targeted LV lead placement is further facilitated by real-time visualization and navigation of the lead in the NavX-created EAM.

Avoiding phrenic nerve stimulation

Phrenic nerve stimulation accounts for failure to deliver proper CRT or urgent need for LV lead relocation in a substantial number of patients. Studies addressing the issue have reported PNS at implantation in 7.6-37% of patients, resulting in failure to pace the target site in 10-14%.³⁸⁻⁴⁰ PNS at follow-up has been reported in 11-33% of patients, requiring LV lead replacement in a substantial proportion of patients and eventual turn-off of CRT in some.³⁸⁻⁴⁰ In the present study, PNS was assessed by systematic pacing of the coronary veins with the tip of the mapping guidewire. The usefulness of this approach for detecting PNS has previously been demonstrated by de Cock et al.¹⁴ In addition, the EAM system used in our study allowed comprehensive annotation of PNS-free areas on the created coronary venous geometry, consequently providing 3D visualization of the anatomical location of these areas with respect to the target LV pacing site and the position of the LV lead tip. Subsequently, real time navigation of the LV lead in the geometry allowed targeting of a PNS-free zone with optimal electrical delay. This approach proved to be effective to avoid PNS at medium-term follow-up (4 ± 1 months) in all study patients.

Limitations

The sample size of this study was relatively small. However, the study was performed on consecutive patients and the study population resembled the typical population of patients with LBBB and heart failure referred for CRT implantation.

Only standard bipolar LV leads were used. The use of new lead technologies, such as multipolar leads and active-fixation leads, may increase the success rate of targeted LV lead placement at the latest activated LV region by improving lead stability and avoiding PNS. Unfortunately, most device vendors did not have multipolar LV leads available at the time the current study was conducted.

Cardiac magnetic resonance imaging was not performed in this study. Therefore, we could not assess the distribution and extent of scar and its potential effect on electrical activation. Also, the mapping method used in the current study did not allow for reliable differentiation between scar and healthy myocardium. Thus, the position of the LV lead with respect to regions of myocardial scar was not taken into account during LV lead placement.

The current study demonstrates a feasible method to guide LV lead placement to the region of latest electrical activation. However, the clinical value of this lead placement strategy

was not proven by acute hemodynamic measurements or long-term echocardiographic or clinical follow-up. Subsequent larger and long-term follow-up studies are therefore required to evaluate the impact of coronary venous mapping-guided LV lead placement on CRT outcome.

Conclusion

Coronary venous EAM using EnSite NavX in combination with a mapping guidewire can be used at the time of CRT implantation to guide LV lead placement to the latest activated region free of PNS. This approach especially contributes to optimization of LV lead electrical delay in patients with multiple target veins. The conventional anatomical LV lead placement strategy does not target the vein with maximal electrical delay in many of these patients. The clinical value of coronary venous mapping-guided LV lead placement needs prospective evaluation.

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Different regions of latest electrical activation during left bundle-branch block and right ventricular pacing determined by coronary venous electroanatomic mapping

Chapter

Masih Mafi Rad, Yuri Blaauw, Trang Dinh, Laurent Pison, Harry J. Crijns, Frits W. Prinzen, Kevin Vernooy

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Abstract

Aim: Current targeted left ventricular (LV) lead placement strategy is directed at the latest activated region during intrinsic activation. However, cardiac resynchronization therapy (CRT) is most commonly applied by simultaneous LV and right ventricular (RV) pacing without contribution from intrinsic conduction. Therefore, targeting the LV lead to the latest activated region during RV pacing might be more appropriate. We investigated the difference in LV electrical activation sequence between left bundle-branch block (LBBB) and RV apex (RVA) pacing using coronary venous electroanatomic mapping (EAM).

Methods: Twenty consecutive CRT candidates with LBBB underwent intraprocedural coronary venous EAM during intrinsic activation and RVA pacing using EnSite NavX. Left ventricular lead placement was aimed at the latest activated region during LBBB according to current recommendations.

Results: In all patients, LBBB was associated with a circumferential LV activation pattern, whereas RVA pacing resulted in activation from the apex of the heart to the base. In 10 of 20 patients, RVA pacing shifted the latest activated region relative to LBBB. In 18 of 20 patients, the LV lead was successfully positioned in the latest activated region during LBBB. For the whole study population, LV lead electrical delay, expressed as percentage of QRS duration, was significantly shorter during RVA pacing than during LBBB (72 ± 13 vs. $82 \pm 5\%$, $P = 0.035$).

Conclusion: Right ventricular apex pacing alters LV electrical activation pattern in CRT patients with LBBB, and shifts the latest activated region in a significant proportion of these patients. These findings warrant reconsideration of the current practice of LV lead targeting for CRT.

Introduction

Cardiac resynchronization therapy (CRT) reduces morbidity and mortality and reverses left ventricular (LV) remodelling in heart failure patients with LV systolic impairment and electrical dyssynchrony.¹⁻³ Unfortunately, a significant proportion of apparently suitable patients do not derive any detectable benefit.⁴ The position of the LV lead with respect to the site of latest activation is considered an important determinant of CRT response. Recent studies have suggested that positioning of the LV lead in the region of latest electrical activation or the segment of latest mechanical contraction provides superior clinical outcome compared with the conventional anatomical LV lead placement approach.⁵⁻¹⁰ Studies investigating targeted LV lead placement have typically focused on the latest activated region during intrinsic ventricular activation.^{9, 10} However, in daily clinical practice the CRT device is most commonly programmed to (almost) simultaneous right ventricular (RV) and LV pacing (i.e. biventricular pacing) without fusion with intrinsic ventricular activation. Ludwig et al. recently demonstrated that the region of latest mechanical activation during RV apex (RVA) pacing often differs from that during LBBB.¹¹ The purpose of the present study was to investigate the difference in LV electrical activation sequence between intrinsic LBBB and RVA pacing using coronary venous electroanatomic mapping (EAM) in patients undergoing CRT implantation.

Methods

Population

Twenty consecutive patients referred for CRT device implantation, with LV ejection fraction (LVEF) <35%, NYHA functional class 2, 3 or ambulatory 4, and LBBB according to European Society of Cardiology (ESC) guidelines¹² were prospectively enrolled. The study protocol was approved by the Institutional Review Board.

CRT implantation and mapping

All patients underwent intraprocedural coronary venous three-dimensional EAM using EnSite NavX (St. Jude Medical). The right atrial lead was placed in the right atrial appendage and the RV lead was placed in the RVA by current practice. Before LV lead placement, an occlusive coronary venous angiogram was recorded under fluoroscopy in right anterior oblique (RAO) and left anterior oblique (LAO) view for optimal visualization of the coronary veins. Subsequently a 0.014 inch guidewire (Vision Wire, Biotronik SE & Co.KG) was inserted into the coronary sinus (CS) and connected to EnSite NavX along with the surface electrocardiogram (ECG). This guidewire has complete polyethylene isolation except for 15 mm at the distal J-shaped tip and 30 mm at the proximal end permitting unipolar sensing and pacing.¹³ The guidewire was manipulated to various branches of the CS, creating an anatomical map along with determining the electrical activation time associated with each anatomic region during both intrinsic LBBB and RVA pacing. Right ventricular apex pacing was performed with the implanted RV lead at 10 beats above intrinsic heart rate, in DDD mode (AV-sequential pacing) with a short AV-delay to ensure full ventricular capture. Local electrical activation time was measured in ms from QRS onset on surface ECG to the peak negative slope on the unipolar intra-cardiac electrogram (EGM) and expressed as a percentage of total QRS duration. All measurements were performed in EnSite NavX at a screen speed of 400 mm/s. After the mapping procedure, the LV lead was connected to EnSite NavX for real-time visualization and navigation of the lead to the latest activated region during intrinsic LBBB based on current evidence and recommendations.^{5, 9, 14} Standard bipolar leads of various vendors were used. Finally, the device implantation was completed.

Figure 1. Angiographic classification of the latest activated region and final LV lead position. (A) The American Heart Association standardized 17-segment heart model, adapted from Cerqueira et al.¹⁵ (B) Coronary venous angiogram in left anterior oblique (LAO). This view, which is comparable to the short axis of the heart, was used to divide the LV wall into four equal parts; anterior, anterolateral, inferolateral and inferior. (C) Coronary venous angiogram in right anterior oblique (RAO). This view, which is representative of the long axis of the heart, was used to classify the latest activated regions and final LV lead position into basal, mid-ventricular and apical segments. AIV, anterior inter-ventricular vein; ALV, anterolateral vein; IIV, inferior inter-ventricular vein; ILV, inferolateral vein.

Classification of the latest activated region and final LV lead position

The location of the latest activated region and the final LV lead position were classified according to the American Heart Association 17-segment heart model¹⁵ by detailed evaluation of pre-implantation coronary venous angiograms and post-implantation LV lead fluoroscopy images (Figure 1). The latest activated regions during intrinsic LBBB and RVA pacing were described as different if located in different myocardial segments according to the 17-segment heart model. The final LV lead position was described as concordant if the LV electrode was located in the same myocardial segment as the latest activated region during intrinsic LBBB.

Statistical analysis

Continuous variables are expressed as mean $\pm$ SD. Categorical variables are expressed as observed number and percentage values. Continuous variables were compared using Mann-Whitney U test. Statistical significance was accepted at the 95% confidence interval ($P < 0.05$). Statistical analysis was performed using SPSS version 20.0 (SPSS Inc.) software.

Results

Patient characteristics

Twenty consecutive patients with LBBB referred for CRT device implantation were included in this study. The patient characteristics are described in Table 1.

CRT implantation and mapping

In 18 patients a *de novo* CRT defibrillator was implanted. One patient was upgraded from an implantable cardioverter-debrillator to a CRT defibrillator and one patient received a CRT pacemaker. LV lead implantation was successful in all patients. The RV lead was positioned in the RVA in all patients. There were no intra- or post-procedural complications. All patients underwent successful coronary venous EAM during both intrinsic LBBB as well as RVA pacing. Three-dimensional electrical activation maps during intrinsic LBBB and RVA pacing were

Table 1. Patient characteristics (n = 20)

Age, years	70 $\pm$ 10
Male gender (n, %)	11 (55)
Ischemic heart disease (n, %)	6 (30)
NYHA functional class (n, %)	
II	9 (45)
III	11 (55)
Echocardiography characteristics	
LV ejection fraction (%)	27 $\pm$ 4
LV end-diastolic diameter (mm)	62 $\pm$ 7
LV end-systolic diameter (mm)	53 $\pm$ 9
LV end-diastolic volume (mL)	158 $\pm$ 43
LV end-systolic volume (mL)	115 $\pm$ 36
ECG characteristics	
LBBB (n, %)	20 (100)
QRS duration (ms)	156 $\pm$ 18
Intrinsic rhythm (n, %)	
Sinus rhythm	17 (85)
Atrial fibrillation	3 (15)
Treatment (n, %)	
Diuretics	15 (75)
ACE-i/ARB	18 (90)
Beta-blockers	16 (80)
Spironolactone	10 (50)
Digoxin	1 (5)
Amiodarone	3 (15)

ACE-i, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

generated from 65 ± 28 and 59 ± 25 unique anatomic points, respectively Mapping time was 18 ± 7 minutes, fluoroscopy time during the entire procedure 21 ± 3 minutes, and total radiation dosage 4492 ± 2097 cGy $\times$ cm².

LV electrical activation pattern during intrinsic LBBB and RVA pacing

Figure 2 shows the coronary venous EAMs of five different study patients during both intrinsic LBBB and RVA pacing. These examples show a distinct difference in LV electrical activation pattern between intrinsic LBBB and RVA pacing, which was consistently observed in all study patients. During intrinsic LBBB, first, activation of the LV septum occurred, as shown by the virtually uniform early electrical activation of all segments of the inter-ventricular veins. From the septum, activation spread across the inferior or anterior wall toward the lateral free wall in a more or less circumferential pattern of activation, and ended in the anterolateral or

Figure 2. Coronary venous electroanatomic maps of five different study patients during both intrinsic left bundle-branch block (LBBB) and right ventricular apex (RVA) pacing together with the corresponding coronary venous angiograms in right anterior oblique view. Local electrical activation time was measured in ms relative to QRS onset and projected on the maps using colour coding. Earliest activation is represented in white and latest activation purple. Gray indicates regions mapped too sparsely to fill data. A distinct difference in LV electrical activation pattern between intrinsic LBBB and RVA pacing can be observed. Intrinsic LBBB was associated with a circumferential pattern of activation, whereas RVA pacing resulted in activation from the apex of the heart to the base. In panels 3-5, RVA pacing shifted the latest activated region relative to intrinsic LBBB. (Panel 1) The latest activated region (purple region) is located in the basal region of the anterolateral vein during both intrinsic LBBB and RVA pacing. (Panel 2) The latest activated region is located in the basal region of the inferolateral vein during both intrinsic LBBB and RVA pacing. (Panel 3) The latest activated region shifts from the mid to the basal region of the anterolateral vein during RVA pacing. (Panel 4) The latest activated region is located in the mid region of the first anterolateral vein during intrinsic LBBB, but shifts to the basal region of the second anterolateral vein during RVA pacing. (Panel 5) The latest activated region is located in the mid region of the inferolateral vein during intrinsic LBBB, but shifts to the basal region of the anterolateral vein during RVA pacing. AIV, anterior inter-ventricular vein; ALV, anterolateral vein; CS, coronary sinus; IIV, inferior inter-ventricular vein; ILV, inferolateral vein.

Figure 3. Location of the latest activated regions during intrinsic LBBB (A) and RVA pacing (B). Each circled number represents a patient. In 10 of 20 patients, the latest activated region during LBBB differed from that during RVA pacing. A, anterior; AL, anterolateral; AS, antero-septal; I, inferior; IL, inferolateral; IS, inferoseptal; L, lateral; S, septal.

inferolateral region at either mid or basal level. In contrast, RVA pacing resulted in LV electrical activation from the apex of the heart to the base. This is illustrated in the EAMs by the gradual increase in local electrical activation time from the distal to the proximal regions of both the inter-ventricular and lateral coronary veins. In the patients depicted in panel 3-5 of Figure 2, the change in activation pattern induced by RVA pacing shifted the latest activated region (purple region) relative to intrinsic LBBB. In contrast, the patients depicted in panel 1 and 2 of Figure 2 had similar latest activated regions during intrinsic LBBB and RVA pacing despite the clear difference in activation pattern observed between both conditions. Figure 3 shows the distribution of the latest activated region during intrinsic LBBB and RVA pacing in the whole study population. The location of the latest activated region during intrinsic LBBB varied between patients, being located anterolaterally in 15 (basal, $n = 8$; mid, $n = 7$) and inferolaterally in 5 (basal, $n = 2$; mid, $n = 3$). The latest activated region during RVA pacing showed a more uniform distribution, being located in the basal anterolateral segment in all but two patients. In total, 10 of 20 patients had different latest activated regions during LBBB and RVA pacing (Nos. 2, 3, 6, 8-12, 15, and 20). In this subgroup of patients, the latest activated region was located in the mid anterolateral (Nos. 2, 3, 6, 8, 10, 11, and 15) or mid inferolateral segment (Nos. 9, 12, and 20) during intrinsic LBBB, but shifted to the basal anterolateral segment during RVA pacing. An overview of the latest activated regions during intrinsic LBBB and RVA pacing of all patients together with the corresponding electrical delays at these sites is provided in Table 2. For the whole study population, local electrical activation time measured during RVA pacing, was significantly shorter at the region that was activated latest during intrinsic LBBB than at the region that was activated latest during RVA pacing [149 ± 39 vs. 171 ± 30 ms (75 ± 12 vs. $87 \pm 5\%$ of QRS duration), $P < 0.01$]. In patients with different latest activated regions, local electrical activation time measured during RVA pacing, was 120 ± 18 ms ($65 \pm 7\%$ of QRS duration) at the region that was latest activated during intrinsic LBBB and 161 ± 26 ms ($87 \pm 4\%$ of QRS duration) at the region that was latest activated during RVA pacing ($P < 0.001$).

Table 2. Overview of the latest activated regions during intrinsic LBBB and RVA pacing and the final LV lead positions in all study patients together with the corresponding electrical delays

Patient No.	Latest activated region during LBBB	LEAT measured during LBBB	Latest activated region during RVA pacing	LEAT measured during RVA pacing	LEAT measured during RVA pacing at latest activated region during LBBB	Final LV lead position	LVLED during LBBB	LVLED during RVA pacing
1	B-IL	131 (85%)	B-IL	151 (89%)	151 (89%)	B-IL	128 (83%)	148 (88%)
2	M-AL	110 (85%)	B-AL	166 (86%)	128 (66%)	M-AL	110 (85%)	99 (51%)
3	M-AL	126 (87%)	B-AL	211 (92%)	147 (64%)	M-AL	126 (87%)	137 (60%)
4	B-AL	130 (85%)	B-AL	155 (84%)	155 (84%)	B-AL	128 (83%)	152 (82%)
5	B-AL	119 (91%)	B-AL	168 (80%)	158 (80%)	B-AL	119 (91%)	161 (76%)
6	M-AL	124 (86%)	B-AL	137 (91%)	118 (78%)	M-AL	124 (86%)	91 (60%)
7	B-AL	149 (93%)	B-AL	176 (86%)	176 (86%)	B-AL	138 (86%)	158 (77%)
8	M-AL	116 (91%)	B-AL	147 (85%)	112 (65%)	M-AL	111 (87%)	112 (65%)
9	M-IL	131 (78%)	B-AL	170 (85%)	123 (61%)	M-IL	131 (78%)	116 (58%)
10	M-AL	111 (76%)	B-AL	119 (79%)	78 (52%)	M-AL	111 (76%)	73 (49%)
11	M-AL	118 (79%)	B-AL	146 (86%)	109 (63%)	M-AL	118 (79%)	102 (60%)
12	M-IL	130 (83%)	B-AL	173 (89%)	124 (64%)	B-AL	116 (74%)	154 (79%)
13	B-AL	128 (83%)	B-AL	151 (87%)	151 (87%)	B-AL	127 (82%)	136 (79%)
14	B-IL	143 (80%)	B-IL	187 (77%)	187 (77%)	B-IL	141 (79%)	185 (76%)
15	M-AL	160 (84%)	B-AL	159 (85%)	131 (70%)	M-AL	155 (81%)	113 (60%)
16	B-AL	140 (83%)	B-AL	256 (92%)	256 (92%)	B-AL	133 (79%)	242 (87%)
17	B-AL	169 (93%)	B-AL	215 (93%)	201 (87%)	B-AL	168 (92%)	201 (87%)
18	B-AL	124 (88%)	B-AL	175 (89%)	169 (86%)	B-AL	121 (86%)	165 (84%)
19	B-AL	129 (81%)	B-AL	164 (93%)	164 (93%)	B-AL	119 (75%)	158 (90%)
20	M-IL	152 (87%)	B-AL	186 (89%)	131 (63%)	B-AL	133 (76%)	175 (84%)
				171 ± 30 (87 ± 5%)	149 ± 39 (75 ± 12%)		82 ± 5%	72 ± 13%

Legend on next page.

Legend of Table 2. Patient numbers correspond with the numbers provided in figure 3 and 5. Local electrical activation time (LEAT) and LV lead electrical delay (LVLED) are reported in ms (percentage of total QRS duration). B, basal; M, mid; AL, anterolateral; IL, inferolateral.

QRS duration was longer during RVA pacing than during intrinsic LBBB (197 ± 32 vs. 156 ± 18 ms, $P < 0.001$). Right ventricular apex pacing was also associated with a longer total LV electrical activation time than intrinsic LBBB, as measured by coronary venous EAM (171 ± 30 vs. 132 ± 16 ms, $P < 0.001$). This increased delay in LV electrical activation during RVA pacing as compared to intrinsic LBBB is illustrated in Figure 4, which highlights one of the examples depicted in Figure 2, only this time with LV electrical activation time projected on the coronary venous geometry using the same color coding for both intrinsic LBBB and RVA pacing.

Figure 4. Increased delay in LV electrical activation during RVA pacing compared with intrinsic LBBB. Local electrical activation time has been projected on the coronary venous EAMs of the patient depicted in panel 4 of Figure 2 using the same colour coding for both intrinsic LBBB and RVA pacing. AIV, anterior inter-ventricular vein; ALV-1, first anterolateral vein; ALV-2, second anterolateral vein; CS, coronary sinus; LEAT, local electrical activation time; RAO, right anterior oblique view.

LV lead electrical delay with respect to mode of ventricular activation

The study protocol involved targeting of the LV lead to the latest activated region during intrinsic LBBB. Figure 5 shows the distribution of the final LV lead position in all patients. The LV lead was positioned anterolaterally in 17 (basal, $n = 10$; mid, $n = 7$) and inferolaterally in three (basal, $n = 2$; mid, $n = 1$). The final LV lead position was concordant with the latest activated region during intrinsic LBBB in 18 of 20 patients. In 2 patients (Nos. 12 and 20), concordant LV lead placement was hampered by phrenic nerve stimulation and lead instability, respectively. These two patients happened to have different latest activated regions during LBBB and RVA pacing, and the LV lead was positioned concordant with the latest activated region during RVA pacing in both. As a result, the final LV lead position was concordant with the latest activated region during RVA pacing in 12 out of 20 patients. An overview of the final LV lead positions in all patients together with the LV lead electrical delays (LVLED) measured during both intrinsic LBBB and RVA pacing is provided in Table 2. For the whole study population, LVLED, expressed as a percentage of QRS duration, was shorter during RVA pacing than during LBBB (72 ± 13 vs. $82 \pm 5\%$, $P = 0.035$). In the 10 patients with different latest activated regions, there was an even more pronounced reduction in LVLED during RVA pacing as compared with LBBB (63 ± 11 vs. $81 \pm 5\%$, $P = 0.002$).

Discussion

Increasing evidence supports the practice of placing the LV lead in the latest activated region as a means of maximizing CRT response.⁵⁻¹⁰ At present, the latest activated region is assessed during intrinsic ventricular activation.^{9,10} However, CRT is most commonly applied by biventricular pacing without contribution from intrinsic conduction. The present study demonstrates that RVA pacing significantly alters the pattern of LV electrical activation in CRT patients with LBBB. This change in activation pattern shifted the latest activated region in half the patients in the present study. Positioning of the LV lead in the region of latest activation during intrinsic LBBB significantly reduced LV lead electrical delay during RVA pacing. Our findings urge reconsideration of the current practice of LV lead targeting for CRT.

Figure 5. Location of the final LV lead positions. Each circled number represents a patient. Numbers correspond with the numbers in Figure 3 and Table 2. A, anterior; AL, anterolateral; AS, antero-septal; I, inferior; IL, inferolateral; IS, inferoseptal; L, lateral; S, septal.

Difference between intrinsic LBBB and LBBB induced by RVA pacing

The present study demonstrates that intrinsic LBBB and RVA pacing, despite having similar QRS morphologies, have different electrical activation patterns. Previous studies have provided detailed information about LV electrical activation pattern in patients with LBBB and during RV pacing. Auricchio et al. previously showed that in patients with LBBB and heart failure, the earliest electrical activation occurs in the septum and that all septal segments are activated relatively simultaneously. Subsequent conduction of electrical activation from the septum to the lateral LV free wall was shown to be impeded by functional lines of block that are usually located on the anterior LV wall, resulting in a U-shaped pattern of activation that turns around the apex and inferior wall of the LV.¹⁶ Other investigators showed that in contrast to LBBB, activation during RV pacing is likely to start at a single point and spreads both circumferentially and longitudinally.^{17,18} However, within-patient comparisons of intrinsic LBBB with RVA pacing-induced LBBB are limited. In the present study, LBBB was associated with a circumferential course of LV activation, while RVA pacing resulted in activation from the apex of the heart to the base. This finding is in agreement with previous observations by Ludwig et al., who demonstrated a similar difference in LV mechanical activation pattern between LBBB and RVA pacing using three-dimensional speckle-tracking echocardiography.¹¹ The same investigators also demonstrated that RVA pacing results in greater mechanical dyssynchrony than LBBB.¹¹ This finding corresponds with our observation that QRS duration and total LV electrical activation time were longer during RVA pacing compared with LBBB.

The LV activation pattern has been shown to vary depending on the site of ventricular pacing.^{16,19} In the present study, the RV pacing electrode was positioned in the RV apex in all patients, which may explain the fairly uniform location of the latest activated region observed during RVA pacing. Conversely, conduction delay in LBBB can be located at different anatomical levels in the conduction system, which may explain our observation of a variable location of the latest activated region during LBBB, consistent with earlier reports.^{16,20,21}

Implications for the current practice of LV lead targeting for CRT

There is increasing evidence to suggest that positioning of the LV lead in the region of latest activation provides superior acute and long-term outcome of CRT.^{5-10,22} Studies investigating this lead placement strategy determined the region of latest mechanical activation preoperatively during intrinsic activation, and this information was subsequently used to guide LV lead placement.^{9,10} Targeting the latest activated region during intrinsic activation is reasonable when CRT involves only LV pacing fused with intrinsic activation.²³ However, CRT is most commonly applied by biventricular pacing without contribution from intrinsic conduction. The present study demonstrates that the region of latest electrical activation during RVA pacing differs from that during LBBB in a significant proportion of CRT patients. In addition, our data show that the practice of placing the LV lead in the latest activated region during LBBB markedly reduces LVLED when CRT utilizes RVA pacing. Our findings, added to previous results of Ludwig et al. showing a similar discordance in the segment of latest mechanical contraction between LBBB and RVA pacing¹¹, imply that LV lead targeting for CRT which is applied by biventricular pacing should rather be directed at the latest activated region assessed during RVA pacing. Alternatively, when limitations of transvenous LV lead placement hamper targeting of the latest activated region during RVA pacing, positioning of the LV lead in the latest activated region during intrinsic activation combined with LV fusion pacing may be considered to achieve optimal ventricular resynchronization. Previously, Singh et al. proposed the “dial in” strategy to overcome the limitations of transvenous LV lead placement when aiming for maximal electrical separation of the LV and RV leads. Their approach involved initial placement of the LV lead at the most suitable anatomic site, and then subsequent selection of an RV pacing site as electrically distant as possible from the obtained LV pacing site.²⁴

While the position of the LV lead with respect to the region of latest activation is a factor that can influence CRT response, several studies have shown that the proximity of the LV lead to an area with myocardial scar is also an important factor.²⁵⁻²⁹ Assessment of scar tissue should therefore be considered before CRT, especially in the population with ischemic heart disease. Integrating information obtained from preprocedural scar imaging with intraprocedural information on LV electrical activation pattern may further optimize LV lead positioning and the clinical response rate.

Clinical applicability of coronary venous EAM for assessment of LV electrical activation pattern during LBBB and RVA pacing

Coronary venous EAM was easy to implement intraprocedurally using a commercially available EAM system in combination with a guidewire that allows mapping and pacing of the coronary veins, making the approach applicable in any catheter laboratory that has access to the relevant instruments. In addition, the same wire used to guide the LV lead was also used to map the coronary veins, which obviated the need for inserting additional electrophysiology mapping catheters during implantation. The mean total fluoroscopy time for CRT implantation in previous studies ranged from 23.9 ± 18.1 min³⁰ to 46 ± 23 min.³¹ In the present study, mean total fluoroscopy time was 21 ± 3 minutes, which indicates that coronary venous EAM can be accomplished intraprocedurally without excessive use of radiation. The intraprocedural setup, which involved initial placement of the RV lead followed by coronary venous EAM allowed assessment of LV electrical activation pattern during both LBBB and RVA pacing. In addition, the NavX system allowed for real-time visualization and navigation of the indwelling LV lead in the created three-dimensional EAM of the cardiac veins, which facilitated targeting of the anatomical area of latest electrical activation. Not every implanting centre has access to an

EAM system. In that case, electrical mapping with the LV lead may be considered as a simpler alternative to assess LV electrical activation sequence during intrinsic LBBB and RVA pacing and target LV lead placement to the latest activated region. Echocardiography and other imaging modalities have also been proposed as methods to assess LV activation pattern.^{7,8,31-34} However, these techniques are challenging to apply in the catheter laboratory and require a preoperative assessment, which limits the possibility of assessing LV activation pattern during RV pacing in patients without a previously implanted pacing device.

Limitations

The sample size of this study was relatively small. However, the study was performed on consecutive patients and the population resembled the typical population of patients with LBBB and heart failure referred for CRT implantation.

In the present study, the RV pacing electrode was implanted in the RVA in all patients, which is common practice in CRT. The impact of alternative RV pacing sites, such as the basal or mid RV septum, on LV electrical activation was not assessed.

Cardiac magnetic resonance imaging was not performed in this study. Therefore, we could not assess the distribution and extent of myocardial scar and its potential effect on LV electrical activation.

The findings of the current study indicate that during LV lead targeting for CRT, one should consider that the latest activated region during RVA pacing may differ from that during intrinsic LBBB. Thus, positioning of the LV lead in the latest activated region during RVA pacing, rather than targeting the latest activated region during intrinsic activation may be more appropriate when CRT is applied by biventricular pacing. However, the small number of patients precluded any systematic analysis of the impact of LV lead positioning based on the latest activated region during RVA pacing on CRT outcome. Neither was the clinical value of this approach proven by acute hemodynamic measurements. Whether such a LV lead placement strategy actually increases the likelihood of a favourable CRT response needs prospective evaluation in larger and preferably randomized studies.

Conclusion

Current targeted LV lead placement strategy is directed at the latest activated region assessed during intrinsic ventricular activation. In contrast, CRT is most commonly applied by biventricular pacing without contribution from intrinsic conduction. The present study demonstrates that right ventricular apex pacing alters the pattern of LV electrical activation in CRT patients with LBBB, and shifts the latest activated region in a substantial proportion of these patients. These findings raise questions about the current practice of LV lead targeting for CRT.

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Regional left ventricular electrical activation and peak contraction are closely related in candidates for cardiac resynchronization therapy

Masih Mafi Rad*, Jetske van 't Sant*, Yuri Blaauw, Pieter A. Doevendans, Maarten J. Cramer, Harry J. Crijns, Frits W. Prinzen, Mathias Meine, Kevin Vernooy

*Authors contributed equally to this manuscript

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Abstract

Aim: Targeting the left ventricular (LV) lead to the region of latest electrical activation or the segment of latest peak contraction has both been shown to improve response to cardiac resynchronization therapy (CRT). Whether these regions correspond within CRT patients is uncertain. We determined the relationship between the timing of LV electrical activation and peak contraction at potential LV pacing locations in candidates for CRT.

Methods: Twenty-eight consecutive CRT candidates underwent intraprocedural coronary venous electroanatomic mapping using EnSite NavX. Peak contraction time of the mapped LV regions was determined using longitudinal strain derived from speckle-tracking echocardiography. Electrical activation and peak contraction times were correlated on a per-patient basis and the regions of latest electrical activation and latest peak contraction were compared.

Results: Successful measurements by both techniques allowed analysis in 23 of 28 patients. There was a strong positive correlation between electrical activation and peak contraction times within each patient ($R^2 = 0.85 \pm 0.09$). However, the magnitude of the electrical activation-peak contraction relationship varied greatly between patients (slope of regression line = 4.05 ± 3.23). The regions of latest electrical activation and latest peak contraction corresponded in 19 of 23 (83%) patients and were adjacent in 4 patients.

Conclusion: There is a strong positive correlation between the timing of LV electrical activation and peak contraction measured at potential LV pacing locations in typical CRT candidates. This finding suggests that a strategy of determining the latest activated LV region based on speckle-tracking echocardiography is equivalent to that based on intra-cardiac measurements of electrical activation.

Introduction

Cardiac resynchronization therapy (CRT) has become an important treatment for heart failure patients with left ventricular (LV) systolic dysfunction and evidence of LV conduction delay. CRT aims to resynchronize the electrical ventricular activation by paced pre-excitation of the delayed LV lateral wall. Doing so, it restores coordinated ventricular contraction, improves LV systolic function and reverses ventricular remodeling.¹ The position of the LV lead with respect to the region of latest activation has been shown to be an important determinant of CRT response. Studies focusing on electrical activation have demonstrated that a greater delay in time from onset of the QRS complex to the locally sensed LV lead electrogram is associated with a greater likelihood of benefit from CRT.² Other studies used speckle-tracking based strain measures of mechanical activation and suggest better CRT outcome when the LV lead position coincides with the segment of latest peak contraction.³ The choice between targeting the region of latest electrical activation or the segment of latest peak contraction is currently a matter of debate. On the one hand, preclinical studies in non-failing canine hearts have previously shown that electrical and mechanical activation of the heart are closely coupled.⁴⁻⁶ On the other hand, echocardiography based time-to-peak measures of mechanical dyssynchrony have recently been questioned for their ability to predict CRT response.^{7,8} Therefore, it remains unclear whether the preclinical results can be extrapolated to the dyssynchronous failing human heart. The results of two recent small-scale studies on this subject have been conflicting.^{9,10} The purpose of the present study was to perform a within-patient comparison of the timing of LV electrical activation and peak contraction at potential LV pacing locations accessible via the coronary veins in patients undergoing CRT.

Methods

Study population

This study was conducted in 28 consecutive patients enrolled for CRT with LV ejection fraction (LVEF) <35%, New York Heart Association (NYHA) functional class II, III or ambulatory IV, left bundle-branch block (LBBB) according to specific criteria¹¹ or non-LBBB with QRS duration >150 ms. The study protocol was approved by the Maastricht University Medical Center's (MUMC) Institutional Review Board.

Electroanatomic mapping

All patients underwent intraprocedural coronary venous electroanatomic mapping (EAM) at the MUMC as described previously.¹² 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 (CS) and connected to EnSite NavX (St Jude Medical). The guidewire was manipulated to various CS branches, creating an anatomic map along with determining local electrical activation time during intrinsic ventricular activation. After the mapping procedure, the LV lead was positioned in a lateral or posterolateral vein according to routine clinical practice.

Classification of coronary venous anatomy

The coronary venous anatomy was classified using the segmental approach¹³ by detailed evaluation of biplane coronary venograms. In the left anterior oblique (LAO) image, the CS was divided into anterior, lateral, and posterior areas, and the distribution of the branches was described similarly. The right anterior oblique (RAO) image was used to divide CS branches into basal, mid-ventricular and apical segments.

Echocardiography

Standard 2-dimensional echocardiography was performed within two weeks prior to CRT implantation at the MUMC using a commercial machine (Philips IE 33, Philips Medical Systems). Routine gray-scale cine loop images were acquired in standard apical views with a frame rate of at least 50 Hz and digitally stored for post-processing offline (Xcelera software R3.3L1). Left ventricular end-diastolic volume, LV end-systolic volume and LVEF were calculated using Simpson’s biplane method. Speckle-tracking 2-dimensional longitudinal strain analysis was performed at the University Medical Center Utrecht (UMCU) by an experienced observer blinded to the electrical data using Cardiac Performance Analysis software version 1.2 (Tomtec Imaging Systems). The endocardial border was manually traced in end-systole. Subsequently, the speckle tracking software automatically analyzed frame-by-frame movement of the stable patterns of acoustic markers (speckles) to generate time-strain curves over the cardiac cycle of the myocardial segments. Since the area of the LV that can be approached for EAM via the CS is limited to the LV free wall, the assessment of segmental time-to-peak contraction was also limited to the LV free wall segments. The time-to-peak contraction of each mapped myocardial segment was measured in ms from QRS onset to peak longitudinal strain. If segmental time-strain curves showed more than one peak, the first peak was assessed. Echocardiographic images that were of insufficient quality for speckle-tracking strain analysis and myocardial segments with likely scar (low amplitude longitudinal strain curves <5.3%, thin wall ≤0.5 cm, abnormal increase in acoustic reflectance, and akinetic wall motion)^{14,15} were handled as missing data. Previously, the intra- and interobserver coefficients of variation for the determination of timing of peak myocardial wall shortening were assessed at the echocardiography laboratory of the UMCU and were 14.2% and 15.6%, respectively.¹⁶

Comparison of electrical activation and peak contraction times

After classification of the coronary venous anatomy according to the segmental approach as described above, the electrical activation time of each mapped myocardial segment was calculated as the average of all electrical activation times measured within a segment during mapping. The electrical activation and peak contraction times of each mapped myocardial segment were then directly compared. Pearson’s correlation coefficient was computed between the electrical activation and peak contraction times observed for each patient. The segments of latest electrical activation and latest peak contraction were determined in each patient.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Categorical values are expressed as observed number and percentage values. Paired samples t-test was used to compare means of continuous variables among different measurement conditions and Mann-Whitney U test was used to compare means of continuous variables among different groups. Within-patient correlation between electrical activation and peak contraction times was calculated using Pearson’s correlation coefficient. Statistical significance was accepted at the 95% confidence interval. Statistical analysis was performed using SPSS version 20.0 (SPSS Inc.) software.

Results

Patient characteristics

Twenty-eight consecutive patients enrolled for CRT were included in the study. The patient characteristics are described in Table 1.

Table 1. Patient characteristics (n = 28)

Characteristic	Value
Age, years	71 ± 9
Male gender (n, %)	18 (64)
Ischemic heart disease (n, %)	13 (46)
NYHA functional class (n, %)	
II	13 (46)
III	15 (54)
Echocardiography characteristics	
LV ejection fraction (%)	28 ± 6
LV end-diastolic diameter (mm)	61 ± 7
LV end-systolic diameter (mm)	52 ± 7
LV end-diastolic volume (mL)	169 ± 51
LV end-systolic volume (mL)	123 ± 38
ECG characteristics	
QRS duration (ms)	154 ± 15
LBBB (n, %)	18 (64)
IVCD (n, %)	10 (36)
Intrinsic rhythm (n, %)	
Sinus rhythm	23 (82)
Atrial fibrillation	5 (18)
Treatment (n, %)	
Diuretics	19 (68)
ACE-i/ARB	27 (96)
Beta-blockers	24 (86)
Spironolactone	15 (54)
Digoxin	2 (7)
Amiodarone	4 (14)

LBBB, left bundle-branch block; IVCD, intra-ventricular conduction delay; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Coronary venous EAM and speckle-tracking strain analysis

Intraprocedural coronary venous EAM was accomplished in all 28 patients without complications. Coronary venous angiography in the 28 patients revealed a total of 96 coronary venous branches, of which 83 (86%) could be mapped. Three-dimensional electrical activation maps were generated from 62 ± 25 unique anatomic points. Mapping time was 19 ± 7 minutes, and fluoroscopy time during the entire procedure was 21 ± 4 minutes.

Figure 1. Analysis of electrical activation-peak contraction relationship in one patient. (A) Coronary venous EAM. The CS and three side branches (basal- and mid-segments) were mapped. Earliest activation is represented in white and red and latest activation in blue and purple. (B) Corresponding time strain curves of the mapped myocardial segments. (C) Electrical activation times (mean $\pm$ standard deviation, red numbers) and corresponding peak contraction times (blue numbers) of the mapped myocardial segments of this patient displayed on a 17-segment bullseye of the heart. (D) Correlation between electrical activation and peak contraction times in this patient. L/RAO, left/right anterior oblique view; CS, coronary sinus; AV, anterior inter-ventricular vein; LV, lateral marginal vein; PV, posterior vein; EAT, electrical activation time; A, anterior; P, posterior; I, inferior; L, lateral; S, septal; AS, antero-septal.

Speckle-tracking strain analysis was accomplished in 23 of 28 patients. In the other 5 patients, this was hampered by insufficient quality of the acquired echocardiographic images ($n = 4$) and frequent premature ventricular beats ($n = 1$). These 5 patients were excluded from further analysis. Myocardial segments with likely scar on echocardiography, which were handled as missing data, were encountered in only 2 of 23 patients, and comprised only 2% of all segments analyzed for time-to-peak strain.

The patient's hemodynamic parameters were similar during both studies. The intrinsic heart rhythm during both studies was unchanged for all patients. The mean heart rate was 69 ± 14 beats per minute during echocardiography and 71 ± 11 beats per minute during EAM ($P = 0.33$). The mean QRS duration was 156 ± 16 ms during echocardiography and 154 ± 15 ms during EAM ($P = 0.17$).

Relationship between left ventricular electrical activation and peak contraction

Successful measurements by both coronary venous EAM and speckle-tracking echocardiography allowed analysis of the electrical activation-peak contraction relationship in 23 of 28 patients. An example of the analysis in one patient is shown in Figure 1. In this patient, the CS and three side branches situated on the basal and mid anterior-, lateral- and posterior wall were mapped (Figure 1A). Earliest electrical activation was found in the mid-segment of the anterior inter-ventricular vein and latest electrical activation in the basal-segment of the posterior vein. Figure 1B shows the corresponding time-strain curves of the mapped myocardial segments obtained by speckle tracking echocardiography. In figure 1C, the average electrical activation times and corresponding peak contraction times of the mapped myocardial segments of this patient are displayed on a bullseye of the heart. Figure 1D shows the regression line between the electrical activation and peak contraction times for this patient. There was a strong correlation between electrical activation and peak contraction times within this patient ($R^2 = 0.90$), and the segment of latest electrical activation corresponded with the segment of latest peak contraction.

A strong linear relationship between electrical activation and peak contraction times, as observed in the example shown in Figure 1, was found in all patients ($R^2 = 0.85 \pm 0.09$).

Figure 2. Inter-individual variability in electrical activation-peak contraction relationship. The regression lines between electrical activation and peak contraction times and the points by which these were created are shown for four representative patients. Each point was determined from measuring the electrical activation and peak contraction time of a myocardial segment within a patient. The electrical activation and peak contraction times of 5 myocardial segments (resulting in 5 points) were assessed in 3 of these patients and those of 6 myocardial segments (resulting in 6 points) were assessed in 1 patient. All regression lines exhibited high and positive correlation values (R^2). Yet the slope and hence the magnitude of the electrical activation-peak contraction relationship varied greatly from patient to patient.

The slope of the regression line between electrical activation and peak contraction times was positive in all patients, indicating that as electrical activation time increases, the peak contraction time increases as well. This implies that the sequence of peak contraction is similar to the electrical activation sequence, also for the non-latest segments. However, the slope and hence the magnitude of this relationship varied greatly between patients (slope of regression line = 4.05 ± 3.23 , Figure 2). Also, the slope of the regression line was above unity in all but one patient, indicating that regional differences in timing of peak contraction were generally greater than those of electrical activation. Subgroup analysis showed no difference in the strength of the electro-mechanical relationship between patients with ischemic vs. non-ischemic LV dysfunction, patients with LBBB vs. IVCD, or patients with sinus rhythm vs. atrial fibrillation (Table 2).

Table 2. Subgroup analysis of the strength of the electro-mechanical relationship

Patient subgroups	R ²	P
Ischemic- vs. non-ischemic LV dysfunction	0.88 ± 0.09 vs 0.84 ± 0.09	0.29
LBBB vs IVCD	0.86 ± 0.10 vs 0.84 ± 0.08	0.69
SR vs AF	0.87 ± 0.05 vs 0.85 ± 0.09	0.70

LBBB, left bundle-branch block; IVCD, non-specific intra-ventricular conduction delay; SR, sinus rhythm; AF, atrial fibrillation; R², Pearson's correlation coefficient computed between the electrical activation and peak contraction times observed for each patient; P, p-value.

Figure 3 shows the spatial distribution of the electrically latest activated and latest contracting segments in all patients. The segment of latest electrical activation was located anteriorly in 11 (basal, $n = 10$; mid, $n = 1$), laterally in 8 (basal, $n = 5$; mid, $n = 3$), and posteriorly in 4 (all basal). The segment of latest peak contraction was located anteriorly in 11 (all basal), laterally in 8 (basal, $n = 5$; mid, $n = 3$), and posteriorly in 4 (all basal). The myocardial segment with the largest electrical activation time also had the largest peak contraction time in 19 of 23 patients (83%). In the other 4 patients, the myocardial segments of latest electrical activation and latest peak contraction were adjacent, which was defined as located directly next to each other on either the apical-basal axis (RAO view) or the short axis projection (LAO view), including touching diagonally.

Discussion

In the present study we investigated the relationship between the timing of regional LV electrical activation and peak contraction in dyssynchronous heart failure patients undergoing CRT implantation. We demonstrated a strong positive correlation between electrical activation and peak contraction times measured at potential LV pacing regions accessible via the coronary veins in all patients. However, the magnitude of the relationship between electrical activation and peak contraction times varied greatly between patients. The myocardial segments of latest electrical activation and latest peak contraction corresponded in 83% of patients. Our data indicate that a strategy of determining the latest activated LV region based on speckle-tracking strain patterns is equivalent to that based on intra-cardiac measurements of electrical activation.

Figure 3. Spatial distribution of the electrically latest activated (left) and latest contracting segments (right) in the 23 patients with successful measurements by both coronary venous EAM and speckle-tracking echocardiography. Each circled number represents a patient, with LBBB patients represented in blue and IVCD patients in green. The segment with the largest electrical activation time also had the largest peak contraction time in 19 of 23 patients (83%). In 4 patients (Nos. 3, 7, 27, and 28), the segments of latest electrical activation and latest peak contraction were adjacent. A, anterior; P, posterior; I, inferior; L, lateral; S, septal; AS, anteroseptal.

Relationship between timing of electrical activation and peak contraction

A number of animal studies have previously studied the relation between the sequence of LV electrical activation and contraction using a combination of electrical mapping techniques and strain measurements. These studies were conducted in healthy spontaneously activated or paced canine hearts and focused on the relation between timing of electrical activation and time-to-onset of contraction, rather than peak contraction. A strong linear relation between timing of electrical activation and onset of contraction was found in these studies. In addition, mechanical delay was shown to be larger than electrical delay.^{4, 6, 17, 18} While time-to-onset of contraction may be a better surrogate for mechanical activation than time-to-peak contraction, in practice, the identification of the first subtle onset of contraction can be cumbersome. Therefore, most clinical studies employed time-to-peak contraction.^{3, 19}

The findings of the present study are consistent with the results of a recent study by Suever et al.,¹⁰ who investigated the relation between electrical and mechanical delay times measured at potential pacing locations within the coronary veins. In this study, the mechanical contraction times were computed using cross correlation of radial displacement curves from high temporal resolution cine cardiac magnetic resonance images, while electrical activation times were derived from intra-procedural local electrograms obtained using the LV lead. Similar to our findings, they found a strong correlation between electrical and mechanical delay times within each patient. Additionally, the electrically latest activated region corresponded with the latest contracting region in 91% of patients.

Our results are also in line with a very recent study by Kroon et al.,²⁰ who used NOGA mapping derived electrograms and local strain derived from the motion of the NOGA catheter to investigate the relation between the timing of LV electrical activation and peak shortening in 10 CRT candidates. In this study, an excellent correlation was found between local electrical activation and peak shortening times in 8 of 10 patients.

However, our findings are in contrast to the results of a previous study that had a similar design as ours. In that study by Fujiwara et al., the electrically latest activated region as determined by coronary venous EAM matched with the latest contracting region as determined by speckle-tracking radial strain analysis in only 18% of patients,⁹ whereas we found that the regions of latest electrical activation and latest peak contraction corresponded in 83% of patients. An important methodological difference between our study and the study by Fujiwara et al. is the use of different types of strain measurements (radial vs. longitudinal). The Longitudinal strain measurements that were used in the present study have been shown to be more feasible and reproducible than radial strain measures.^{21, 22} Also, in contrast to Fujiwara et al., we only measured peak contraction times of LV regions accessible via the coronary veins. In doing so, we neglected the data on mechanical activation of the septum, because this part of the LV wall is not accessible from the CS and, most importantly, is unlikely to be activated late in LBBB-like conduction abnormalities. It was previously shown in computer simulations that septum strain patterns can be complicated and multiphasic, and can sometimes show a relatively late peak in systole, even in LBBB,²³ which may lead to erroneously finding the latest peak contraction in the septum.

In the present study, the latest activated region was located on the anterior wall in 11 of 28 patients. This observation may be explained by the fact that seven of these patients did not have a typical LBBB morphology on ECG, and that the remaining four had an ischemic etiology of heart failure with myocardial scarring. In patients with non-ischemic LV dysfunction and LBBB, the latest activated region is typically located on the lateral or posterolateral wall.²⁴ In contrast, the LV activation pattern in patients with non-LBBB QRS morphology or patients with ischemic LV dysfunction has been shown to be more variable.^{25, 26}

Inter-individual variability in electrical activation-peak contraction relationship

In the present study, we found a strong linear relationship between timing of electrical activation and peak contraction within each patient. In addition, the relationship was positive in each patient, indicating that as electrical activation time increases, peak contraction time increases as well. However, the slope of the best fit line between electrical activation and peak contraction times was 4.06 ± 3.23 , which indicates that the electrical activation-peak contraction relationship varied greatly between patients and that timing differences of myocardial contraction were greater than those of electrical activation. The differences in the electrical activation-peak contraction relation between hearts may be caused by inter-individual differences in local myocardial tissue properties, such as viability, contractility and stiffness of the myocardium.²⁰ The “amplification” of dyssynchrony when using mechanical measures is likely explained by the fact that peak contraction occurs much later in the cardiac cycle and the fact that early activated regions show a very early peak contraction whereas late activated regions are initially pre-stretched and subsequently show a more pronounced and prolonged contraction.^{4, 5, 23} In computer models of LBBB, the more pronounced mechanical rather than electrical delay has been attributed to the higher mechanical load that needs to be overcome by late activated regions, which causes onset of contraction to occur relatively late.⁵

Clinical implications

In the present study, we demonstrated that there is a strong correlation between timing of electrical activation and peak contraction and that the regions of latest electrical activation and latest peak contraction largely correspond within CRT patients. These findings suggest that current targeted LV lead placement strategies which are based on either direct intra-cardiac measurements of electrical activation or speckle-tracking strain echocardiography will most likely target the same myocardial region and as such can be regarded as equivalent. In this respect, the present study can be regarded as a validation of the speckle-tracking approach. This validation is not trivial, because echocardiographic measures of mechanical dyssynchrony have recently been questioned with respect to their ability to predict CRT response.^{7, 8} Proposed explanations for these disappointing results have been that time-to-peak contraction may depend on other factors than electrical activation time alone and that there is a high variability in the way echocardiographic dyssynchrony parameters are acquired and analyzed. However, most of the problems faced with echocardiographic measures of mechanical dyssynchrony relate to difficulties in determining contraction time of the early-activated septum with its complicated, multi-phasic contraction patterns. In current practice, the LV lead is placed epicardially via the coronary veins, which only allow access to the LV free wall segments. Therefore, assessment of mechanical activation of the septum is not as important as that of the LV free wall for guiding LV lead placement. Limiting the assessment of time-to-peak contraction to the LV free wall avoids most of the problems faced during echocardiographic assessment of mechanical dyssynchrony. In daily clinical practice, speckle tracking time-to-peak contraction analysis of the LV free wall segments could be performed prior to CRT implantation during a separate pre-operative assessment which takes only a matter of minutes. This information can then be provided to the implantor during CRT implantation, who can then, after performing invasive coronary venous angiography, use the segmental approach¹³ to identify and match the location of the cardiac veins to the underlying LV myocardial segments and target the LV lead to the segment of latest peak contraction to enhance cardiac synchrony.

Limitations

The relatively small sample size is a limitation of this study. However, the study was performed on consecutive patients and the study population resembled the typical population of patients with dyssynchronous heart failure referred for CRT.

The small sample size did however preclude any systematic analysis of a relationship between targeting LV lead placement to the latest activation region and clinical response. Whether such a LV lead placement strategy actually increases the likelihood of a favourable CRT response needs prospective evaluation in larger and preferably randomized studies.

Epicardial mapping through the coronary veins is limited by coronary venous anatomy. The electrical activation time of some LV free wall segments could therefore not be assessed because they did not contain any veins.

Speckle-tracking echocardiography relies on the availability of echocardiographic images with sufficient quality for reliable assessment of strain patterns. Insufficient image quality and frequent premature ventricular beats hampered reliable assessment of segmental peak contraction times in 5 patients in this study. In these patients, the electrical activation-peak contraction relationship could therefore not be analyzed.

Conclusion

The present study demonstrates that there is a strong positive correlation between the timing of LV electrical activation and peak contraction measured at potential LV pacing locations accessible via the coronary veins in typical CRT candidates. Additionally, the regions of latest electrical activation and latest peak contraction largely correspond within CRT patients. These findings suggest that a strategy of determining the latest activated LV region based on speckle-tracking echocardiography is equivalent to that based on intra-cardiac measurements of electrical activation.

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Chapter

Identifying delayed left ventricular lateral wall activation in patients with non-specific intra-ventricular conduction delay using coronary venous electroanatomic mapping

Masih Mafi Rad*, Antonius M. W. van Stipdonk*,
Justin G.L.M. Luermans, Harry J. Crijns, Frits W. Prinzen,
Kevin Vernooy

*Authors contributed equally to this manuscript

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Abstract

Aim: 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 a cohort of CRT candidates with IVCD using coronary venous electroanatomic mapping (EAM), and investigated whether baseline QRS characteristics on the ECG can identify delayed LVLW activation in this group of patients.

Methods: Twenty-three consecutive CRT candidates with IVCD underwent intraprocedural coronary venous EAM using EnSite NavX. Electrical activation time (AT) was measured in ms from QRS onset and expressed as percentage of QRS duration. LVLW activation was considered delayed if maximal AT measured at the LVLW (LVLW-AT) exceeded 75% of QRS duration. QRS morphology, -duration, -fragmentation, -axis deviation, and left anterior/posterior fascicular block were assessed on baseline ECGs.

Results: Delayed LVLW activation occurred in 12 of 23 patients [maximal LVLW-AT = 133 ± 20 ms ($83 \pm 5\%$) of QRS duration]. 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. QRS characteristics on the ECG seem unable to identify delayed LVLW activation in this subgroup of patients.

Introduction

The supposed mechanism of the benefit of cardiac resynchronization therapy (CRT) is that delayed activation of the left ventricular (LV) lateral wall (LVLW) 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 LVLW.¹⁻³ Non-specific intra-ventricular 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 electroanatomic mapping (EAM) 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 EAM can be used at the time of CRT implantation to determine the presence of delayed LVLW activation in patients with IVCD, and (2) to investigate whether QRS characteristics on the ECG, other than QRS morphology, can identify delayed LVLW activation as determined by coronary venous EAM 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. Non-specific intra-ventricular conduction delay was defined as a QRS duration ≥ 120 ms without typical features of LBBB or right bundle-branch block (RBBB), according to accepted criteria.¹¹ The study protocol was approved by the Institutional Review Board.

Electroanatomic mapping

Coronary venous 3D EAM 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 (CS) and connected to an EnSite NavX system (St Jude Medical). The guidewire was manipulated to all CS 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 (AT) during intrinsic ventricular activation. Local AT was measured in ms from QRS onset on surface ECG and expressed as percentage of total QRS duration. Activation of the LVLW was considered delayed if maximal AT measured at the LVLW (maximal LVLW-AT) exceeded 75% of 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 timepoint within the QRS complex. We believe that an electrical activation time exceeding 75% of QRS duration is a reasonable definition for delayed LVLW 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 total QRS duration is associated with superior CRT outcome. 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.^{13, 14}

ECG assessment

Twelve-lead ECGs were assessed by 2 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 (LAD) and right axis deviation (RAD), as well as the presence of left anterior (LAFB) and posterior fascicular block (LPFB) were defined according to AHA/ACC/HRS criteria,¹¹ excluding the criterion of QRS duration <120 ms because of coexisting IVCD. QRS fragmentation was defined according to Das et al.,¹⁵ >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 ± standard deviation and were compared using 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 (CI) (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 electroanatomic mapping

Coronary venous EAM was accomplished without complications in all patients. A mean number of 2.8 ± 0.7 CS branches were mapped during the procedure, of which 1.9 ± 0.5 were located on the LVLW. 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 LVLW activation, defined as maximal LVLW-AT exceeding 75% of total QRS duration, occurred in 12 of 23 (52%) patients. In Table 2, LVLW-AT data are presented for patients with and without delayed LVLW activation. In patients with delayed LVLW activation, maximal LVLW-AT was 133 ± 20ms (83 ± 5% of QRS duration) and ranged from 103 to 181ms (75% - 93% of QRS duration). In patients without delayed LVLW activation, maximal LVLW-AT was 100 ± 19ms (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 LVLW activation (P = 0.92). Also, baseline characteristics did not differ between the two groups. In patients with delayed LVLW activation, the most delayed lateral region was more frequently located on the “basal” lateral wall than in patients without delayed LVLW 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 EAMs of 2 patients with and without delayed LVLW activation. In the example shown in panel A, the CS and three side branches located on the anterior, inferior and inferolateral wall were mapped. Delayed activation [139 ms (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. Coronary venous EAM of a patient with (A) and without (B) delayed LVLW activation together with the corresponding 12 lead ECGs (left). Local electrical activation time was measured in ms 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 inter-ventricular vein; MCV, mid cardiac vein; ILV, inferolateral vein; ALV, anterolateral vein; CS, coronary sinus.

ECG parameters in patients with and without delayed LVLW activation

The ECG characteristics of patients with and without delayed LVLW activation are presented in Table 3. QRS duration did not differ between patients with and without delayed LVLW activation. Neither was there a difference in the prevalence of LAD, RAD, LAFB, LPFB or QRS fragmentation between patients with and without delayed LVLW 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 ± 19	157 ± 27	0.46
Left axis deviation	5 (46)	6 (55)	1.00
Right axis deviation	1 (9)	0	1.00
Left anterior fascicular block	4 (36)	6 (55)	0.67
Left posterior fascicular block	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 in means ± standard deviations or numbers (percentage values). LVLW, left ventricular lateral wall.

Discussion

Delayed activation of the LVLW is considered the electrical substrate underlying LV dysfunction amenable to CRT, and may be present in patients without LBBB QRS morphology.^{6, 16} The present study demonstrates that coronary venous EAM can be used at the time of CRT implantation to determine the presence of delayed LVLW activation and specify the latest activated region in CRT candidates with IVCD. Delayed LVLW 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 LVLW. Baseline 12-lead ECG QRS characteristics were not able to identify the presence of delayed LVLW activation as determined by coronary venous EAM.

Delayed LVLW activation in IVCD patients.

The present study demonstrates that coronary venous EAM can be used at the time of CRT implantation to identify IVCD patients with delayed LVLW 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 characterized LV epicardial electrical activation of 15 IVCD patients referred for CRT implantation using non-invasive 3D electrocardiographic imaging (ECGi) 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, 17, 18}

Latest activated region

In patients with delayed LVLW activation, the region of latest activation was similar to that observed in previous mapping studies of patients with LBBB.^{2, 3, 6, 19} 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 LVLW activation, the location of the latest activated region was more heterogeneous, which suggests that QRS widening in these patients may have a different underlying etiology 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 Eschalier et al. who characterized 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.²⁰

Diagnostic performance of ECG parameters for delayed LVLW 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 LVLW activation in patients with IVCD. This may be explained by the fact that QRS duration is merely a surface depiction of biventricular depolarization 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 LVLW activation in the present study. Especially the lack of delayed LVLW 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.^{21, 22} 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 LVLW activation.

Given the fact that the presence of myocardial scar and ischemic cardiomyopathy in a more broader sense have been shown to reduce the likelihood of a favorable response to CRT,²³⁻²⁵ we hypothesized that ECG markers of myocardial scarring/fibrosis have an inverse relationship with delayed LVLW activation. Various ECG parameters have been related to the presence or extent of myocardial scarring.²⁶ 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.^{15, 27} However, in the present study a significant relationship between QRS fragmentation and delayed LVLW 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.^{28, 29}

Limitations

The present study demonstrates the presence of delayed LVLW activation in approximately 50% of IVCD patients. Admittedly, the study lacks data on acute hemodynamic response and long-term clinical outcome. Whether delayed LVLW 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 EAM to determine the presence of delayed LVLW activation in CRT candidates with IVCD.

Conclusion

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

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Chapter

Vectorcardiographic QRS area identifies delayed left ventricular lateral wall activation determined by electroanatomic mapping in candidates for cardiac resynchronization therapy

Masih Mafi Rad, Gilbert W.M. Wijntjens, Eljen B. Engels, Yuri Blaauw, Justin G.L.M. Luermans, Laurent Pison, Harry J. Crijns, Frits W. Prinzen, Kevin Vernooy

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Abstract

Aim: Delayed left ventricular (LV) lateral wall (LVLW) activation is considered the electrical substrate underlying LV dysfunction amenable to cardiac resynchronization therapy (CRT). The purpose of this study was to assess LVLW activation in CRT candidates using coronary venous electroanatomic mapping (EAM) and to investigate whether the QRS area (QRS_{AREA}) on the vectorcardiogram (VCG) can identify delayed LVLW activation.

Methods: Fifty-one consecutive CRT candidates (29 left bundle-branch block [LBBB], 15 intra-ventricular conduction delay [IVCD], 7 right bundle-branch block [RBBB]) underwent intraprocedural coronary venous EAM using EnSite NavX. VCGs were constructed from preprocedural digital 12-lead ECGs using the Kors method. QRS_{AREA} was assessed and compared to QRS duration and 5 different LBBB definitions.

Results: Delayed LVLW activation (activation time >75% of QRS duration) occurred in 38 of 51 patients (29/29 LBBB, 8/15 IVCD, 1/7 RBBB). QRS_{AREA} was larger in patients with than in patients without delayed LVLW activation (108 ± 42 vs. 51 ± 27 μ Vs, $P < 0.001$), and identified delayed LVLW activation better than QRS duration (area under the curve 0.89 [95% confidence interval 0.79-0.99] vs. 0.49 [95% confidence interval 0.33-0.65]). $QRS_{AREA} > 69$ μ Vs diagnosed delayed LVLW activation with a higher sum of sensitivity (87%) and specificity (92%) than any of the LBBB definitions. Of the different LBBB definitions, the European Society of Cardiology textbook definition performed best with sensitivity of 76% and specificity of 100%.

Conclusions: Coronary venous EAM can be used during CRT implantation to determine the presence of delayed LVLW activation. QRS_{AREA} is a noninvasive alternative for intracardiac measurements of electrical activation, which identifies delayed LVLW activation better than QRS duration and LBBB morphology.

Introduction

Despite compelling evidence of the benefits of cardiac resynchronization therapy (CRT), the issue remains that a substantial proportion of apparently suitable patients fail to show a favorable response.¹ The supposed mechanism of CRT is that delayed activation of the left ventricular (LV) lateral wall (LVLW) causes mechanical dysfunction, which is remediable by paced pre-excitation of this delayed LV region.² Currently, the primary marker for delayed ventricular electrical activation is QRS duration. Yet, QRS duration is a reflection of total ventricular activation and therefore is not a reliable marker of LV activation. A left bundle-branch block (LBBB) morphology has been recognized as a potentially better indicator of delayed LVLW activation. However, current LBBB definitions differ between European and American recommendations^{3,4} and between clinical trials that investigated LBBB as a predictor of CRT effectiveness.^{5,6} This complicates a uniform diagnosis. In addition, patients with right bundle-branch block (RBBB) or nonspecific intraventricular conduction delay (IVCD) may have occult LVLW activation delay that still is amenable to resynchronization therapy.⁷

Recently, the QRS area (QRS_{AREA}) on the vectorcardiogram (VCG) was shown to predict CRT response better than QRS duration and conventionally defined LBBB morphology.⁸ Therefore, we hypothesized that the VCG, which contains 3-dimensional information of electrical forces within the heart, provides better indicators for delayed LVLW activation. In the present study, we investigated whether the VCG contains information about LVLW activation by comparing VCG measurements with data from coronary venous electroanatomic mapping (EAM). We recently introduced coronary venous EAM as a tool to assess LV electrical activation during CRT implantation.⁹

The objectives of the present study were (1) to assess LVLW electrical activation in a cohort of LBBB and non-LBBB CRT candidates using coronary venous EAM, (2) to investigate whether the VCG can identify delayed LVLW activation as determined by coronary venous EAM, and (3) to compare the diagnostic performance of the VCG for delayed LVLW activation with that of QRS duration and various frequently used LBBB definitions.

Methods

Study population

Fifty-one consecutive patients enrolled for CRT with a class I/IIa indication according to European Society of Cardiology (ESC) guidelines¹⁰ were included. The Institutional Review Board approved the study protocol.

Electroanatomic mapping

Coronary venous EAM was performed intraprocedurally as described previously.⁹ In brief, before LV lead placement, a guidewire (Vision Wire, Biotronik SE & Co.KG) that permits unipolar sensing and pacing, was inserted into the coronary sinus (CS) and connected to EnSite NavX (St. Jude Medical). The guidewire was manipulated to all CS branches located on the inferolateral or anterolateral LV wall, creating an anatomic map along with determining local electrical activation time (AT). RBBB patients underwent additional right ventricular (RV) endocardial mapping with a quadripolar diagnostic electrophysiology catheter (St. Jude Medical). Local AT was measured in ms from QRS onset and expressed as percentage of QRS duration. LVLW activation was considered delayed if maximal AT measured at the LVLW (maxLVLW-AT) exceeded 75% of QRS duration.⁹

Vectorcardiography

Vectorcardiograms were synthesized from preprocedural standard 12-lead ECGs as described previously.¹¹ In brief, 12-lead ECGs were recorded digitally, analyzed semi-automatically using custom made software (MATLAB R2010b, Math Works), and converted to VCGs using the Kors method.¹² A VCG consists of three orthogonal leads X, Y and Z, which together form a 3D vector loop (Figure 1). The maximum QRS and T vector were defined, and their direction in space was calculated. The 3D angle between the maximum QRS and T vector was described as QRS-T angle. The magnitude of the maximum QRS vector was expressed as QRS vector amplitude (QRS_{AMPL}). QRS_{AREA} was calculated as the integral between the ventricular deflection curve and the baseline from QRS beginning to end in leads X, Y, and Z.

Figure 1. Vectorcardiogram consisting of three orthogonal leads X, Y and Z (left), which together form a 3D vector loop (right). The green/red loop represents the QRS vector loop and the blue/purple loop the T vector loop. Blue arrow represents the maximal QRS vector, and black arrow the maximal T vector. QRS_{AREA} is calculated using the integral between the ventricular deflection curve and the baseline from QRS beginning to end in leads X, Y, and Z.

Assessment of QRS duration and morphology

QRS duration and morphology were assessed on preprocedural 12-lead ECGs. LBBB was defined according to five different definitions:

- ESC Textbook of Cardiovascular Medicine⁴ (LBBB_ESCT): QRS duration ≥ 120 ms, QS/rS in leads V1 and V2, broad notched R wave in leads I, aVL, V5, and V6, absent q-wave in leads I, aVL, V5, and V6.
- American Heart Association³ (LBBB_AHA): QRS duration ≥ 120 ms, R-peak time ≥ 60 ms in leads V5 and V6 but normal in leads V1, V2 and V3 when small initial r-waves can be discerned in these leads, broad notched/slurred R wave in leads I, aVL, V5 and V6, occasional RS pattern in V5 and V6, absent q wave in leads I, V5 and V6.
- MADIT-CRT trial⁶ (LBBB_MADIT): QRS duration ≥ 130 ms, QS/rS in lead V1, broad R wave in leads I, aVL, V5 or V6, absent q waves in leads V5 and V6.

- REVERSE trial⁵ (LBBB_REVERSE): QRS duration ≥ 120 ms, QS/rS in lead V1, broad R waves in lead I, aVL, V5, or V6, absent q-waves in lead V5 and V6.
- Strauss et al.¹³ (LBBB_Strauss): QRS duration ≥ 130 ms for women and ≥ 140 ms for men, QS/rS in leads V1 and V2, mid-QRS notching/slurring in ≥ 2 contiguous leads of I, aVL, V1, V2, V5 and V6.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation and categorical variables as number and percentage. Continuous variables were compared using Mann-Whitney U test and categorical variables using Fisher exact test. The performance of electrical parameters for identifying delayed LVLW activation was evaluated using receiver operating characteristic (ROC) curve analysis. Continuous variables were dichotomized for comparison with discrete variables by computing cutoff values with maximal sum of sensitivity and specificity. Subsequently, sensitivity, specificity, positive predictive value, and negative predictive value for delayed LVLW activation were calculated for all parameters. Statistical significance was accepted at the 95% confidence interval. Statistical analysis was performed using SPSS version 20.0 (SPSS Inc.).

Results

Patient characteristics

Fifty-one consecutive patients referred for CRT implantation for a class I/IIa indication according to ESC guidelines¹⁰ were included. Patient characteristics are given in Table 1.

Electroanatomic mapping

Coronary venous EAM was accomplished in all patients without complications. In 39 patients, a CS branch on both the anterolateral and inferolateral LV wall was mapped. In 12 patients, coronary venography revealed a single anterolateral or inferolateral vein, which could be successfully mapped. The 3D electrical activation maps were generated from 69 ± 28 unique anatomic points. Mapping time was 19 ± 6 minutes, total fluoroscopy time 21 ± 4 minutes, and total radiation dosage 4132 ± 2057 cGy $\times$ cm².

QRS duration and LVLW-AT data for the entire study cohort and per QRS morphology classified according to ESCT criteria are given in Table 2. Delayed LVLW activation occurred in 38 of 51 patients. In patients with delayed LVLW activation, maxLVLW-AT was 131 ± 15 ms ($84 \pm 6\%$ of QRS duration) and ranged from 103 to 169 ms (75-96% of QRS duration). QRS duration did not differ between different QRS morphologies. However, maxLVLW-AT was significantly larger in LBBB patients than in IVCD and RBBB patients. Delayed LVLW activation occurred in all 29 LBBB patients (EAM example in Figure 2A), 8 of 15 IVCD patients, and 1 of 7 RBBB patients. Figures 2B and 2C show EAMs of 2 IVCD patients, and Figures 2D and 2E show EAMs of 2 RBBB patients with and without delayed LVLW activation. As can be seen on the ECG in Figure 2E, the RBBB patient with delayed LVLW activation did not have a typical RBBB and showed a leftward axis deviation suggestive of left anterior hemiblock, which most probably was the cause of LV conduction delay in this patient. In contrast, all of the RBBB patients without delayed LVLW activation showed a classic RBBB QRS morphology without leftward axis deviation (example in Figure 2D). In the IVCD group, however, we found no difference in the prevalence of leftward axis deviation between patients with and without delayed LVLW activation (38% vs. 43%, respectively, $P = 1$). In RBBB patients, total RV activation time was larger than maxLVLW-AT (111 ± 21 ms [$69 \pm 10\%$ of QRS duration] vs. 85 ± 21 ms [$53 \pm 13\%$ of QRS duration], $P = 0.02$).

Table 1. Patient characteristics (n = 51)

Characteristics	Value
Age, years	72 ± 9
Male gender	33 (65)
Ischemic heart disease	31 (61)
NYHA functional class	
II	26 (51)
III	25 (49)
Echocardiography characteristics	
LV ejection fraction (%)	27 ± 4
LV end-diastolic diameter (mm)	61 ± 6
LV end-systolic diameter (mm)	52 ± 8
LV end-diastolic volume (mL)	157 ± 33
LV end-systolic volume (mL)	114 ± 26
ECG characteristics	
LBBB*	29 (57)
RBBB	7 (14)
IVCD	15 (29)
QRS duration (ms)	157 ± 13
Intrinsic rhythm	
Sinus rhythm	39 (76)
Atrial fibrillation	12 (24)
Treatment	
Diuretics	39 (76)
ACE-i/ARB	46 (90)
Beta-blockers	45 (88)
Spironolactone	26 (51)
Nitrates	13 (25)
Digoxin	7 (14)
Amiodarone	7 (14)

Values are mean ± standard deviations or no. (%).

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; LBBB, left bundle-branch block; LV, left ventricle; RBBB, right bundle-branch block; IVCD, intraventricular conduction delay;

*LBBB according to the ESC Textbook of Cardiovascular Medicine definition.⁴

Table 2. QRS duration and LVLW activation timing

Data	All patients (n = 51)	LBBB* (n = 29)	IVCD (n = 15)	RBBB (n = 7)
QRS duration (ms)	157 ± 13	158 ± 16	155 ± 7	159 ± 7
maxLVLW-AT (ms)	119 ± 28	133 ± 15†	107 ± 30‡	85 ± 21
maxLVLW-AT (% of QRS duration)	76 ± 16	86 ± 5†	72 ± 24‡	53 ± 13
maxLVLW-AT >75% of QRS duration	38 (75)	29 (100)	8 (53)	1 (14)

Values are mean ± standard deviations or no (%).

IVCD, intraventricular conduction delay; LBBB, left bundle-branch block; maxLVLW-AT, maximal left ventricular lateral wall activation time; RBBB, right bundle-branch block.

*LBBB according to the ESC Textbook of Cardiovascular Medicine definition.⁴

†P <0.01 versus IVCD and RBBB.

‡P <0.05 versus RBBB.

VCG parameters in patients with and those without delayed LVLW activation

The values of different VCG parameters in patients with and those without delayed LVLW activation are given in Table 3. The frontal and sagittal QRS vector angles and the QRS-T angle did not differ between patients with and those without delayed LVLW activation. However, the transverse QRS vector angle, QRS_{AMPL} and QRS_{AREA} were significantly larger in patients with than in patients without delayed LVLW activation. The difference between the 2 groups was most pronounced for QRS_{AMPL} and QRS_{AREA}.

Table 3. VCG values in patients with and without delayed LVLW activation

Parameter	Delayed LVLW activation (n = 38)	No delayed LVLW activation (n = 13)	P value
QRS vector angle, frontal (°)	3 ± 77	-31 ± 71	NS
QRS vector angle, transverse (°)	-64 ± 55	-17 ± 84	0.03
QRS vector angle, sagittal (°)	-5 ± 49	12 ± 90	NS
QRS-T angle (°)	160 ± 20	135 ± 46	NS
QRS _{AMPL} (mV)	1.6 ± 0.5	1.0 ± 0.4	<0.001
QRS _{AREA} (μVs)	108 ± 42	51 ± 27	<0.001

Values are given as mean ± standard deviations.

LVLW, left ventricular lateral wall; QRS_{AMPL}, QRS amplitude; QRS_{AREA}, QRS area; NS, non-significant.

Diagnostic performance of ECG and VCG parameters for delayed LVLW activation

Figure 3 displays ROC curves, showing the abilities of QRS duration, QRS_{AMPL} and QRS_{AREA} to identify delayed LVLW activation. QRS duration performed poorly with an area under the curve (AUC) of 0.49. Both QRS_{AREA} and QRS_{AMPL} identified delayed LVLW activation significantly better than QRS duration. QRS_{AREA} performed best with an AUC of 0.89. At a cutoff value of 69 μVs,

Figure 2. Coronary venous EAM of (A) an LBBB patient demonstrating delayed activation of the LV anterolateral wall, (B) an IVCD patient demonstrating absence of delayed LV lateral wall activation, (C) an IVCD patient demonstrating delayed activation of the LV inferolateral wall, (D) a RBBB patient demonstrating absence of delayed LV lateral wall activation and a longer activation time of the RV than the LV lateral wall, and (E) a RBBB patient with a potential left anterior hemiblock, demonstrating delayed activation of the LV anterolateral wall. 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; RA, right atrium; RV, right ventricle.

Figure 3. Receiver operating characteristic curves for QRS duration, QRS_{AMPL} and QRS_{AREA} . The area under the curve (AUC) signifies the performance of each parameter for identifying delayed left ventricular lateral wall activation and is given for each parameter with the 95% confidence interval (CI).

QRS_{AREA} identified delayed LVLW with the best combined sensitivity and specificity of 87% and 92%, respectively. The LV end-diastolic volume did not differ between patients with a QRS_{AREA} above and below the cutoff value of 69 μV_s (177 ± 40 vs 187 ± 45 ml, respectively, $P = 0.29$).

QRS_{AREA} diagnosed delayed LVLW activation with a higher sum of sensitivity and specificity than any of the LBBB definitions (Table 4). The LBBB_REVERSE and LBBB_MADIT definitions had the highest sensitivity of all LBBB definitions (82% and 79%, respectively), but relatively low specificity (54% for both). The LBBB_ESCT and LBBB_AHA definitions had the highest specificity (100% and 92%, respectively) but only moderate-to-low sensitivity (76% and 50%, respectively). Moderate sensitivity and specificity (68% and 77%, respectively) was found for the LBBB_Strauss definition. Figure 4A shows QRS_{AREA} plotted as a function of maxLVLW-AT for the entire study cohort, illustrating the excellent diagnostic performance of QRS_{AREA} for delayed LVLW activation. Using the cutoff value of 69 μV_s correctly identified 33 of 38 patients with and 12 of 13 patients without delayed LVLW activation. Figures 4B-F of figure 4 display the same plot but with LBBB diagnosed according to a different definition in each panel, illustrating the difference in QRS morphology classification caused by disparity in LBBB definitions.

Table 4. Diagnostic performance of QRS_{AREA} and different LBBB definitions for delayed LVLW activation

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
QRS _{AREA} >69 μ Vs	87	92	97	71
LBBB_ESCT	76	100	100	59
LBBB_AHA	50	92	95	39
LBBB_MADIT	79	54	83	47
LBBB_REVERSE	82	54	84	50
LBBB_Strauss	68	77	90	45

AHA, American Heart Association; ESCT, European Society of Cardiology Textbook; LBBB, left bundle-branch block; LVLW, left ventricular lateral wall; PPV, positive predictive value; NPV, negative predictive value.

Discussion

Delayed activation of the LVLW causing mechanical dyssynchrony is considered the mechanism underlying LV dysfunction that may be improved through CRT. In the present study, we assessed LVLW activation timing in CRT candidates using intraprocedural coronary venous EAM. Delayed LVLW activation was found in all LBBB patients, approximately half the IVCD patients, and 1 of 7 RBBB patients. The VCG parameter QRS_{AREA} identified delayed LVLW activation better than QRS duration or LBBB morphology according to 5 different definitions. Compared to LBBB morphology, QRS_{AREA} had the additional advantage of being objectively quantifiable as a continuous parameter.

Delayed LVLW activation in LBBB and non-LBBB patients

The finding that delayed LVLW activation occurred in all LBBB patients is in line with previous mapping studies¹⁴ and consistent with the results of a study by Varma who demonstrated late LV inferolateral wall activation (>100 ms) in 87% of LBBB patients with QRS duration of 120-150 ms and in 100% of LBBB patients with a QRS duration of >150 ms.⁷

In the present study, delayed LVLW activation occurred in approximately half the IVCD patients and in 1 of 7 RBBB patients. Data on LV electrical activation in non-LBBB patients are limited. Fantoni et al. performed extensive measurements of RV and LV endocardial electrical activation in 6 heart failure patients with RBBB and demonstrated the presence of LV activation delays equivalent to those found in LBBB in 4 of these patients.¹⁵ Notably, the QRS morphology in these 4 patients showed a specific ECG pattern, previously defined as RBBB masking LBBB¹⁶, which is characterized by broad, slurred, sometimes notched R waves in leads I and aVL, together with leftward axis deviation. In the present study, we observed a somewhat similar ECG pattern in the RBBB patient with delayed LVLW activation, whereas the other RBBB patients without delayed LVLW activation exhibited a more classic RBBB pattern. In the study by Varma, late LV inferolateral wall activation occurred in 45% of RBBB patients.⁷ However, characteristic differences in QRS morphology between RBBB patients with and those without late activation were not reported. Ploux et al. characterized LV epicardial electrical activation of 15 CRT candidates with IVCD using noninvasive 3D ECG imaging (ECGi) and found significant LV activation delay in 3 (20%) of these patients.¹⁷

Figure 4. (A) QRS_{AREA} plotted as function of maximal left ventricular lateral wall activation time (maxLVLW-AT) expressed as % of QRS duration (QRSd) for the entire study cohort. Each dot represents a patient. (B-F) Same plot as A, but with left bundle-branch block (LBBB) diagnosed according to the definition provided by the REVERSE⁵(B), MADIT-CRT trial⁶(C), ESC Textbook of Cardiovascular Medicine⁴(D), AHA³(E), and Strauss et al.¹³(F). IVCD, intraventricular conduction delay; RBBB, right bundle-branch block.

Several studies have suggested that CRT may be beneficial in a subset of non-LBBB patients with evidence of LV activation delay.¹⁷⁻¹⁹ The present study demonstrates that intra-cardiac measurements of electrical activation such as performed by coronary venous EAM or by electrical mapping with the LV lead, may be particularly useful to identify non-LBBB patients with an electrical substrate for CRT. The ECGi technique has been proposed as a noninvasive alternative to characterize the electrical substrate of patients before CRT implantation.¹⁷ ECGi provides a detailed 3D view of epicardial electrical activation. However, the technique requires a multi-electrode vest combined with a computed tomography scan, which precludes widespread application of this approach in clinical practice.

QRS_{AREA} identifies delayed LVLW activation

The present study demonstrates the potential of a relatively easy and noninvasive approach to identify patients with an electrical substrate for CRT using the QRS_{AREA} on the VCG. We demonstrated that a QRS_{AREA} >69 μ Vs accurately identifies delayed LVLW activation in CRT candidates. In the present study, all patients with a QRS_{AREA} >69 μ Vs had a maxLVLW-AT >100 ms and >70% of QRS duration. Positioning the LV lead over an area of the heart with an electrical activation time >95 ms or >50% of QRS duration has previously been shown to provide superior CRT outcome.^{20,21}

Van Deursen et al. recently demonstrated that a large QRS_{AREA} is associated with higher odds of long-term volumetric CRT response.⁸ It was hypothesized that strong unopposed electrical forces generated within the heart, are the underlying mechanism of a large QRS_{AREA}.

In a previous study, the average QRS_{AREA} in normal adult hearts was found to be 34 μV s,²² a value of approximately one-third of that associated with LBBB⁸ and half of that associated with delayed LVLW activation in the present study.

QRS_{AREA} has been shown to be smaller in patients with heart failure of ischemic etiology, which may be explained by the presence of non-conducting fibrotic tissue.⁸ In the present study, five patients had a $QRS_{AREA} < 69 \mu V$ s despite evidence of delayed LVLW activation during EAM. Four of these patients had a previous myocardial infarction which may partly explain the small QRS_{AREA} despite the presence of delayed LVLW activation. This observation suggests that QRS_{AREA} is not only useful to determine whether there is an electrical substrate for CRT but that it also may reflect the presence of determinants known to reduce the chance of CRT benefit, such as an ischemic etiology of heart failure.

In the present study, one patient had $QRS_{AREA} > 69 \mu V$ s without evidence of delayed LVLW activation during EAM. In this patient, coronary venography revealed only a single anterolateral vein, which could be successfully mapped. The constraints imposed by coronary venous anatomy during mapping may explain the absence of delayed LVLW activation in this particular case.

QRS_{AREA} compared to QRS duration and LBBB morphology

In the present study, QRS duration performed poorly in identifying delayed LVLW activation. This may be explained by the fact that QRS duration is merely a surface depiction of biventricular depolarization time, sensitive to conduction delay in either the left or right ventricle.

LBBB according to any of the definitions identified delayed LVLW activation better than QRS duration. However, the LBBB_MADIT and LBBB_REVERSE definitions had a relatively low specificity for delayed LVLW activation. As a result, a significant proportion of patients that lacked delayed LVLW activation were not identified as such. Recently, Strauss et al. suggested that QRS notching/slurring should be present for the diagnosis of LBBB.¹³ The lack of requirement for QRS notching/slurring in the LBBB_MADIT and LBBB_REVERSE definitions may have included patients in whom QRS widening was caused by LV hypertrophy, LV enlargement or incomplete LBBB.²³ The LBBB_ESCT and LBBB_AHA definitions included QRS notching/slurring and as a result had a high specificity for delayed LVLW activation. In addition, these definitions appeared to be more accurate for diagnosing delayed LVLW activation than the LBBB_Strauss definition, which may be explained by the requirement of QRS notching/slurring in at least 4 leads, whereas the LBBB_Strauss definition requires QRS notching/slurring in only 2 or more contiguous leads. However, the high specificity of the LBBB_ESCT and LBBB_AHA definitions came at the expense of their sensitivity. In particular, the LBBB_AHA definition, which is the strictest definition of all, had a relatively low sensitivity. As a result, a significant proportion of patients that had delayed LVLW activation were not identified as such. The LBBB_ESCT definition provided the best compromise between sensitivity and specificity of all LBBB definitions.

However, in the present study, we demonstrated that the diagnostic performance of even the best LBBB definition for delayed LVLW activation was inferior to having $QRS_{AREA} > 69 \mu V$ s. In addition, QRS_{AREA} had the advantage of being an objective continuous measurement, which is not subject to different definitions or subjective interpretations of QRS notching/slurring.

Clinical implications

The present study demonstrates that coronary venous EAM can be used during CRT implantation to identify patients with an electrical substrate for CRT.

Vectorcardiograms are usually recorded using a dedicated 3D VCG system, but they may also be synthesized from standard 12-lead ECGs as performed in the present study. In fact,

most commercially available ECG machines have algorithms to construct VCGs using the inverse Dower or Kors regression transformation.^{12,22} From this, the QRS_{AREA} can be automatically computed. The simple and noninvasive analysis provided by the VCG combined with the excellent diagnostic performance of QRS_{AREA} for delayed LVLW activation indicates that this technique can be easily applied in clinical practice to identify appropriate CRT candidates before CRT implantation.

The present study also emphasizes the importance of including the presence of QRS notching/slurring as described by the ESC textbook and AHA into the criteria for diagnosing LBBB. In this respect, the present study may be regarded as a validation study for LBBB definitions that are currently frequently used.

Study limitations

The present study demonstrates that QRS_{AREA} identifies delayed LVLW activation in CRT candidates. Admittedly, the study lacks long-term clinical follow-up. Whether delayed LVLW activation is also associated with CRT response needs to be confirmed in subsequent, larger and long-term follow-up studies.

Epicardial mapping through the coronary veins is limited by coronary venous anatomy, which means that some areas cannot be mapped because they do not contain any veins.

Data on local myocardial wall thickness and scar derived from cardiac magnetic resonance were not available in the present study. Therefore, we could not assess the contribution of transmural conduction delay to LVLW activation time. The effect of CRT may differ between patients in whom delayed LVLW activation is primarily caused by transmural conduction abnormalities (due to hypertrophy or scar) and those in which the main part of activation delay occurs in the conduction system of the heart.

We used an adapted version of the Kors method to calculate VCGs from standard 12-lead ECGs, which is an estimation of the gold standard Frank VCG. However, previous studies have demonstrated that the Kors method shows the best resemblance to the Frank VCG,²⁴ and the method recently has also been validated for use in CRT patients.²⁵

Conclusion

Coronary venous EAM can be used at the time of CRT implantation to determine the presence of delayed LVLW activation, an electrical substrate amenable to resynchronization therapy. This approach seems particularly useful for identifying non-LBBB patients with an electrical substrate for CRT. QRS_{AREA} derived from the VCG is a noninvasive alternative for intra-cardiac measurements of electrical activation, which identifies delayed LVLW activation better than QRS duration and LBBB morphology. This parameter can be easily applied in daily clinical practice to identify appropriate CRT candidates before CRT implantation. The ESC textbook LBBB definition appears superior to other frequently used LBBB definitions for identifying delayed LVLW activation.

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Chapter

Feasibility and acute hemodynamic effect of left ventricular septal pacing by transvenous approach through the interventricular septum

Masih Mafi Rad, Justin G.L.M. Luermans, Yuri Blaauw, Michel Janssen, Harry J. Crijns, Frits W. Prinzen, Kevin Vernooy

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Abstract

Aim: Left ventricular septal (LVS) pacing reduces ventricular dyssynchrony and improves cardiac function relative to right ventricular apex (RVA) pacing in animals. We aimed to establish permanent placement of an LVS pacing lead in patients using a transvenous approach through the interventricular septum.

Methods: Ten patients with sinus node dysfunction scheduled for dual-chamber pacemaker implantation were prospectively enrolled. A custom pacing lead with extended helix was introduced via the left subclavian vein and, after positioning against the right ventricular septum (RVS) using a preshaped guiding catheter, driven through the interventricular septum to the LVS. The acute hemodynamic effect of RVA, RVS and LVS pacing was evaluated by invasive LVdP/dtmax measurements.

Results: The lead was successfully delivered to the LVS in all patients. Procedure time and fluoroscopy time shortened with experience. QRS duration was shorter during LVS pacing (144 ± 20 ms) than during RVA (172 ± 33 ms, $P = 0.02$ vs. LVS) and RVS pacing (165 ± 17 ms, $P = 0.004$ vs. LVS). RVA and RVS pacing reduced LVdP/dtmax compared with baseline atrial pacing ($-7.1 \pm 4.1\%$ and $-6.9 \pm 4.3\%$, respectively), whereas LVS pacing maintained LVdP/dtmax at baseline level ($1.0 \pm 4.3\%$, $P = 0.001$ vs. RVA and RVS). R-wave amplitude and pacing threshold were 12.2 ± 6.7 mV and 0.5 ± 0.2 V at implant and remained stable during 6-months follow-up without lead-related complications.

Conclusion: Permanent placement of an LVS pacing lead by transvenous approach through the interventricular septum is feasible in patients. LVS pacing preserves acute left ventricular pump function. This new pacing method could serve as an alternative and hemodynamically preferable approach for antibradycardia pacing.

Introduction

Cardiac pacing is the only effective treatment for symptomatic bradycardia that is caused by sinus node dysfunction (SND) or atrioventricular (AV) block. The right ventricular apex (RVA) has become the preferred site for ventricular lead placement because it is easily accessible for implantation and yields chronically stable lead positions and stimulation thresholds. In general, RVA pacing is well tolerated and effective. However, there is increasing evidence that the dyssynchronous left ventricular (LV) electrical activation and contraction, induced by RVA pacing, has detrimental effects on LV structure and function, which is associated with increased risk of cardiac morbidity and mortality.¹⁻³ New pacemaker algorithms have minimized the percentage of undesirable ventricular pacing in patients with SND and patients with implantable cardioverter-defibrillators.⁴⁻⁶ However, in many patients, continuous ventricular pacing is unavoidable because of unreliable or absent AV conduction. In recognition of this, interest has also been focused on alternative ventricular pacing sites to preserve LV pump function. Alternative pacing sites within the right ventricle (RV) such as the RV septum (RVS) or RV outflow tract, have been intensively studied but show mixed results.⁷⁻⁹ Studies in animals have shown that pacing at the LV septum (LVS) yields LV pump function closely approximating that during normal ventricular conduction and significantly better than that during RVS pacing.^{10, 11} In the animal experiments, the LVS lead was permanently placed by introducing a custom pacing lead with extended helix transvenously into the RV and driving it from the RV side through the interventricular septum (IVS) to the LVS.¹¹ This was shown to be a feasible and safe procedure, and leads remained mechanically and electrically stable during 4 months follow-up in the otherwise healthy and active canines. The objectives of this study were (1) to perform a first-in-man study, investigating the feasibility of permanently implanting an LVS lead in patients using a transvenous approach through the interventricular septum; and (2) to compare the acute hemodynamic effect of LVS pacing with that of RVS pacing and conventional RVA pacing.

Methods

Study population

We prospectively enrolled patients with a pacemaker indication for symptomatic SND, who were thus not ventricular pacing dependent and, therefore, considered at relatively low risk of adverse events in case of lead failure. Exclusion criteria were second- or third-degree AV block, history of septal myocardial infarction, IVS wall thickness >10 mm on echocardiography, permanent atrial fibrillation, or severe aortic valve stenosis. The study protocol was approved by the Institutional Review Board, and all patients gave written informed consent to participate in the study.

Ventricular pacing lead

A custom 4.15-Fr bipolar, fixed-screw, steroid-eluting ventricular pacing lead (Model 09066; Medtronic Inc., Minneapolis, MN) was used, which was exclusively delivered for this study. The lead Model 09066 is a modification of the market-released Select Secure model 3830 (Medtronic Inc.) with an extended helix (Figure 1A). Instead of the short 1.8-mm helix of the Model 3830, the Model 09066 has been fitted with a longer 4-mm helix to provide better lead fixation and a higher pull-through force for deeper penetration into the IVS. The helix is partially coated with a thin nonconductive polyurethane layer to have an electrically active portion of only the distal 1.27 mm, which serves as electrode. The helix-ring distance is 5 mm. However, the electrical tip-ring spacing is ≈ 8 mm due to the nonconductive coating on the proximal

Figure 1. (A) Lead design of the lead Model 09066. The lead is a modification of the market-released Select Secure Model 3830 with an extended helix. The lead has been fitted with a 4-mm helix instead of the standard 1.8-mm helix of the Model 3830. The helix is partially insulated to have an electrically active portion of only the distal 1.27 mm. (B) Schematic representation of lead positioning. The lead Model 09066 is introduced transvenously into the right ventricle (RV), and after positioning against the RV septum, driven through the interventricular septum (IVS) with the screw-in tip until the left ventricular (LV) septum is reached, without perforating the IVS. The ring stimulates the RV side and the tip, the LV side of the IVS. RA, right atrium; LA, left atrium.

part of the helix. The lead is introduced transvenously into the RV, and after positioning against the RV septum, driven through the IVS with the screw-in tip until the LV is reached, without perforating the IVS (Figure 1B).

Implantation procedure

Figure 2 illustrates the different steps performed during the implantation procedure. Two venous accesses were obtained by left cephalic vein cutdown or left subclavian vein puncture. A standard atrial bipolar active fixation pacing lead was positioned in the right atrial appendage according to routine clinical practice (Figure 2A). A Certus Pressure Wire (St Jude Medical Systems

Legend of Figure 2. Images of the implantation procedure. The atrial lead is positioned in the right atrial (RA) appendage and a Certus Pressure Wire is positioned in the left ventricle (LV) for acute hemodynamic measurements (A). A right ventricular (RV) angiogram is performed in right anterior oblique (RAO; A) and left anterior oblique (LAO; B). The custom left ventricular septal (LVS) pacing lead is positioned perpendicularly against the interventricular septum (IVS) using a preshaped guiding catheter (C). The tip of the lead is positioned as close to the middle of the IVS as possible by using fluoroscopy in both RAO (C) and LAO (D) with reference to the corresponding RV angiogram (A and B). Intracardiac echocardiography ultrasound catheter (ICE) is used to verify the position of the lead tip on the IVS achieved using fluoroscopy before screwing the lead into the IVS (E). The intracardiac echocardiogram shows the RV in a long axis view that parallels the septum with the lead tip located at mid-level between the apex and base and the anterior and posterior border of the RV. (F), A schematic representation of the intra-cardiac echocardiogram. After proper positioning of the LVS lead on the IVS, the lead is screwed through to the left side of the IVS. (G), The tip of the lead resting perpendicularly against the IVS (indicated by the dashed yellow line) before screwing the lead in. While rotating the lead, repeated hand injections of contrast medium through the guiding catheter against the IVS are used to assess the penetration depth (H and I). The part of the lead tip that protrudes into the IVS is not covered by contrast medium. Based on beforehand knowledge of the lead tip dimensions and the patient's IVS wall thickness, this provides an estimation of penetration depth in the IVS. TV, tricuspid valve; AO, aorta; PA, pulmonary artery.

Figure 2. Legend on previous page.

AB, Uppsala, Sweden) was positioned in the LV for acute hemodynamic measurements (see below). The Certus wire was introduced via a left femoral arterial puncture and positioned in the LV by the retrograde aortic approach using a 4-Fr multipurpose catheter. Subsequently, the multipurpose catheter was withdrawn into the aorta leaving the soft tip of the pressure wire in a stable position in the LV cavity (Figure 2A). An RV angiogram was made in right anterior oblique (RAO; Figure 2A) and left anterior oblique (LAO; figure 2B) view to visualize the IVS borders using a 6-Fr pigtail catheter introduced into the RV via the second venous access. The pigtail catheter was replaced with a quadripolar diagnostic electrophysiology catheter that was positioned in the RVA for temporary pacing. Next, the acute hemodynamic effect of RVA pacing was evaluated. Subsequently, the electrophysiology catheter was removed, and the custom ventricular pacing lead was introduced into the RV using a 7-Fr preshaped guiding catheter (Model C315-S10; Medtronic Inc.; Figure 2C). The specific shape of the C315-S10 catheter allows straightforward positioning of the catheter tip perpendicularly against the IVS. During lead placement, the implanter repeatedly alternated between RAO (Figure 2C) and LAO (Figure 2D) view to position the tip of the lead as close to the middle of the IVS as possible while using the RV angiogram in RAO (Figure 2A) and LAO (Figure 2B) as a reference. Hereby, the RAO view was used to direct the lead to halfway between apex and base, whereas the LAO view was used to position the lead halfway between the anterior and posterior septal borders. An 8-Fr ACUSON AcuNav diagnostic ultrasound catheter (Siemens Medical Solutions USA, Inc.) was introduced via a right femoral venous puncture and advanced to the right atrium for intra-cardiac echocardiography (ICE). ICE was used to verify the position of the lead tip on the IVS achieved using fluoroscopy before screwing the lead into the IVS (Figure 2E and 2F). Subsequently, the pacing electrode was screwed through the IVS until the LVS was reached, without perforating the IVS. While rotating the lead, the implanter repeatedly assessed the penetration depth in the IVS by injecting small amounts of contrast medium through the guiding catheter against the IVS under fluoroscopy in LAO (figure 2G and 2I). Because the contrast medium is restrained by the IVS, the part of the lead tip that protrudes into the IVS is not covered by contrast medium. In combination with beforehand knowledge of the lead tip dimensions and the patient's IVS wall thickness (preprocedurally assessed by echocardiography), this provided an estimation of penetration depth in the IVS. In addition, pacing was repeatedly performed from the tip electrode while advancing the helix through the IVS to assess changes in paced QRS morphology that indicated that the left side of the IVS had been reached. Pacing thresholds and impedances were measured to ensure that the helix did not protrude in the LV cavity. Subsequently, acute hemodynamic measurements were performed as described below. All patients received a dual-chamber pacemaker. The pacemaker was programmed to AAI with DDD (AV-sequential pacing) backup.

Acute hemodynamic measurements

The acute hemodynamic effect of RVA pacing (with the temporary electrophysiology catheter), RVS pacing (unipolar pacing from the ring of the custom lead) and LVS pacing (unipolar pacing from the tip of the custom lead) was evaluated by invasive measurement of LVdP/dtmax using the Certus Pressure Wire and PhysioMon software (St Jude Medical Systems AB). All pacing was performed at 10 beats per minute above intrinsic sinus rate. For each ventricular site, LVdP/dtmax was measured during AV sequential pacing (DDD mode) with a paced AV delay 60 ms shorter than intrinsic activation to ensure full ventricular capture. Baseline LVdP/dtmax measurements were performed during atrial pacing (AAI mode) before and after each DDD measurement. A waiting period of at least 30 seconds was respected after each measurement

to allow for hemodynamic stabilization. During each measurement, LVdP/dtmax was measured and averaged over an interval of 20 seconds. The acute hemodynamic effect of pacing at each ventricular site was calculated as the relative change in LVdP/dtmax compared with the average of the two adjacent baseline AAI measurements.

Follow-up

R-wave amplitude, pacing thresholds, and impedances were recorded immediately after implantation; the day after implantation; as well as 10 days, 1 month, 3 months, and 6 months after the implantation.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD). Categorical variables are expressed as observed number and percentage values. Means of continuous variables were compared among pacing conditions using repeated measures ANOVA with Bonferroni multiple comparisons procedure applied to pairwise comparisons. A P value <0.05 was used to denote statistically significant differences. Statistical analysis was performed using SPSS version 20.0 (SPSS Inc.) software.

Results

Patients

Ten patients (mean age, 72 ± 10 years; 5 men) were included in the study. The baseline characteristics of the patients are shown in Table 1. All patients were in sinus rhythm, had a normal QRS duration on standard 12-lead ECG, and had a normal LV ejection fraction at echocardiographic evaluation. Mean IVS thickness assessed by echocardiography was 9 ± 1 mm.

Table 1. Patient characteristics

No.	Age	Gender	Pacing indication	Intrinsic rhythm	QRS duration (ms)	LVEF (%)	LVEDD (mm)	IVS thickness (mm)
1	73	M	SND	SR	90	62	55	8
2	80	F	SND	SR	92	65	48	9
3	85	F	SND	SR	84	66	42	9
4	62	M	SND	SR	90	54	53	10
5	62	M	SND	SR	92	50	64	10
6	53	M	SND	SR	98	61	63	10
7	77	F	SND	SR	80	60	47	8
8	74	F	SND	SR	88	52	45	9
9	81	M	SND	SR	94	54	50	10
10	70	F	SND	SR	96	65	48	7
Mean ± SD	72 ± 10				90 ± 5	59 ± 6	52 ± 7	9 ± 1

M, male; F, female; SND, sinus node dysfunction; SR, sinus rhythm; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; IVS, interventricular septum.

Implantation

All patients underwent a successful implantation of an LVS lead through the IVS in a single procedure. In 8 of 10 patients, a lead position at the midlevel of the LVS (halfway between the apex and base) was achieved (Table 2). In patients 2 and 7, the lead was positioned in a more apical and basal region of the LVS, respectively. The mean time required to implant the LVS lead was 29 ± 24 minutes (limits 9-90 minutes) and the mean fluoroscopy time during the entire procedure was 20 ± 9 minutes (limits 10-44 minutes) with a clear trend of shortening times with increasing experience (Table 2). During implantation of the last two patients, the implanter felt safe enough with the procedure to accomplish implantation of the LVS lead without guidance by ICE.

Lead stability and complications

There were no clinically significant changes in pacing threshold, R-wave amplitude, or impedance of the LVS lead between implantation and the day after implantation, as well as at 10-days, 1-month, 3-month, and 6-month follow-up. Mean pacing threshold, R-wave amplitude, and impedance at implant were 0.5 ± 0.2 V, 12.2 ± 6.7 mV, and 715 ± 83 ohms, respectively. At 6-month follow-up, mean pacing threshold, R-wave amplitude and impedance were 0.9 ± 0.3 V, 16.0 ± 8.7 mV, and 550 ± 55 ohms, respectively.

No periprocedural complications related to the LVS lead were observed. None of the patients developed ventricular conduction disturbances during the procedure. During 6-month follow-up, none of the patients showed signs of dislodgement of the LVS lead, loss of capture, prolongation of the paced or intrinsic QRS duration, or infections associated with the implantation procedure.

ECG characteristics

Figure 3 shows the ECG from patient 2 (Table 1) during intrinsic activation, RVA, RVS, and LVS pacing. During RVA and RVS pacing, a left bundle-branch block-like QRS morphology was observed, and QRS duration was considerably prolonged relative to intrinsic activation. During LVS pacing, a right bundle-branch block-like QRS morphology was observed in the precordial leads and QRS duration was considerably less prolonged than during RVS and RVA pacing. For the entire study cohort, QRS duration during intrinsic activation was 90 ± 5 ms. During RVA and RVS pacing, QRS duration was almost twice as long as during intrinsic activation (RVA pacing, 172 ± 33 ms [$P = 0.004$ vs. intrinsic activation]; RVS pacing, 165 ± 17 ms, [$P < 0.001$ vs. intrinsic activation]). QRS duration during LVS pacing was 144 ± 20 ms, which was prolonged compared with intrinsic activation ($P = 0.002$), yet significantly shorter than during RVA pacing ($P = 0.02$) and RVS pacing ($P = 0.004$).

Acute hemodynamic measurements

The LVdP/dtmax measurements were successfully obtained in all patients without complications. Figure 4 shows the acute change in LV dP/dtmax during RVA, RVS and LVS pacing relative to baseline atrial pacing for the entire study cohort, as well as the individual hemodynamic responses to pacing at the different ventricular sites. RVA and RVS pacing reduced LVdP/dtmax as compared with baseline atrial pacing by $7.1 \pm 4.1\%$ and $6.9 \pm 3.4\%$, respectively, whereas LVS pacing maintained LVdP/dtmax at baseline level ($1.0 \pm 4.3\%$; $P = 0.001$ vs. RVA and RVS). This acute hemodynamic benefit of LVS pacing over RVA and RVS pacing was observed in all patients (Figure 4).

Table 2. Implantation procedure details

No.	Successful LVS lead implantation	No. of implantation procedures	Lead tip location in LVS	LVS lead implantation time (min)	Total procedure time (min)	Total fluoroscopy time (min)	Total radiation dosage (mGy)	Total dosage area product (cGy x cm ²)
1	Yes	1	mid	90	237	44	1700	14911
2	Yes	1	apical	33	204	21	400	6435
3	Yes	1	mid	47	135	14	300	3953
4	Yes	1	mid	30	158	25	447	3692
5	Yes	1	mid	23	103	19	147	1435
6	Yes	1	mid	19	103	14	333	4102
7	Yes	1	basal	18	125	17	56	975
8	Yes	1	mid	9	115	16	117	1888
9	Yes	1	mid	11	93	22	287	3482
10	Yes	1	mid	12	83	10	26	418
Mean $\pm$ SD				29 $\pm$ 24	136 $\pm$ 50	20 $\pm$ 9	381 $\pm$ 485	4129 $\pm$ 4193

LVS, left ventricular septum.

Discussion

The present study demonstrates that permanent implantation of a pacing lead with extended helix in the LVS using a transvenous approach through the IVS is feasible and safe, at least in this small group of patients. Compared with RVA and RVS pacing, LVS pacing reduces electrical dyssynchrony and preserves acute LV pump function. Electrical and mechanical lead properties remain stable during 6-month of follow-up.

Feasibility of LVS pacing

The feasibility of LVS pacing using a transvenous approach through the IVS has previously only been demonstrated in animal experimental studies. Grosfeld et al. were the first to demonstrate implantation of a custom pacing lead with a long insulated screw in the LVS through the IVS in six goats.¹² In a later study, Mills et al. achieved permanent and stable LVS pacing over a period of 16 weeks in eight adult mongrel dogs using a custom pacing lead with extended helix, similar to the one used in the present study.¹¹

The present study translates the results of these preclinical studies into clinical practice by demonstrating that this form of LVS pacing is also feasible in patients. Implantation of an LVS lead was successfully accomplished in all patients in a single procedure. There were no short- or long-term lead-related complications. Pacing thresholds and sensing characteristics were within an adequate range and in keeping with that during RVA pacing, and the leads remained electrically and mechanically stable during 6-month follow-up. Because it is a novel implantation technique, procedure time and total fluoroscopy time were relatively long during the first implantations. However, both procedure time and fluoroscopy time steeply

Figure 3. Twelve-lead ECG from patient 2 (Table 1) during intrinsic activation, right ventricular apex (RVA), right ventricular septal (RVS) and left ventricular septal (LVS) pacing. During RVA and RVS pacing a left bundle-branch block-like QRS morphology was observed. During LVS pacing, a right bundle-branch block-like QRS morphology was observed in the precordial leads. RVA and RVS pacing considerably prolonged QRS duration relative to intrinsic activation. QRS duration during LVS pacing was prolonged compared with intrinsic activation, yet considerably shorter than during RVA and RVS pacing.

declined with increasing experience. The study protocol initially involved ICE as an additional visualization tool to increase the safety of the procedure. However, the experience gained throughout the study allowed omission of ICE during the last two procedures without compromising safety, thereby increasing feasibility of the implantation procedure in clinical practice. Furthermore, implantation of the LVS lead could be accomplished using a commercially available preshaped guiding catheter, making the procedure applicable in any implanting center with access to the relevant instruments.

LVS pacing versus RVA and RVS pacing

The finding that RVA pacing induces electrical dyssynchrony and impairs acute hemodynamic function is well known from literature.^{1, 13} Subanalyses of different clinical trials have shown that a higher RVA pacing burden is associated with heart failure worsening, atrial fibrillation and death.^{2, 14, 15}

In the present study, RVS pacing did not show a better ventricular electrical activation pattern or an acute hemodynamic benefit compared with RVA pacing. The RVS has been suggested as an alternative pacing site, but comparative studies have found conflicting results. Small acute hemodynamic studies generally show a tendency toward an advantage of RVS over RVA pacing.⁷ However, three randomized trials comparing RVS with RVA pacing in

Figure 4. Acute change in left ventricular (LV)dP/dtmax (mean $\pm$ SD) during pacing at different ventricular sites relative to baseline atrial pacing. Dashed lines represent individual hemodynamic responses to pacing at different ventricular sites. RVA, right ventricular apex; RVS, right ventricular septum; LVS, left ventricular septum. * $P = 0.001$ vs. RVA and RVS.

patients with congestive heart failure and chronic atrial fibrillation and patients with total AV block showed no differences in LV ejection fraction, quality of life, exercise capacity, and brain natriuretic peptide levels at long-term follow-up.^{8, 16, 17}

Previous acute hemodynamic studies in dogs with normal ventricular conduction have demonstrated that pacing at the LVS maintains LV systolic and diastolic function at sinus rhythm level, whereas LV function is depressed during RVA and RVS pacing.^{10, 11} The data from the present study extrapolate these preclinical findings on the beneficial hemodynamic effect of LVS pacing to the human population. In the animal studies, electrical activation mapping and MRI tagging showed that the superior hemodynamic effect of LVS pacing is related to the more physiological sequence of LV electrical activation and contraction, resulting in less LV electric and mechanical dyssynchrony.¹¹ In the present study, reduction in electric dyssynchrony was reflected by the shorter QRS duration during LVS pacing compared with RVA and RVS pacing. During normal ventricular conduction, electric activation of the working myocardium starts at the LV septal endocardium, which may explain why pacing at or near this site maintains a closer to normal electric activation as well as mechanical synchrony and coordination. Activation of the RV wall has been shown to remain moderately delayed during LVS pacing,¹¹ which may explain why in the present study QRS duration during LVS pacing, although shorter compared with RVA and RVS pacing, was still prolonged compared with intrinsic ventricular activation. A remarkable finding of the present study is the large difference in QRS duration and hemodynamic effect between pacing at the RV and LV side of the IVS despite the fact that these sites were not more >1 cm apart. These observations are consistent

with earlier observations in animals and patients^{11, 18} and have been related to a significant delay in transeptal conduction during RVS pacing which causes considerably later LV mechanical activation and peak contraction of the LV lateral wall, thereby inducing both inter- and intraventricular asynchrony.

Another pacing site that is capable of preserving native ventricular activation is the His bundle. Similar to our observations in LVS pacing, His bundle pacing in patients has been shown to result in less inter- and intraventricular dyssynchrony¹⁹ and better hemodynamic performance than RVA pacing.²⁰⁻²² Permanent His bundle pacing has been achieved in patients with SND,²³ in patients with atrial fibrillation post-AV nodal ablation,¹⁹ and in patients with AV block.²⁴ Although the various studies have demonstrated beneficial effects of this alternative pacing site, at present, His bundle pacing is not recommended in patients requiring permanent cardiac pacing because of technical challenges during lead positioning and concerns about lead stability and threshold.²⁵

Currently, the most common way to reverse or prevent pacing-induced dyssynchrony is the application of biventricular pacing. An upgrade of RVA pacing to biventricular pacing in patients with permanent AV block, severe symptoms of heart failure, and depressed LV ejection fraction is likely to improve their symptoms and cardiac function and reduce hospitalization.²⁶⁻²⁹ In addition, several small randomized trials have suggested that patients with a conventional indication for antibradycardia pacing with moderate to severe LV dysfunction might benefit from de novo biventricular pacing compared with RV pacing in terms of LV function and remodeling, hospitalization, heart failure symptoms, and quality of life.³⁰⁻³² However, biventricular pacing also has drawbacks, such as the more complex and time-consuming implantation procedure,³³ the higher rate of complications, failed implantations, and loss of pacing associated with a coronary sinus lead with the consequent need for reoperation,³³⁻³⁶ the shorter battery life of biventricular devices and the additional costs.

The excellent feasibility of permanently implanting an LVS pacing lead through the IVS in combination with the acute hemodynamic benefit of LVS pacing as demonstrated in the present study suggests that this pacing technique could serve as an alternative for a biventricular upgrade or primary implantation of a biventricular system in patients with a conventional indication for antibradycardia pacing.

Limitations

As with any implanted lead, possible future complications, such as lead fracture or lead infection, may necessitate lead extraction. Extraction of a deep septal lead could potentially pose the risk of creating a ventricular septal defect, and temporary protrusion of the extraction sheath in the LV cavity could potentially create risk of systemic embolization. The present study lacks data on the magnitude of these potential risks of a possible LVS lead extraction.

During implantation, protrusion of the LV septal lead into the LV cavity was avoided by repeated injection of small amounts of contrast medium through the guiding catheter and by repeated assessment of pacing thresholds (see Methods). In the present study, no protrusion into the LV cavity was observed, guaranteeing integrity of the LV endocardial surface. In case of protrusion, the lead should be withdrawn a few millimeters to its final position. This would leave a small wound at the LV endocardium, which is likely to be healed soon, but the exact amount and nature of the final damage are not known.

The sample size of this study was small, though can be considered sufficient to make an initial statement about the feasibility of permanently implanting a pacing lead in the LVS

through the IVS. Although the procedure was also safe in this small group, a larger study is required to ultimately show safety of large-scale use of the LVS lead.

Because this is a novel pacing technique with unknown success rate and complications, the study was conducted in patients with SND, a group that is generally not ventricular pacing dependent and, therefore, considered at relatively low risk of adverse events in case of lead failure.

The different shape of the ring and tip electrode of the pacing lead may have flawed the comparison between RVS and LVS pacing. Yet, we chose to test these sites in this way to minimize the time interval between the hemodynamic measurements during RVS and LVS pacing, and thus the variability between these measurements.

The findings of this study clearly require further clinical validation in larger and prospective studies. These studies should also indicate whether the acute hemodynamic benefit of LVS pacing, as demonstrated in the present study, translates into preservation of LV pump function on the longer term.

Conclusion

This study demonstrates that permanent placement of a pacing lead in the LVS using a transvenous approach through the IVS is feasible and safe, at least in this small group of patients. Compared with RVA and RVS pacing, LVS pacing reduces electric dyssynchrony and preserves acute LV pump function. The LVS lead remains electrically and mechanically stable during 6-month follow-up. The clinical benefit of this pacing method needs prospective evaluation. The results of this study suggest that LVS pacing could serve as a better alternative for RVA pacing in patients with a conventional indication for antibradycardia pacing, while lacking some of the disadvantages of biventricular pacing.

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Evaluation of left ventricular endocardial cardiac resynchronization therapy in a non-responder with ventricular arrhythmias

Chapter

Masih Mafi Rad, Yuri Blaauw, Luuk Debie, Hans-Peter Brunner-
La Rocca, Kevin Vernooy

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Abstract

Approximately one-third of patients treated with cardiac resynchronization therapy do not derive any detectable benefit. In these patients, acute invasive hemodynamic evaluation can be used for therapy optimization. This report describes the use of systematic invasive hemodynamic measurements for clinical decision making in a patient who experienced severe ventricular arrhythmias and clinical deterioration following a biventricular upgrade.

Introduction

Cardiac resynchronization therapy (CRT) has been established as an effective treatment for heart failure patients with severe left ventricular (LV) systolic impairment and electrical dyssynchrony.¹ Unfortunately, a significant proportion of apparently suitable patients fail to benefit.² In this subset of patients, acute invasive hemodynamic evaluation can be used to optimize CRT with alternative LV pacing sites or atrio-ventricular (AV) and inter-ventricular pacing delays.^{3,4} We describe a patient who experienced severe ventricular arrhythmias and clinical deterioration following upgrade to a biventricular (BiV) system. CRT was discontinued, based on the outcome of invasive hemodynamic measurements.

Case report

A 65-year-old male patient with non-ischemic dilated cardiomyopathy, left ventricular ejection fraction of 20%, intraventricular conduction delay with a QRS duration of 148 ms, and New York Heart Association class 3 was scheduled for upgrade of an implantable cardioverter defibrillator (ICD) to a cardiac resynchronization therapy - defibrillation (CRT-D) system. The ICD had previously been implanted for primary prevention. Echocardiography prior to the BiV upgrade demonstrated myocardial scarring of the LV lateral wall and showed no evidence of mechanical dyssynchrony. Unfavorable coronary venous anatomy required epicardial LV lead placement in the lateral position via minimal lateral thoracotomy. Four weeks later, the patient was admitted with multiple ICD discharges due to incessant ventricular tachycardia (VT) (Figure 1).

Figure 1. Incessant VT, 4 weeks after onset of BiV pacing.

He was sedated and Amiodarone was initiated, whereupon VT recurrences were no longer observed. In the following months his clinical condition deteriorated despite continuation of BiV pacing.

An invasive hemodynamic pacing study was performed to evaluate the hemodynamic effect of conventional BiV pacing and to explore whether LV endocardial pacing could effectuate hemodynamic improvement. For this purpose, a temporary pacing electrode and a RADI pressure wire were positioned within the LV cavity, another temporary pacing electrode was placed in the right atrium (Figure 2). The RADI wire allowed determination of maximal rate of LV pressure rise (LVdP/dtmax) as a measure of LV function.³ The pacing protocol consisted of a baseline without ventricular pacing (atrial pacing) alternated with AV-sequential BiV, LV and right ventricular (RV) pacing using the implanted system and LV endocardial pacing using the temporary LV pacing electrode. To exclude hemodynamic variability induced by spontaneous changes in heart rate, pacing was performed at 10 beats per minute above intrinsic heart rate. Average LVdP/dtmax was measured during 10 seconds of pacing for each pacing configuration.

Neither LV, RV or BiV pacing with the implanted system nor LV endocardial pacing at different sites improved LVdP/dtmax as compared to baseline (Figure 3). Furthermore, the number of premature ventricular complexes (PVCs) increased upon LV stimulation. This was confirmed by 24 hour Holter monitoring, which demonstrated 40,000 PVCs during BiV pacing vs. 4,000 PVCs when ventricular pacing was programmed off (Figure 4). Considering the unfavourable hemodynamic and pro-arrhythmic effects of LV pacing, placement of a permanent endocardial LV lead was not performed and the ICD was programmed to ventricular pacing off (AAI-DDD mode). Our patient was scheduled for left ventricular assist device placement.

Discussion

Patient selection plays an important role in CRT response. According to the ESC heart failure guidelines available at the time of device implantation, our patient had a class I indication for CRT.⁵ However, based on the most recent guidelines, he may not have been an “ideal” candidate due to the absence of a typical left bundle-branch block.¹ This is supported by the outcome of the acute hemodynamic measurements. Although a definite relationship between acute LVdP/dtmax increase and long-term clinical response needs to be confirmed, our findings suggest that acute invasive hemodynamic testing could help to guide the decision on whether or not to implant a CRT device in cases where there is less consensus for a clinical benefit.

The presence of myocardial scar at the area targeted by the LV lead is an important determinant of CRT response.⁶ Lead position optimization in the coronary sinus is usually limited by side branch anatomy. A surgical

Figure 2. X-ray detail of the invasive hemodynamic pacing study setup. The right atrial (RA), right ventricular (RV) and LV epicardial (LV-Epi) lead of the implanted system are shown, together with the temporary right atrial (RA-Temp) and LV endocardial electrode (LV-Endo). The RADI pressure wire is located in the LV cavity.

Figure 3. Percentage change in LVdP/dtmax compared to baseline (AAI pacing) during AV-sequential BiV, LV and RV only pacing using the implanted system and LV endocardial pacing at different sites using the temporary LV endocardial electrode. Epi, epicardial; Endo, endocardial.

Figure 4. 24 hour Holter recordings demonstrating 40,000 PVCs during BiV pacing vs. 4,000 PVCs during ventricular pacing programmed off (AAI mode).

epicardial LV lead implantation may then be preferred. Our patient had extensive scarring of the LV lateral wall which limited the possibility of placing an epicardial LV lead outside the scar region. Recently, LV endocardial pacing has been suggested as a potentially better alternative to the epicardial approach.⁷ This method allows more liberty in lead positioning, which can help to avoid pacing in infarcted areas. However, the risk of thrombo-embolic complications is unknown and requires further investigation. Although the potential of acute LVdP/dtmax measurements to predict long-term outcome needs to be confirmed, our findings suggest that acute hemodynamic testing of LV endocardial pacing in a temporary setup may help to identify the optimal pacing site and may also prevent implantation of a potentially profitless endocardial LV lead with a yet unknown risk of hazardous complications.

In a small percentage of patients, CRT may potentiate ventricular tachyarrhythmias.⁸ The exact mechanisms of proarrhythmia remain largely unclear but our findings suggest that pacing in the region of myocardial scar may facilitate its development. This conception is supported by the morphology of the VT which suggested a lateral exit site close to the LV epicardial pacing lead. A suggested underlying mechanism is a potential increase in local myocardial oxygen demand by pacing, precipitating ischemia in the peri-infarct zone and making it vulnerable to re-entry.^{8,9} The currently available evidence is however too limited to develop strategies for stratifying patients at risk for proarrhythmia in the setting of CRT.

Conclusion

This case report illustrates the potential contribution of acute invasive hemodynamic evaluation to clinical decision making in CRT. Acute hemodynamic testing may also be considered as a step-up approach to justify implantation of an LV endocardial lead and to guide lead positioning optimization. Finally, this case underlines the importance of considering the possibility of CRT related proarrhythmia, whenever CRT treated patients develop new ventricular tachyarrhythmias.

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Chapter

The role of acute invasive hemodynamic measurements in cardiac resynchronization therapy: looping towards prediction of long-term response and therapy optimization

Masih Mafi Rad, Yuri Blaauw, Frits W. Prinzen, Kevin Vernooy

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Editorial on 'Prediction of long-term outcome of cardiac resynchronization therapy by acute pressure-volume loop measurements', by G.J. de Roest et al. Eur J Heart Fail. 2013 Mar;15(3):299-307

Cardiac resynchronization therapy (CRT) has been established as an effective treatment strategy for heart failure patients with severe left ventricular (LV) systolic impairment and electrical dyssynchrony.¹ Despite the striking effectiveness of CRT in improving echocardiographic and clinical outcomes as well as prognosis, the issue remains that a substantial proportion of apparently suitable patients fails to benefit.² Efforts to increase response rate have mainly focused on improving patient selection and optimizing therapy delivery by better lead positioning and device programming. However, criteria for electrical and mechanical dyssynchrony are thus far of limited value in improving patient selection.^{3,4} In addition, the best strategy to optimize lead positioning and atrio-ventricular (AV) and inter-ventricular (VV) delay remains to be established. In clinical practice, echocardiographic techniques assessing stroke volume or mitral inflow patterns are the most widely employed for CRT optimization. However, these techniques are subject to large measurement errors and intra- and interobserver variability.

A potentially more accurate technique is invasive measurement of acute hemodynamic response to CRT, which has been used in several studies to determine the optimal LV lead position and optimize device programming.^{5,6} The rationale behind this approach is that CRT acutely improves LV contractility and that this translates into beneficial effects in the longer term. The most widely used invasive hemodynamic parameter is the maximum rate of LV pressure rise (LVdP/dtmax). However, evidence for a strong relation between invasively measured acute LVdP/dtmax increase and long-term outcome is conflicting. A recent study by Duckett et al. demonstrated a strong relationship between the magnitude of increase in LVdP/dtmax and reverse remodeling, as well as improvement in functional status.⁷ However, these results are not supported by several other studies. Stellbrink et al. demonstrated that an acute LVdP/dtmax increase did not predict reverse remodeling.⁸ More recently, two larger studies comprising a total of 353 patients found no relation between acute change in LVdP/dtmax and cardiac morbidity or survival.^{9,10}

A few studies have assessed CRT response using LV pressure-volume (PV) loop measurements.¹¹ The study by de Roest et al. in this issue of the *European Journal of Heart Failure*¹² is the first to investigate the relationship between acute hemodynamic response, assessed as an increase in LV stroke work (SW), and long-term response to CRT. This group optimized the position of the right ventricular and LV lead using LV SW measurements. A clear association was demonstrated between acute LV SW increase and reverse remodeling (defined as a >15% decrease in end-systolic volume [ESV]) after 6 months of CRT. An acute increase in LV SW of >20% predicted reverse remodeling with a sensitivity of 90% and a specificity of 75%. In contrast, a predictive value of LVdP/dtmax for long-term response to CRT was not observed. The authors should be complemented for this innovative and carefully conducted study. Although the small sample size as well as the absence of a control group are obvious limitations for extrapolation to larger populations and require confirmation in large multicentre randomized trials, these results highlight the potential of invasively measured LV SW to guide lead placement and improve CRT response rates.

At present, it is unclear which hemodynamic index is the best predictor for long-term response. However, the accumulating evidence against a relationship between acute change in LVdP/dtmax and long-term outcome combined with the recent positive findings on LV SW by de Roest et al. indicate that the latter might be a stronger predictor of pump function improvement. From a theoretical perspective, this may be explained by the fact that LVdP/dtmax reflects only a short period of the cardiac systole, while LV SW comprises the full systolic phase and incorporates both LV pressure and volume changes.

Measurements of LV SW require the acquisition of PV loops using a conductance catheter that is positioned in the LV cavity. Unfortunately, this method has some limitations. Acquisition of reliable volume signals using a conductance catheter is challenging, especially in dilated and dyssynchronous hearts. de Roest et al. calculated LV SW as the area of the PV loop. Their Figure 2 shows that these loops contain certain specific artefacts, such as the “tail” on the lower right side of the loop. In the calculation this is neglected in both the responders and the non-responders. Other publications show even more complicated loops¹³, and this is also our experience in dogs with LBBB and in CRT patients.¹⁴ One possible explanation of such artefacts could be mitral valve regurgitation, as suggested by de Roest et al. Another possible explanation relates to limitations of the conductance technique that assumes the catheter to be in the middle of a perfectly cylindrical cavity and that all ventricular walls move towards the catheter to a similar extent during systole. In practice, positioning of the catheter through the aortic valve causes the catheter to be close to the septum, a wall that is known to show very abnormal motion in dyssynchronous hearts. In order to show the effect of abnormal wall motion on the volume signal, we inserted a conductance catheter into a rubber balloon filled with saline. When moving the closed balloon around the catheter, a significant volume change was detected (see Figure 1). Based on these observations, we think that the absolute volumetric changes measured by PV loops in dyssynchronous hearts should be interpreted with care, and so should the values of LV SW calculated from the loop area. This idea is also supported by the finding of de Roest et al. that the mean increase in SW (~50%) is considerably larger than the product of stroke volume and systolic blood pressure. The “artefacts” caused by abnormal wall motion are, however, not necessarily useless, we just propose to avoid the term SW in this respect. An elegant alternative analysis has been published by Lieberman et al. These investigators calculated cycle efficiency from conductance measurements using the formula $\text{cycle efficiency} = \text{SW} / (\Delta \text{LV pressure} \times \Delta \text{LV volume})$, in other words the ratio of the area of the generated loop to that of the external rectangle (“ideal loop”). Indeed, cycle efficiency was highest during LV and biventricular pacing.¹³ These observations suggest that the high sensitivity of PV loops to predict CRT response may relate to a measurement artefact that, fortunately, is sensitive to dyssynchrony. Therefore, a preferable way to express the changes in PV-loops may be cycle efficiency, rather than SW. This being said, one still has to consider that additional limitations of the conductance technique are its lower accuracy in dilated hearts with low ejection fractions, the need for time-consuming calibration, and the larger size and higher costs of the conductance catheters compared with the pressure wires used for LVdP/dtmax measurements.

Considering the substantial clinical and economical implications of CRT non-response, the potential of acute PV loop measurements to improve response rate may compensate for the technical challenges and higher costs associated with the conductance technique. Theoretically, a number of approaches employing PV loop measurements could be applied to achieve a higher rate of favorable response. The measurements could be performed to improve patient selection. An interesting aspect of the protocol used by de Roest et al. is that the hemodynamic measurements were performed during a separate procedure, preceding the implantation of the CRT device. The strong predictive power of the PV loop measurements, shown in this study, could allow a strategy in which CRT would be denied to patients who do not show a significant PV loop response. This approach may have important additional value in subsets of patients in whom there is less consensus for a clinical benefit, i.e. patients with right bundle-branch block, intraventricular conduction delay, or narrow QRS. PV loop measurements could also be performed to optimize the LV lead position, which has been shown to improve response to CRT. This approach may particularly benefit patients with ischemic cardiomyopathy, in

whom implantation of the LV lead at areas with myocardial scar has been shown to reduce CRT effectiveness.¹⁵ de Roest et al. performed PV loop-guided lead position optimization and observed a considerably higher response rate compared with those reported in the literature. Unlike the lower response rates in patients with ischemic compared with non-ischemic cardiomyopathy reported in large randomized CRT trials, they found comparable numbers of responders in both subgroups. PV loop measurements could also be used to optimize AV and VV delays. Although the role of AV and VV optimization in improving long-term outcomes in CRT remains unclear, optimizing these timing intervals has been shown to have acute hemodynamic benefits. The results of de Roest et al. indicate that acute PV loop benefit translates into long-term improvement, suggesting the potential role of PV loop-guided AV and VV delay optimization to maximize therapy benefit and increase response rates in CRT. Finally, a systematic invasive hemodynamic evaluation using acute PV loop measurements may be applied in CRT non-responders to determine whether the treatment can be optimized with alternative LV stimulation sites or adjusted AV and VV pacing delays.

Figure 1. Volume signal obtained from a fixed conductance catheter positioned in a closed saline-filled rubber balloon. The arrow indicates the onset of manual balloon movement. Motion of the balloon wall relative to the fixed catheter resulted in detection of significant volume changes, even though actual balloon volume remained unchanged.

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General discussion

Chapter

Introduction

The general aims of the research presented in this thesis were three-fold:

1. To optimize targeted left ventricular (LV) lead placement for cardiac resynchronization therapy (CRT).
2. To improve identification of patients with an appropriate electrical substrate for CRT.
3. To investigate the feasibility of a novel method of ventricular lead placement for antibradycardia pacing therapy that targets an alternative ventricular pacing site, which may prevent pacing-induced dyssynchrony and the adverse effects associated with this condition.

Aims 1 and 2 were achieved by using a novel method of epicardial mapping via the coronary veins at the time of CRT implantation to evaluate the LV electrical activation (chapter 2-6). In addition, data obtained from coronary venous electroanatomic mapping were used to demonstrate the potential of a relatively easy and non-invasive approach to identify patients with an electrical substrate for CRT using the area of the QRS complex (QRS_{AREA}) on the vectorcardiogram (VCG) (chapter 6), and to validate the use of speckle-tracking based time-to-peak strain measures of mechanical activation to guide LV lead placement (chapter 4).

Aim 3 was achieved by performing a first-in-man study demonstrating the feasibility of permanently implanting an LV septal lead in patients using a transvenous approach through the interventricular septum.

The main findings from the research presented in this thesis were:

- Coronary venous electroanatomic can be used at the time of CRT implantation to identify patients with an electrical substrate for CRT and guide LV lead placement to the latest activated region.
- Right ventricular apex pacing significantly alters the pattern of LV electrical activation in CRT patients with LBBB, and shifts the latest activated region in a substantial proportion of these patients. This may have potential implications for the optimal pacing site.
- There is a strong positive correlation between the timing of LV electrical activation and peak contraction in candidates for CRT, which suggests that a strategy of LV lead targeting based on speckle-tracking based time-to-peak strain measures of mechanical activation is equivalent to that based on intra-cardiac measurements of electrical activation.
- QRS_{AREA} derived from the VCG provides a non-invasively acquired parameter that identifies the electrical substrate for CRT better than the conventional electrical markers QRS duration and LBBB morphology.
- Permanent placement of an LV septal lead using a transvenous approach through the interventricular septum is feasible and safe in patients. This new pacing method is hemodynamically preferable to conventional RV apex pacing and could serve as an alternative for biventricular pacing in patients with a conventional indication for antibradycardia pacing.

In this general discussion, these results are put in broader perspective. The first part of this chapter discusses improvement of patient selection in CRT by better identification of patients with an appropriate electrical substrate. For this purpose, a survey of the literature is provided discussing the limitations of conventional electrical markers of dyssynchrony to identify patients likely to benefit from CRT, the insights that have been gained in the electrical substrate for CRT from electroanatomic mapping studies, and the use of these insights in order to deliver better electrocardiographic markers of CRT response. The second part of the chapter concerns the role of electroanatomic mapping in optimization of LV lead placement for CRT, and the third part discusses the prevention of pacing-induced dyssynchrony by alternative site pacing.

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

Based on:

Masih Mafi Rad, Elien B. Engels, Antonius M.W. van Stipdonk, Kevin Vernooy, Frits W. Prinzen.

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

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Part

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 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 in 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-center 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 COMPANION¹² and the CARE-HF¹ 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 multicenter automatic defibrillator implantation trial (MADIT)-CRT,¹⁵ and resynchronization/defibrillation for ambulatory heart failure trial (RAFT) trials¹⁶). 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 (Figure 1).¹⁷ This evidence resulted in the addition of a class I indication to CRT for patients presenting with NYHA class II, a reduced LVEF, and a QRS duration >150 ms, in the 2010 guidelines.¹⁸

Figure 1. Effect of CRT on composite clinical events in patients with moderately prolonged (QRS duration of 120-150 ms) and severely prolonged QRS duration (>150 ms) (reprinted from¹⁷).

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 >150 ms. However, the best cutoff 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 RAFT¹⁶ 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 >150 ms only if a non-LBBB morphology is present.^{3, 4}

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 studies²³ 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-center 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

Figure 2. Cumulative probability of HF event or death (left) and of death alone (right) according to QRS morphology in the CRT with defibrillator (CRT-D) arm of the MADIT-CRT (adjusted from²¹).

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 user 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 multi-center SMART-AV trial showed that patients with a Q-LV >95 ms show significantly improved odds of reverse remodeling and quality of life response.³¹ Conversely, experimental studies and computer simulations have shown that pacing induced

pre-excitation in a heart without 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 EchoCRT trial.³⁵ This was a randomized trial that evaluated the effect of CRT in patients with a narrow QRS complex (<130 ms) and evidence of mechanical dyssynchrony. 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 an 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 toward 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 remodeling.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 electroanatomical reconstruction contact (CARTO, NOGA) or non-contact (EnSite) mapping. Studies that performed endocardial mapping in patients with heart failure 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) transseptal 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 anatomy⁴⁵ 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 concomitant 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. The novel technique of intra-procedural coronary venous electroanatomic mapping described in this thesis provides a middle ground between complete mapping and single Q-LV measurements. In chapter 6 of this thesis, we used this technique to assess the LV electrical activation in a cohort of 51 CRT candidates.⁵¹ 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. 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.

Instead, our technique of coronary venous electroanatomic 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

Figure 3. Example of a left ventricular activation time (LVAT) measurement. LVATmax is measured as the time difference between the first notch after 40 ms of QRS onset and the end of the QRS.

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 analyzed 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 40 ms of QRS onset and the end of the QRS on the baseline ECG was indicated as the LV activation time (LVATmax, Figure 3). A longer LVATmax was shown to be predictive for CRT response (OR[CI] = 1.30[1.11-1.52] for each 10 ms increase up to 125 ms). In addition, the Selvester QRS score for LBBB was used to quantify LV

scar extent. A higher Selvester score was negatively associated with reverse remodeling (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

Recently, the value of the vectorcardiogram (VCG) for characterizing the electrical substrate and predicting CRT response has been explored. The VCG 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 area of the QRS complex on the VCG (QRS_{AREA}). Van Deursen et al. assessed QRS_{AREA} in 81 consecutive CRT candidates and showed that a large QRS_{AREA} was associated with higher 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 smaller in ischemic than in non-ischemic patients.²⁴ Further support comes from observations in the aforementioned study described in chapter 6 of this thesis. In this study, VCGs were constructed from pre-procedural standard 12-lead ECGs for all patients using an adapted Kors algorithm. A large QRS_{AREA} (>69 μ Vs) on the VCG was shown to be highly predictive of delayed LV lateral wall activation as determined by coronary venous mapping.⁵¹ On the other hand, QRS_{AREA} has been shown to be smaller in patients with heart failure of ischemic etiology, which may be explained by the presence of non-conductive fibrotic tissue.²⁴ 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 etiology of heart failure. These considerations might explain the power of QRS_{AREA} for prediction of CRT response, but more research is required to better understand all determinants of QRS_{AREA} .

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 Figure 4C and 4D). The VCG-derived T-wave area was shown to predict echocardiographic CRT response better than QRS_{AREA} .⁵⁵ In a larger cohort consisting of 335 CRT recipients in which the primary endpoint was the composite of HF hospitalization, heart 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 (Figure 4E and 4F).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 large 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 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

Figure 4. 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 from the composite endpoint HTLD (HF hospitalization, heart transplantation, LVAD implantation, death) after 3 years of CRT. Large QRS or T area are values $\geq$ median value and small QRS or T area are values $<$ median value. (Adapted from^{55, 56})

interpretations of QRS notching/slurring, as illustrated in the study described in chapter 6 of this thesis. 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 provided in this thesis (chapter 6) 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.

Optimization of left ventricular lead placement for cardiac resynchronization therapy: Role of electroanatomic mapping

Part

Coronary venous electroanatomic mapping as compared to other mapping techniques

The novel method of coronary venous electroanatomic mapping (EAM) described in this thesis (chapter 2-6) allowed for detailed collection of data on the sequence of left ventricular (LV) electrical activation during cardiac resynchronization therapy (CRT) device implantation. This information could subsequently be used to target the LV lead to the latest activated region. An important finding of coronary venous mapping in chapter 2 was that in most patients with more than one target vein on the lateral wall, maximal electrical delay was found in another vein than the anatomically targeted vein. This shows that the anatomical (empirical) site of first choice often does not correspond with the site of latest activation, thereby illustrating the additional value of mapping-guided LV lead placement as compared to the conventional anatomical approach for optimization of LV lead positioning.

Previous investigators used three-dimensional (3D) contact or non-contact LV endocardial mapping techniques to characterize the LV activation pattern.^{39-41, 43, 60} Yet, these techniques require the insertion of mapping catheters or multi-electrode arrays into the LV cavity, which is cumbersome, time-consuming and not without risk. In addition, LV endocardial mapping provides no information on the electrical activation of the epicardium, which is the region where the LV lead is usually positioned in clinical practice.

Recently, 3D electrocardiographic imaging (ECGi) has been introduced as a non-invasive alternative that provides a detailed reconstruction of the epicardial electrical activation prior to CRT implantation.^{54, 61} In this way, detailed information on LV epicardial electrical activation can be readily obtained without increasing the invasiveness of the implantation procedure or prolonging procedure time. However, so far, coronary venous anatomy has not been integrated in these ECGi activation maps. Thus identifying the region of latest activation using ECGi does not necessarily allow positioning of the LV lead in this region because a suitable target vein with acceptable pacing parameters may not be found overlying the desired LV area. In contrast, direct mapping within the coronary veins as we performed in this thesis provides information on timing of electrical activation in anatomical regions where the LV pacing electrode can most likely also be positioned.

Other investigators did not perform full electroanatomic mapping of the coronary veins in favor of a simpler approach where the electrical delay at potential LV pacing sites is determined by measuring the time from QRS onset to the locally sensed LV lead electrogram (Q-LV).^{30, 31, 62-64} This approach, although easier and less time consuming, does have its disadvantages. For instance, the latest activated region may be missed, because other potential LV pacing sites are usually not tested when electrical delay at the anatomically (empirically) targeted LV region is deemed late enough. Besides, Q-LV measurements are usually performed after final LV lead implantation. If the measured electrical delay is deemed unsatisfactory, the LV lead may have to be relocated to an alternative target vein, which can be a cumbersome venture with extended procedure and fluoroscopy time. In contrast, our method of coronary venous EAM provides detailed information on electrical activation timing of all potential LV pacing sites prior to LV lead placement. The LV lead can then be targeted to the latest activated region in a single approach, thus reducing placement attempts at unsuitable sites. Moreover, in comparison with other invasive mapping techniques, this can be achieved at only minor prolongation of procedure time and without increasing the invasiveness of the implantation procedure by performing mapping with the same guide wire over which the LV lead is subsequently advanced.

However, the practical benefits of our mapping approach and the potential profit it yields in terms of CRT outcome have to be weighed against the additional costs. In the current thesis, the clinical value of this lead placement strategy was not evaluated by long-term follow-up data. The impact of coronary venous mapping-guided LV lead placement on CRT outcome and the cost-effectiveness of this approach require further investigation.

Mapping-guided LV lead placement: which patients will benefit most?

The additional value of mapping-guided LV lead placement will most likely depend on the type of conduction disorder and aetiology of LV dysfunction. In patients with non-ischemic LV dysfunction and LBBB, the latest activated region is typically located on the lateral or posterolateral wall.^{39,65} Furthermore, the area from where LV pacing is effective in these patients, the so-called sweet spot, has been shown to be quite large.⁶⁶ LV sites yielding >70% of maximal acute hemodynamic improvement were found to cover approximately 43% of the LV free wall, indicating that in non-ischemic failing hearts with LBBB, optimal CRT can be achieved by pacing over a fairly broad area of the LV.⁶⁶ In these patients, mapping-guided LV lead placement may therefore provide only little profit in terms of CRT outcome and may not be cost-effective. In contrast, the optimal pacing site in patients with non-LBBB QRS morphology or patients with ischemic LV dysfunction appears to be more restricted and to vary significantly.⁶⁷⁻⁷¹ Thus, the sweet spot for pacing the LV in these patients is most likely both smaller and more variable. Studies have shown that these groups of patients show reduced response to CRT.^{22,68,72-74} Mapping-guided LV lead placement may therefore be especially of value in these groups of patients, both in terms of CRT outcome and cost-effectiveness. Support for this notion comes from a recent study by Kandala et al. who demonstrated that patients with non-LBBB conduction in whom the LV lead was positioned in a region with significant electrical delay (Q-LV >50 % of QRS duration) had less heart failure hospitalizations and an improved composite outcome of all-cause mortality, heart failure hospitalization, LV assist-device implantation, and cardiac transplantation at 3 years.⁶³ The benefit of mapping for optimizing LV lead placement in these patients comes on top of the benefit it provides with regard to patient selection by determining whether these patients have an electrical substrate amenable to CRT at all, as already discussed in part one of this general discussion.

Optimizing the right ventricular lead position by electroanatomic mapping

Even though the latest activated region of the LV can be identified using electrical mapping techniques, it is common for the implanter not to find a suitable target vein with acceptable pacing parameters overlying the region of interest. In contrast to the limited number of suitable

Legend of Figure 1. Preprocedural 3D CE-CMR segmentation using CAAS-MRV 3.4 software (Pie Medical Imaging BV, Maastricht, the Netherlands) and intraprocedural integration with coronary venous electroanatomic map to guide LV lead placement to the region with maximal electrical delay free of scar in a patient with ischemic cardiomyopathy. CE-CMR showed a large basal to apical inferior to inferolateral scar. Coronary venous angiography revealed 2 target veins situated on the anterolateral and inferolateral wall. Maximal electrical delay was found in the mid segment of the anterolateral vein during coronary venous electroanatomic mapping. The LV lead was successfully positioned in the latest activated region and the electroanatomic map and 3D CE-CMR segmentation were integrated to verify positioning of the LV lead outside the region of scar. CS, coronary sinus; RV, right ventricle; LV-epi, left ventricular epicard; LV-endo, left ventricular endocard; AIV, anterior interventricular vein; ALV, anterolateral vein; ILV, inferolateral vein.

Figure 1. Legend on previous page.

LV pacing sites due to constraints of coronary venous anatomy, RV pacing can typically be performed over a large region of the RV. Recently, Singh et al. proposed to select an RV pacing site complementary to the chosen LV site to compensate for a suboptimal LV lead position. This would involve initial placement of the LV lead at the most suitable anatomical site. Subsequently, the RV endocardial surface is tested with the RV lead to maximize electrical separation of the leads by either RV pacing and sensing the electrical delay at the LV lead position, or by LV pacing and sensing the electrical delay at the RV lead position.⁷⁵ Kiuchi et al. demonstrated acute hemodynamic benefit of this so-called “dial in” strategy in thirteen consecutive CRT candidates. LV leads were positioned according to the conventional anatomical approach (anterolateral in 1, lateral in 9, and posterolateral in 3). Subsequently, a detailed electroanatomic map of the RV septum was generated during LV pacing to identify the most delayed activated region. Compared to conventional biventricular pacing at the RV apex, biventricular pacing at the most delayed site induced a significantly greater increase in LVdP/dtmax and pulse pressure relative to baseline.⁷⁶ The results of this study suggest that mapping-guided RV lead placement may improve the degree of cardiac resynchronization and that this can be obtained across a broad range of LV pacing sites.

Future directions: Scar integration

While the position of the LV lead with respect to the latest activated region is a factor that can influence CRT response, the proximity of the LV lead to an area with myocardial scar is considered an important factor as well. Several studies, using different imaging modalities, including myocardial contrast echocardiography, single photon emission computed tomography and contrast enhanced cardiac magnetic resonance (CE-CMR) have shown that implantation of the LV lead at an area with myocardial scar may reduce the effectiveness of CRT.^{67, 77-79} Thus pacing at the site with maximal electrical delay, while avoiding a region of scar is desired. Electroanatomic mapping may help to identify regions of myocardial scar by means of voltage acquisition.^{80, 81} However, a precise scar description cannot be guaranteed by electroanatomic data.^{82, 83} CE-CMR is considered the gold standard for myocardial scar delineation and has also been shown to identify non-transmural scars and infarct grey zones not detected by electroanatomic voltage mapping according to currently used voltage criteria.⁸³ Integrating information obtained from CE-CMR regarding myocardial scar with data on electrical delay and venous anatomy obtained from coronary venous EAM may give a better representation of the pacing possibilities within a patient and help to further optimize LV lead positioning. Hence, we are currently developing a strategy of preprocedural 3D scar segmentation from CE-CMR images and intraprocedural integration of these segmentations with the coronary venous EAM obtained in real-time to guide LV lead placement. Figure 1 shows preliminary results of the procedure in a patient with ischemic cardiomyopathy. Integrating these techniques also allows us to investigate whether voltages and other electrogram characteristics during coronary venous EAM can distinguish scar from viable myocardium. Since CE-CMR may not always be available in clinical practice, such knowledge may still help to avoid pacing in scarred regions.

Prevention of pacing-induced dyssynchrony by alternative site pacing

Part

Left ventricular septal pacing through the interventricular septum: a new, feasible, safe and hemodynamically preferable approach for anti-bradycardia pacing

In the study described in chapter 7 of this thesis we translated the results of previous canine experiments⁸⁴ into clinical practice by demonstrating the feasibility and safety of permanently implanting a left ventricular (LV) septal lead using a trans-interventricular septal approach in a cohort of 10 patients. The implantation of the custom ventricular pacing lead with extended helix in the LV septum was accomplished in all patients in a single procedure. Procedure and fluoroscopy time steeply declined with increasing experience to values comparable to those during lead implantation at the conventional RV apex site. In addition, implantation was accomplished with a commercially available pre-shaped guiding catheter, making the procedure applicable in any center with access to the relevant instruments. Pacing and sensing threshold were within an adequate range and in keeping with that during RVA pacing and the leads remained electrically and mechanically stable during long-term follow-up without lead-related complications.

Similar to pre-clinical findings on the beneficial effects of LV septal pacing,^{84, 85} our study showed that LV septal pacing induced less electrical dyssynchrony and preserved acute LV pump function, compared to RV apex and RV septal pacing. The underlying mechanism of the more natural activation pattern during LV septal pacing may be that pacing is performed at or near the normal breakout site during physiological impulse conduction, namely the LV septal endocardium.

The excellent feasibility of the trans-interventricular septal lead implantation approach in combination with the electrical and hemodynamic benefit of LV septal pacing shown in this thesis suggest that this new pacing method could serve as a better alternative for RV apex pacing in patients with a conventional indication for antibradycardia pacing. Admittedly, the findings of our study require further clinical validation in larger and prospective, long-term follow-up studies.

LV septal pacing as compared to other alternative pacing sites and biventricular pacing

Small acute hemodynamic studies in patients generally showed a tendency towards a benefit of RV septal over RV apex pacing.⁸⁶ However, three randomized trials comparing RV septal with RV apex pacing have shown no differences in LV pump function or clinical status.⁸⁷⁻⁸⁹ In our study, RV septal pacing showed no advantage over RV apex pacing in terms of electrical activation or hemodynamic performance. A remarkable finding was the large difference in QRS duration and acute hemodynamic effect between RV septal and LV septal pacing despite the fact that these sites were no more than 1 cm apart. Both findings are consistent with observations in animals and have been related to a significant delay in transseptal conduction which causes considerable later LV mechanical activation and peak contraction of the LV lateral wall during RV septal pacing, thereby inducing both inter- and intra-ventricular dyssynchrony. A similar but reverse dyssynchrony is to be expected during LV septal pacing, but several animal and human studies showed that earlier LV activation and contraction is to be preferred over RV pre-excitation.⁹⁰⁻⁹²

A potentially even better and more physiological activation pattern can be achieved using His bundle pacing. Indeed, several studies have shown that His bundle pacing results in less dyssynchrony and better hemodynamic performance than RV apex pacing.⁹³⁻⁹⁶ Several investigators have achieved permanent His bundle pacing in patients,^{97,98} and recently it was shown in a double-blind randomized cross-over study that His pacing preserves LV ejection

fraction and mechanical synchrony as compared to RV septal pacing at long-term follow-up in patients with AV block.⁹⁹ Yet, despite its beneficial effects, His bundle pacing is not recommended in patients requiring permanent cardiac pacing because of technical challenges during lead positioning and concerns about lead stability and threshold.¹⁰⁰

Several studies have suggested that an upgrade of RV apex pacing to biventricular pacing¹⁰¹⁻¹⁰⁴ or de novo implantation of a biventricular device¹⁰⁵⁻¹⁰⁷ in patients with AV block and reduced ejection fraction reverses or prevents pacing-induced dyssynchrony and further deterioration of cardiac function. Accordingly, this has been included in current international guidelines.³ Yet, the benefit of biventricular pacing has to be weighed against the more complex and time-consuming procedure, the higher rate of complications, failed implantations and loss of pacing associated with a coronary sinus (CS) lead with the consequent need for re-operation,¹⁰⁸⁻¹¹⁰ the shorter battery life and the additional costs. Our data suggest that LV septal pacing could serve as an easier, less complication- and failure-sensitive and more cost-effective alternative for biventricular pacing to prevent or reverse pacing-induced dyssynchrony in patients requiring pacing because of symptomatic bradycardia. Yet, this requires further investigation in preferably large randomized controlled trials that directly compare these two pacing methods with regard to long-term effect on LV pump function, clinical outcome with particular focus on complication- and re-operation rates, and cost-effectiveness.

Possible role of LV septal pacing in cardiac resynchronization therapy

Another possible application of LV septal pacing might be cardiac resynchronization therapy (CRT). In CRT, most commonly, a pacing electrode is inserted into a CS branch on the LV epicardial lateral wall. However, introduction of the lead into the tortuous CS is often difficult and time-consuming, and failure to access the CS occurs in 5-10% of patients.^{111, 112} In addition, problems encountered during positioning and fixation of the lead in the coronary vein, such as lead dislodgment,¹¹² phrenic nerve stimulation¹¹³⁻¹¹⁵ or elevated pacing thresholds,¹⁰⁸ account for suboptimal or loss of CRT in a substantial number of patients, which may require re-operation during follow-up.

In canine hearts with normal ventricular conduction, LV septal pacing reduced dyssynchrony and improved LV pump function as compared to conventional RV pacing, but interestingly, also performed at least as good as conventional biventricular pacing. Recent unpublished data from our group show that pacing at the LV septum, alone or in combination with RV pacing, also decreases electrical dyssynchrony (Figure 1) and accordingly improves LV systolic function to a similar degree as conventional biventricular pacing in canine hearts with left bundle-branch block (LBBB) and in CRT candidates.[Rademakers et al. unpublished]

These findings may be explained because a considerable part of the electrical dyssynchrony in LBBB hearts originates from the delay in conduction across the interventricular septum.^{42, 116} Therefore, LV septal pacing can reduce inter-ventricular dyssynchrony considerably. In addition, pacing at or near the LV septal endocardium also takes advantage of the more rapid conduction in the inner (~1mm) layer of the ventricular wall as compared to the other layers of the working myocardium,¹¹⁷⁻¹¹⁹ which allows quick spread of the electrical impulse from the septum to the lateral wall, thereby reducing intra-ventricular dyssynchrony.

From this point of view, LV septal pacing fits in the more general concept of LV endocardial pacing for CRT. Studies in canine hearts with LBBB and in CRT candidates have previously shown that the use of an LV endocardial pacing electrode increases the efficacy of CRT owing to the more physiological activation achieved by LV endocardial pacing as compared to conventional

Figure 1. Reconstruction of the electrical activation times of the RV and LV of a canine heart at mid ventricular level during LBBB (intrinsic conduction), simultaneous RV septal and LV epicardial lateral wall pacing (RV + LVlat), simultaneous RV septal and LV septal pacing (RV + LVs), and LV septal pacing alone (LVs). Electrical activation times as measured by 108 epicardial and 5 endocardial electrodes were interpolated and plotted on a model of the ventricles. Dots represent electrodes and stars active pacing sites. LV septal pacing alone, or in combination with RV septal pacing decreased electrical dyssynchrony to a similar degree as conventional biventricular pacing. (Adapted with permission from Rademakers et al. unpublished)

epicardial LV pacing.¹¹⁹⁻¹²² In patients, chronic LV endocardial pacing has been achieved using a trans-atrial septal approach.¹²³ However, this approach has an enhanced risk of thrombo-embolic complications due to the contact of the lead with the LV cavity which requires anti-coagulant therapy.

Theoretically, pacing into the Purkinje system, such as performed during direct His-bundle pacing, would be an even more physiological approach to treat a bundle-branch block. Previously, Narula reported that he could abolish the electrocardiographic signs of LBBB in 25 patients by distal His-bundle pacing, thereby curing the conduction disease.¹²⁴ However, as mentioned in the previous section, chronic implantation of a lead into the His bundle remains a technically challenging procedure.

The above mentioned beneficial effects of LV septal pacing in dyssynchronous hearts and the promising results of permanent LV septal lead implantation via the trans-interventricular septal route demonstrated in the current thesis suggest that LV septal pacing could become an equal alternative for biventricular pacing that avoids the difficult access route through the CS. This approach would also allow CRT to be performed using a single ventricular lead in combination with a simpler 2-chamber pacemaker, thereby reducing the complication rate as well as implantation costs and prolonging battery life.

In conclusion, if clinical experience with LV septal pacing turns out to be positive, the results of our study may have a practice-changing impact on future pacing therapy. The LV septum may become the universal pacing site, being preferred for antibradycardia pacing as well as CRT.

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Appendix

Summary

Under normal conditions, electrical activation of the chambers of the heart occurs very fast and nearly synchronous. This synchronous activation is considered of utmost importance to maintain coordinate ventricular contraction and normal cardiac pump function. In the presence of conduction abnormalities such as left bundle-branch block (LBBB) or during right ventricular (RV) pacing, left ventricular (LV) activation occurs slower and in a dyssynchronous manner. Intrinsic or pacing-induced dyssynchrony impairs LV pump function and, on the long run is associated with adverse structural changes and increased risk of heart failure and cardiac mortality. In the past decade and a half, cardiac resynchronization therapy (CRT) has emerged as a successful treatment for symptomatic heart failure patients with impaired LV systolic function and electrical dyssynchrony due to LBBB. The positive impact of CRT on LV pump function is attributed to the restoration of synchronous ventricular electrical activation by simultaneous biventricular pacing. However, up to half of CRT-treated patients do not show clinical and/or echocardiographic signs of response. The response rate of CRT may be improved by better identification of patients who have an appropriate electrical substrate for CRT and by optimizing therapy delivery by targeting LV lead placement to the latest activated region. In patients requiring continuous ventricular pacing because of symptomatic bradycardia, pacing at alternative ventricular sites rather than the standard site at the RV apex may produce less pacing-induced ventricular dyssynchrony and preserve LV pump function. In this respect, previous animal studies have shown that pacing at the LV septum yields LV pump function closely approximating that during normal ventricular conduction. However, a suitable method for application of LV septal pacing in clinical practice remains to be established.

The general background and introduction to the studies presented in this thesis are provided in **chapter 1**. The general aims of the research presented in **chapter 1** are:

- 1) To optimize targeted LV lead placement for CRT.
- 2) To improve identification of patients with an appropriate electrical substrate for CRT.
- 3) To perform a first-in man study investigating the feasibility of a novel method of ventricular lead placement for anti-bradycardia pacing therapy that targets the LV septum.

An increasing literature supports the practice of placing the LV lead in the latest activated region as a means of maximizing CRT efficacy. Conventional LV lead placement strategy involves an anatomic approach, targeting a coronary venous branch on the lateral or posterolateral wall which is based on the contention that most patients eligible for CRT have LBBB, where the lateral or posterolateral wall is typically the latest activated region. However, studies have shown considerable inter-individual differences in activation patterns between LBBB patients. Also, a significant percentage of CRT candidates do not have LBBB. Moving away from a one size-fits-all strategy towards a more patient-tailored approach of LV lead placement may thus improve therapy delivery and increase the rate of CRT response. In the study described in **chapter 2** we developed a novel method of LV epicardial mapping via the coronary veins, which utilizes a commercially available electroanatomic mapping system in combination with a mapping guide wire, to evaluate the LV electrical activation pattern of CRT candidates. The study demonstrates that this novel method of coronary venous electroanatomic mapping (EAM) can be used at the time of CRT implantation to guide LV lead placement to the latest activated region. In addition, this was achieved without increasing the invasiveness of the implantation procedure and at only minor prolongation of procedure time.

In **chapter 3** we used the novel method of coronary venous EAM to investigate the difference in LV electrical activation sequence between LBBB and RV apex pacing and the

potential implications thereof for LV lead placement. Current targeted LV lead placement strategy is directed at the latest activated region during intrinsic activation. However, in daily clinical practice the CRT device is most commonly programmed to (almost) simultaneous RV and LV pacing (i.e. biventricular pacing) without fusion with intrinsic ventricular activation. Although LBBB and RV apex pacing have similar QRS morphologies on the surface ECG, suggesting that the conditions are electrically equivalent, their activation patterns may be quite different, which may have implications for the choice of the optimal pacing site. To investigate this we assessed the LV electrical activation pattern of CRT candidates during both intrinsic LBBB and RV apex pacing using coronary venous EAM. The study showed that RV apex pacing significantly alters the pattern of LV electrical activation in CRT candidates with LBBB, and shifts the latest activated region in a half of these patients. These findings, added to results of a previous study showing a similar discordance in the mechanical activation pattern between LBBB and RV apex pacing, urge for reconsideration of the current practice of LV lead targeting for CRT.

Current LV lead targeting strategies are based on targeting either the region of latest electrical activation or the segment of latest peak contraction. Which of these regions to target, is currently a matter of debate. In **chapter 4**, we investigated whether these LV lead targeting strategies are comparable by performing a within-patient comparison of the timing of LV electrical activation obtained from coronary venous EAM and the timing of LV peak contraction derived from speckle-tracking echocardiography in CRT candidates. The analysis showed that there is a strong positive correlation between the timing of LV electrical activation and peak contraction and that the regions of latest electrical activation and latest peak contraction largely correspond in CRT candidates. These findings suggests that a strategy of LV lead targeting based on speckle-tracking time-to-peak strain measures of mechanical activation is equivalent to that based on intra-cardiac measurements of electrical activation. The results of this study can be regarded as a validation of the strain-based approach to guide LV lead placement.

It is becoming increasingly clear that an appropriate electrical substrate, consisting of a sufficient amount of LV activation delay, needs to be present in order for CRT to be effective. At present, the key clinical markers to detect and evaluate the extent of LV activation delay remain the QRS duration and morphology on the surface electrocardiogram (ECG). Yet, QRS duration appears insufficiently accurate whereas the classification of QRS morphology (LBBB or not) is operator dependant. In **chapter 5 and 6**, we demonstrate that coronary venous EAM can be used at the time of CRT implantation to determine the presence of delayed LV lateral wall activation, the primary electrical substrate for CRT. This technique represents a middle ground between invasive mapping methods and the standard ECG. Ideally, characterization of the electrical substrate is performed before the start of the implantation procedure in order to guide the decision on whether or not to implant a CRT device. We hypothesized that QRS characteristics other than QRS duration and morphology may be able to identify delayed LV lateral wall activation. In **chapter 5**, we investigated this by comparing ECG measurements with data from coronary venous EAM in a cohort of patients with nonspecific intraventricular conduction delay. The analysis showed that baseline QRS characteristics were unable to identify delayed LV lateral wall activation in this subgroup of patients. Recently, the value of the vectorcardiogram (VCG) for predicting CRT response has been explored. The VCG contains three-dimensional information of the electrical forces within heart, which led us to hypothesize that this technique may provide better indicators for delayed LV lateral wall activation than the one-dimensional ECG. In **chapter 6**, we investigated this by comparing VCG measurements

with data obtained from coronary venous EAM in a cohort of LBBB and non-LBBB patients. We found that the area of the QRS complex derived from the VCG (QRS_{AREA}) accurately identifies the electrical substrate for CRT, performing better than the conventional electrical markers QRS duration and LBBB morphology. QRS_{AREA} has the additional practical advantage that this parameter is measured in an objective manner and quantified as a continuous variable, as opposed to LBBB which is a dichotomous measurement that is subject to the use of different definitions and subjective interpretations. Another practical feature of QRS_{AREA} is that it can easily be derived from the standard 12-lead ECG because most commercially available ECG machines have algorithms to construct VCGs from standard 12-lead ECGs. The non-invasive and simple nature of VCG analysis combined with the evidence provided in this thesis that QRS_{AREA} reflects the electrical substrate for CRT indicates that this parameter can be easily applied in clinical practice to identify appropriate candidates for CRT, thereby potentially improving response to this therapy.

Chapter 7 describes the first-in-man study on the use of LV septal pacing for antibradycardia treatment, in order to prevent RV pacing-induced dyssynchrony. This idea was based on previous animal studies, showing that LV septal pacing leads to a more physiological sequence of LV electrical activation and contraction. In the animal experiments, permanent and stable implantation of an LV septal lead was achieved by introducing a custom pacing lead with extended helix transvenously into the RV and driving it from the RV side to the LV side of the interventricular septum. In **chapter 7**, the results of the previous animal studies were translated into clinical practice by demonstrating the feasibility and safety of permanently implanting an LV septal lead using a transvenous approach through the interventricular septum in a cohort of 10 patients. Similar to the pre-clinical findings, the study showed that LV septal pacing induces less electrical dyssynchrony and provides hemodynamic benefit as compared to conventional RV apex pacing. The excellent feasibility of the trans-interventricular septal lead implantation approach in combination with the electrical and hemodynamic benefit of LV septal pacing shown in this study suggest that this new pacing method could serve as a better alternative for RV apex pacing in patients with a conventional indication for antibradycardia pacing. In addition, our results suggest that this new pacing method could serve as an easier, less complication- and failure-sensitive and more cost-effective alternative for biventricular pacing to prevent or reverse pacing-induced dyssynchrony in patients requiring pacing because of symptomatic bradycardia. If clinical experience with LV septal pacing turns out to be positive, our results may have a practice-changing impact on future pacing therapy.

Chapter 8 and 9 of this thesis discuss the potential value of measurements of acute hemodynamic response to CRT for improving patient selection and optimizing CRT delivery by systematic hemodynamic evaluation of potential LV pacing sites and atrio-ventricular and inter-ventricular stimulation intervals.

Conclusions

- Coronary venous EAM can be used at the time of CRT implantation to characterize the electrical substrate of CRT candidates and to guide LV lead placement to the latest activated region.
- RV apex pacing significantly alters the pattern of LV electrical activation in CRT candidates with LBBB, and shifts the latest activated region in a substantial proportion of these patients. This suggests that LV lead targeting for CRT which is applied by biventricular pacing should be directed at the region latest activated during RV apex pacing rather than the region latest activated during intrinsic activation.

- Regional LV electrical activation and peak contraction are closely related in candidates for CRT. This suggests that a strategy of determining the latest activated region based on speckle-tracking time-to-peak measures is equivalent to that based on intra-cardiac measurements of electrical activation.
- QRS_{AREA} derived from the VCG provides a relatively easy and non-invasively acquired parameter that identifies the electrical substrate for CRT better than the conventional electrical markers QRS duration and LBBB morphology, while having the additional advantage of being objectively quantifiable as a continuous parameter. The simple and non-invasive nature of VCG analysis indicates that QRS_{AREA} can be easily applied in clinical practice to identify appropriate CRT candidates, thereby potentially improving response to this therapy.
- Permanent placement of an LV septal lead using a transvenous approach through the interventricular septum is feasible and safe in patients. This new pacing method is hemodynamically preferable to conventional RV apex pacing and could serve as an alternative for biventricular pacing to prevent or reverse pacing induced-dyssynchrony in patients requiring continuous pacing because of symptomatic bradycardia.

Samenvatting

In een normaal hart zorgt een speciaal geleidingsstelsel voor snelle en bijna gelijktijdige elektrische activatie van de rechter en linker hartkamer, waardoor beide hartkamers vrijwel gelijktijdig samentrekken. Dit zorgt voor een optimale pompfunctie van het hart. Bij patiënten met een ziek geleidingsstelsel ontstaat een ongecoördineerde samentrekking waardoor de pompfunctie van het hart vermindert en hartfalen kan optreden. Bij patiënten met hartfalen wordt het probleem van ongecoördineerde (niet gelijktijdige) samentrekking van de hartspeer tegenwoordig behandeld met Cardiale Resynchronisatie Therapie (CRT). Deze therapie heeft als doel de abnormale impulsgeleiding over de hartkamers te herstellen zodat de pompfunctie van het hart verbetert. Hiervoor wordt een speciale pacemaker geïmplantéerd met pacemakerdraden op de rechter en linker kamer. Het uiteinde (ook wel elektrode genoemd) van elke draad kan een elektrische prikkel afgeven. De pacemaker geeft gelijktijdig elektrische impulsen af aan beide elektroden (ook wel pacen genoemd) waardoor de rechter en de linker kamer weer min of meer gelijktijdig gaan samentrekken. Hierdoor kan de pompfunctie van het hart verbeteren. Veel patiënten met hartfalen die behandeld worden met CRT hebben minder klachten van hartfalen, kunnen zich beter inspannen en ervaren een betere kwaliteit van leven. Maar helaas heeft een belangrijk deel van hen (ongeveer een derde) weinig tot geen baat bij deze behandeling. Dit grote aantal vraagt om een verbetering en verdere ontwikkeling van CRT.

De algemene achtergrond en doelstellingen van de studies in dit proefschrift zijn uiteengezet in **hoofdstuk 1**.

Een van de manieren voor het verbeteren van CRT is door de elektrode van de linker kamer draad van de pacemaker op de meest gunstige plek op de linker kamer te leggen. In de huidige dagelijkse klinische praktijk wordt de linker kamer elektrode bij elke patiënt op nagenoeg dezelfde plek op de linker kamer gelegd. De resultaten van recente onderzoeken suggereren echter dat de optimale plek voor de linker kamer elektrode het gebied is dat zonder pacen het laatst de normale elektrische prikkel ontvangt. Doordat het activatiepatroon van de linker kamer behoorlijk kan verschillen tussen patiënten, varieert ook de optimale elektrode positie van patiënt tot patiënt. Dit vraagt om een meer patiënt-specifieke benadering voor het plaatsen van de linker kamer elektrode. Een manier om dit te doen zou kunnen zijn door gebruik te maken van *“electroanatomic mapping”*, een techniek waarmee men het elektrische activatie patroon van het hart 3-dimensionaal in kaart kan brengen. De techniek wordt gewoonlijk door cardiologen gebruikt als hulpmiddel bij de diagnose en behandeling van hartritme-stoornissen. In **hoofdstuk 2** tonen wij aan hoe *electroanatomic mapping* ook gebruikt kan worden om tijdens een CRT pacemaker implantatie het laatst geactiveerde gebied van de linker kamer te bepalen en de linker kamer elektrode in het desbetreffende gebied te plaatsen.

Momenteel wordt het laatst geactiveerde gebied bepaald tijdens eigen activatie van de linker kamer. In de dagelijkse klinische praktijk wordt CRT echter meestal toegepast door de rechter en linker kamer gelijktijdig te pacen zonder bijdrage van de eigen activatie. In **hoofdstuk 3** laten we met behulp van *electroanatomic mapping* zien dat pacen van de rechter kamer het activatiepatroon van de linker kamer in belangrijke mate verandert en in de helft van de patiënten het laatst geactiveerde gebied verschuift. In theorie zou dit betekenen dat de linker kamer elektrode eerder geplaatst zou moeten worden in het gebied dat het laatst geactiveerd wordt tijdens rechter kamer pacen en niet in het gebied dat het laatst geactiveerd wordt tijdens eigen activatie van de linker kamer.

Tot op heden is er geen consensus over de methode welke gebruikt dient te worden om het laatst geactiveerde gebied te bepalen. Sommige studies gebruiken elektrische mapping methoden om te meten waar in de linker kamer het elektrische signaal het laatst aankomt, andere studies bepalen met behulp van echografische beelden van het hart (ook wel

echocardiografie genoemd) welk deel van de linker kamer het laatst samentrekt, wat minder invasief is. In **hoofdstuk 4** laten we zien dat de gebieden in de linker kamer waar het elektrische signaal het laatst aankomt grotendeels overeenkomen met die gebieden die volgens echocardiografie het laatst samentrekken. Deze bevindingen suggereren dat beide methoden gelijkwaardig zijn voor het bepalen van het laatst geactiveerde gebied.

Een andere manier voor het verbeteren van CRT is door die patiënten te identificeren die een grote kans hebben om beter te worden door deze behandeling. De resultaten van eerdere onderzoeken duiden er op dat patiënten met een vertraagde elektrische activatie van de linker hartkamer de grootste kans hebben om baat te hebben bij CRT. Momenteel is de belangrijkste techniek voor het vaststellen van de aanwezigheid en mate van vertraagde linker kamer activatie nog steeds het standaard hartfilmpje, ook wel electrocardiogram (ECG) genoemd. Echter, de conventionele ECG markers voor vertraagde linker kamer activatie zijn ontoereikend gebleken voor het accuraat identificeren van patiënten met grote kans op baat bij CRT. In **hoofdstuk 5 en 6** tonen wij aan dat de boven beschreven *electroanatomic mapping* methode gebruikt kan worden om de aan-/afwezigheid van vertraagde linker kamer activatie van potentiële CRT kandidaten tijdens de implantatieprocedure te bepalen. Idealiter gebeurt dit uiteraard vóór de implantatie, zodat deze informatie gebruikt kan worden om de beslissing tot het wel of niet implanteren van een CRT pacemaker te sturen. Daarom hebben we in **hoofdstuk 6** de mapping data vergeleken met metingen van het vectorcardiogram (VCG). Anders dan het standaard ECG dat 1-dimensionale informatie bevat over de elektrische activatie van het hart, is het VCG een hartfilmpje dat 3-dimensionale informatie bevat over de elektrische krachten in het hart. In **hoofdstuk 6** tonen wij aan dat VCG metingen vertraagde linker kamer activatie nauwkeurig kunnen identificeren en daarbij beter presteren dan de conventionele ECG markers. Het VCG zou in de dagelijkse klinische praktijk makkelijk kunnen worden toegepast om geschikte CRT kandidaten te identificeren voorafgaand aan de CRT implantatie.

Een ongecoördineerde samentrekking van het hart wordt niet alleen gezien bij patiënten met een ziek geleidingssysteem, maar ook bij patiënten die een standaard pacemaker hebben ontvangen vanwege een te trage hartslag. Bij een standaard pacemaker wordt alleen één pacemakerdraad in de punt (ook wel “apex” genoemd) van de rechter hartkamer geplaatst. Pacen van de apex van de rechter kamer leidt ook tot een ongecoördineerde samentrekking van het hart, waardoor de pompfunctie van het hart afneemt en hartfalen kan ontstaan. Eerder verricht dieronderzoek heeft aangetoond dat het mogelijk is om dergelijke achteruitgang van de pompfunctie van het hart te voorkomen door bij een standaard pacemaker de elektrode van de pacemakerdraad aan de linker kant van het tussenschot van de hartkamers (ook wel “septum” genoemd) te plaatsen in plaats van in de apex van de rechter kamer. Dit werd in het dieronderzoek gedaan door de elektrode van de draad vanuit de rechter kamer door het septum heen te schroeven, tot de linker kant van het septum bereikt was. In **hoofdstuk 7** onderzochten wij de haalbaarheid van deze implantatiemethode voor het eerst in patiënten. Permanente implantatie van een pacemaker draad aan de linker kant van het septum bleek haalbaar en veilig in een groep van 10 patiënten. Daarnaast toonden we aan dat pacen van de linker kant van het septum, ten opzichte van de apex van de rechter kamer, een snellere elektrische activatie van het hart geeft en de pompfunctie van het hart behoudt. Onze bevindingen suggereren dat deze nieuwe implantatiemethode zou kunnen dienen als een beter alternatief voor de conventionele methode bij patiënten met een indicatie voor een standaard pacemaker. Als de klinische ervaring met deze nieuwe implantatiemethode positief blijkt, zouden de resultaten van ons onderzoek een praktijk-veranderende invloed kunnen hebben op toekomstige pacemakertherapie.

In **hoofdstuk 8 en 9** wordt de potentiële waarde van het meten van acute hemodynamische respons op CRT voor het verbeteren van patiëntselectie en optimaliseren van de toepassing van CRT bediscussieerd.

Conclusies

- *Electroanatomic mapping* kan tijdens een CRT pacemaker implantatie gebruikt worden om het elektrische activatiepatroon van de linker kamer in kaart te brengen en de de linker kamer elektrode in het laatst geactiveerde gebied te plaatsen.
- Pacen van de rechter kamer tijdens CRT verandert het activatiepatroon van de linker kamer in belangrijke mate en verschuift het laatst geactiveerde gebied in een aanzienlijk deel van de patiënten. Dit suggereert dat de linker kamer elektrode eerder geplaatst zou moeten worden in het gebied dat het laatst geactiveerd wordt tijdens rechter kamer pacen en niet in het gebied dat het laatst geactiveerd wordt tijdens eigen activatie van de linker kamer.
- De elektrisch laatst geactiveerde gebieden van de linker kamer komen grotendeels overeen met de gebieden die volgens echocardiografie het laatst samentrekken. Dit suggereert dat elektrische mapping methoden en echocardiografie gelijkwaardig zijn voor het bepalen van het laatst geactiveerde gebied.
- Het VCG is een relatief makkelijke en non-invasieve techniek die vertraagde linker kamer activatie beter identificeert dan de conventionele ECG markers. Deze techniek zou in de dagelijkse klinische praktijk makkelijk kunnen worden toegepast om geschikte CRT kandidaten te identificeren voorafgaand aan de CRT implantatie.
- Permanente implantatie van een pacemaker draad door het septum heen aan de linker kant van het septum is haalbaar en veilig in patiënten. Pacen van de linker kant van het septum behoudt de pompfunctie van het hart. Deze nieuwe implantatiemethode zou kunnen dienen als een beter alternatief voor de conventionele methode bij patiënten met een indicatie voor een standaard pacemaker.

Valorisation

At present, approximately 142.000 people in the Netherlands are suffering from heart failure. This has a great socio-economic impact on our society because heart failure leads to almost 30.000 hospital admissions and approximately 6800 deaths per year. The annual costs in 2011 were already estimated at 940 million euro's. The costs for the care of heart failure accounted for 11.4% of the total costs for cardiovascular disease and 1.1 % of the total health care costs in the Netherlands. It is estimated that the prevalence of heart failure will increase significantly in the coming years as a consequence of growth and ageing of the population, improved treatment and survival of patients with acute myocardial infarction and chronic coronary artery disease, and an increase in the prevalence of risk factors for heart failure such as diabetes and obesity.

A quarter to one-third of patients with heart failure has concomitant ventricular conduction abnormalities, most commonly due to a left bundle-branch block (LBBB). This conduction abnormality leads to a dyssynchronous electrical activation and contraction of the heart, which either causes or contributes to the left ventricular (LV) systolic dysfunction in these patients. The treatment of cardiac dyssynchrony has greatly improved with the advent of cardiac resynchronization therapy (CRT). This therapy improves the prognosis and reduces symptoms and the number of hospitalizations of patients with dyssynchronous heart failure. At present, approximately 3000 CRT pacemakers are implanted in the Netherlands each year. However, the issue remains that one-third to half of patients that receive a CRT pacemaker do not benefit from this therapy. This lack of response is not desirable for a treatment which involves a relatively expensive therapy and requires essentially irreversible implantation of a device and leads with potential risk of complications such as lead dislocations and infections. Improving identification of patients likely to benefit from this therapy and optimizing therapy delivery by better lead positioning are of utmost importance to improve the response rate of CRT.

In this thesis, a novel method of epicardial electroanatomic mapping (EAM) via the coronary veins was developed that can be used at the time of CRT implantation to determine the electrical activation sequence of the heart in patients with systolic heart failure and prolonged QRS duration. This new technique can be used to identify patients with delayed LV activation (the primary electrical substrate for CRT), who are more likely to benefit from CRT, and to target the LV lead to the latest activated region, a lead placement strategy that has been associated with improved outcome of CRT. This new coronary venous mapping technique provides detailed information on LV electrical activation without increasing the invasiveness of the CRT implantation procedure and at only minimal prolongation of procedure time. It therefore provides a middle ground between previously used mapping methods such as complete invasive endocardial EAM which is time-consuming and not without risk and simple electrical mapping with the LV lead, which provides only limited information on LV electrical activation. The results of this thesis suggest that coronary venous EAM has the potential to improve identification of patients likely to benefit from CRT and optimize therapy delivery by improving lead placement, thereby increasing the response rate to this therapy. Future studies are required to evaluate the actual impact of coronary venous EAM-guided patient selection and LV lead placement on CRT outcome and to assess the cost-effectiveness of this approach.

The data derived from coronary venous EAM were also used to demonstrate the potential of a relatively easy and noninvasive approach to identify patients with an appropriate electrical substrate for CRT using the area of the QRS complex (QRS_{AREA}) on the vectorcardiogram (VCG). At present, the key clinical markers to detect and evaluate the extent of LV activation delay remain the QRS duration and LBBB morphology on the surface electrocardiogram (ECG). Yet, QRS duration is a reflection of total ventricular activation and therefore not a reliable marker of delayed LV activation. Thus patient selection based on QRS duration alone will most likely

result in a substantial number of patients receiving a CRT device without deriving any detectable benefit. Classification of QRS morphology (LBBB or not) faces the problem of being operator dependent due to the presence of different LBBB definitions in the literature and the subjective interpretation of QRS notching and slurring. In addition, the refined LBBB definition 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. The present thesis demonstrates that vector-cardiographic QRS_{AREA} identifies delayed LV activation better than the conventional electrical markers QRS duration and LBBB morphology. The great practical benefit of QRS_{AREA} is that this parameter is measured in an objective manner and quantified as a continuous variable, as opposed to LBBB, which is a dichotomous measurement that is subject to the use of different definitions and subjective interpretations. Another practical feature of QRS_{AREA} is that it can be easily derived from the standard 12-lead ECG since most commercially available ECG machines have algorithms to construct VCGs from standard 12-lead ECGs. The simple and non-invasive nature of VCG analysis combined with the excellent diagnostic performance of QRS_{AREA} for delayed LV activation implies that this parameter can be easily used in clinical practice to identify appropriate CRT candidates before CRT implantation. This may potentially improve the response to this therapy and prevent ineffective and costly CRT device implantations with potential risk of complications. In addition, it may allow application of CRT in a substantial number of patients to whom treatment is currently wrongfully denied based on current guideline criteria.

A second topic in this thesis is the prevention of cardiac dyssynchrony, as caused by right ventricular (RV) pacing. Cardiac dyssynchrony is not only observed in patients with conduction disorders but also in patients receiving RV pacing because of symptomatic bradycardia. At present, approximately 8000 patients in the Netherlands are implanted with a pacemaker for anti-bradycardia treatment each year. Especially in patients with pre-existent impaired LV pump function, pacing-induced dyssynchrony can cause further deterioration of pump function and increase the risk of heart failure. Several studies have suggested that an upgrade of RV pacing to biventricular pacing or de novo implantation of a biventricular device in patients with atrio-ventricular block and reduced ejection fraction reverses or prevents pacing-induced dyssynchrony and further deterioration of cardiac function. Yet, the benefit of biventricular pacing comes at the expense of a more complex and time-consuming procedure, a higher rate of complications, failed implantations with the consequent need for re-operation, a shorter battery life and additional costs.

In this thesis, a first-in-man study was performed on the use of LV septal pacing for anti-bradycardia treatment, in order to prevent RV pacing-induced dyssynchrony. The feasibility of permanently implanting an LV septal lead using a transvenous approach through the interventricular septum has previously only been demonstrated in animal experimental studies. These animal studies showed that LV septal pacing leads to a more physiological sequence of left ventricular electrical activation and contraction. In this thesis, the results of the previous animal studies were translated into clinical practice by demonstrating the feasibility and safety of permanently implanting an LV septal lead using a transvenous approach through the interventricular septum in a cohort of 10 patients. Similar to the pre-clinical findings, the study showed that LV septal pacing induces less electrical dyssynchrony and provides acute hemodynamic benefit as compared to conventional RV apex pacing. These results suggest that this new pacing method could serve as a better alternative for RV apex pacing in patients with a conventional indication for anti-bradycardia pacing. If clinical experience with the

trans-interventricular septal lead placement approach turns out to be positive and if subsequent larger and prospective studies indicate that the acute hemodynamic benefit of LV septal pacing translates into preservation of LV pump function on the longer term, the LV septum may become the preferred site for anti-bradycardia pacing. This may reduce the number of patients that develop heart failure due to pacing-induced dyssynchrony. In addition, the study results suggest that LV septal pacing could serve as an easier, less complication- and failure-sensitive and more cost-effective alternative for biventricular pacing to prevent pacing induced-dyssynchrony in patients requiring pacing because of symptomatic bradycardia.

Another possible application of LV septal pacing might be CRT. Recent research has shown that pacing at the LV septum, also decreases electrical dyssynchrony and accordingly improves LV systolic function to a similar degree as conventional biventricular pacing in canine hearts with LBBB and heart failure patient with LBBB. The beneficial effects of LV septal pacing in dyssynchronous hearts and the promising results of permanent LV septal lead implantation via the trans-interventricular septal route demonstrated in the present thesis suggest that LV septal pacing could become an equal alternative for biventricular pacing in CRT. Yet, compared with biventricular pacing, this approach would allow CRT to be performed using a single ventricular lead in combination with a simpler 2-chamber pacemaker, thereby reducing the complication rate as well as implantation costs and prolonging battery life. Yet, this requires further investigation in preferably large randomized controlled trials that directly compare LV septal pacing and biventricular pacing with regard to long-term effect on left ventricular pump function, clinical outcome with particular focus on complication- and re-operation rates, and cost-effectiveness.

In conclusion, the research performed in this thesis could lead to improvement of the treatment and prevention of cardiac dyssynchrony. This may reduce death and morbidity due to dyssynchronous heart failure and the health care costs associated with this disease.

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About the Author

Masih Mafi Rad

was born on September 16, 1984
in Tehran, Iran.

He attended high school at the Regionale Scholengemeenschap in Steenwijk where he obtained his gymnasium diploma in 2002. The same year he moved to Maastricht where he started his medical training at the Faculty of Health Medicine and Life Sciences at Maastricht University. In his final year of medical training he did a clinical internship at the Cardiology department of the Orbis Medical Center in Sittard under the supervision of Dr. D.J.W. van Kraaij. This was followed by a research internship at the department of Cardiology of the University Hospital of Heidelberg under supervision of Prof. Dr. T.J. Dengler. The research focused on the role of tumor necrosis factor proteins in the pathogenesis of atherosclerosis. After graduating as Medical Doctor at Maastricht University in July 2008 he continued his research at the University Hospital of Heidelberg. This work led to the doctoral thesis entitled "Involvement of LIGHT in atherosclerosis and the large scale production of soluble LIGHT receptor TR2 for in vivo application" with which he obtained a Medical Doctor degree at the Medical Faculty of the University of Heidelberg in 2009. From February 2009 until December 2010 he worked as a physician at the Cardiology departments of the Orbis Medical Center in Sittard and the Maastricht University Medical Center. In December 2010 he started a PhD-track focused on cardiac dyssynchrony at the Cardiology department of the Maastricht University Medical Center under supervision of Prof. Dr. H.J.G.M. Crijns, Prof. Dr. F.W. Prinzen and Dr. K. Vernooij. The results of his research were presented at various national and international congresses and finally resulted in this thesis. On September 1, 2015, he started his Cardiology training at the Maastricht University Medical Center under supervision of Prof. Dr. H.J.G.M. Crijns and Dr. E.C. Cheriex. In the context of this training, he is currently doing his residency in Internal Medicine at the Maastricht University Medical Center under supervision of Prof. Dr. C.D.A. Stehouwer and Prof. Dr. R.P. Koopmans.

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