Cardiac Resynchronization Therapy Optimization

Comparison and Evaluation of Non-invasive Methods

ELENA SCIARAFFIA
Dissertation presented at Uppsala University to be publicly examined in Robergsalen, Akademiska Sjukhuset, Ing. 40, Uppsala, Friday, October 5, 2012 at 13:00 for the degree of Doctor of Philosophy. The examination will be conducted in English.

Abstract

The general purpose of this thesis was to investigate new cardiac resynchronization therapy (CRT) optimization techniques and to assess their reliability when compared to invasive measurements of left ventricular contractility (LV dP/dt_{max}). We first assessed whether cardiac output (CO) measured by trans-thoracic impedance cardiography could correctly identify the optimal interventricular (VV) pacing interval while using invasive measurements of LV dP/dt_{max} as reference. We did not find any significant statistical correlation between the two optimizing methods when their corresponding optimal VV intervals were compared.

We also tested the hypothesis that measurements of right ventricular contractility (RV dP/dt_{max}) could be used to guide VV delay optimization in CRT. The comparison of optimal VV intervals obtained from the left and right ventricular dP/dt_{max} did not show a statistically significant correlation; however, a positive correlation was found when broader VV intervals were evaluated and we concluded that this finding deserves further investigation.

An interesting alternative for CRT optimization is the use of device integrated algorithms or sensors capable to adapt the CRT settings to the current needs of the individual patient. In this respect we investigated the use of cardiogenic impedance (CI) measurements obtained through the CRT-D device as a method for CRT optimization with invasive measurements of LV dP/dt_{max} as a reference. Our results showed that CI could be measured through the device after implantation and that a patient-specific impedance-based prediction model was capable to accurately predict the optimal AV and VV delays. To follow up on these positive results we re-evaluated the patient-specific impedance-based prediction models 24 hours post implantation and investigated the possibility of calibrating them using parameters derived from non-invasive measurements of arterial pressure obtained by finger plethysmography at implantation. The results showed that the patient-specific impedance-based prediction models did not perform as well on the follow-up data as they did on the data from implantation day and that they correlated poorly with plethysmographic parameters.

Our studies suggest that novel methods for CRT optimization should be thoroughly evaluated and compared to established measures of left ventricular function prior to introduction into clinical practice.

Keywords: cardiac resynchronization therapy, device optimization, left ventricular contractility

Elena Sciarraffia, Uppsala University, Department of Medical Sciences, Cardiology-Arrhythmia, Akademiska sjukhuset, SE-751 85 Uppsala, Sweden.

© Elena Sciarraffia 2012

ISSN 1651-6206
ISBN 978-91-554-8450-7
urn:nbn:se:uu:diva-179785 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-179785)
This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I  Elena Sciaraffia, Helena Malmborg, Stefan Lönnerholm, Per Blomström, Carina Blomström Lundqvist. The use of impedance cardiography for optimizing the interventricular stimulation interval in cardiac resynchronization therapy – a comparison with left ventricular contractility. *Journal of Interventional Cardiac Electrophysiology* 2009;25(3):223-228

II  Elena Sciaraffia, Helena Malmborg, Stefan Lönnerholm, Per Blomström, Carina Blomström Lundqvist. Right ventricular contractility as a measure of optimal interventricular pacing setting in cardiac resynchronization therapy. *Europace* 2009;11(11):1496-1500


IV  Elena Sciaraffia, Matthew R. Ginks, John Gustafsson, Andreas Karlsson, C. Aldo Rinaldi, Carina Blomström Lundqvist. The reliability of cardiogenic impedance and correlation with echocardiographic and plethysmographic parameters for predicting CRT time intervals post implantation. *Submitted*

Reprints were made with permission from the respective publishers.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV</td>
<td>Atrioventricular</td>
</tr>
<tr>
<td>CI</td>
<td>Cardiogenic impedance</td>
</tr>
<tr>
<td>CO</td>
<td>Cardiac Output</td>
</tr>
<tr>
<td>CRT</td>
<td>Cardiac Resynchronization Therapy</td>
</tr>
<tr>
<td>CRT-D</td>
<td>Cardiac Resynchronization Therapy device with defibrillation capabilities</td>
</tr>
<tr>
<td>CRT-P</td>
<td>Cardiac Resynchronization Therapy device with pacing capabilities</td>
</tr>
<tr>
<td>LBBB</td>
<td>Left Bundle Branch Block</td>
</tr>
<tr>
<td>LV</td>
<td>Left ventricle/Left Ventricular</td>
</tr>
<tr>
<td>LV dP/dt</td>
<td>Rate of systolic left ventricular pressure rise</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left Ventricular Ejection Fraction</td>
</tr>
<tr>
<td>LVOT</td>
<td>Left Ventricular Outflow Tract</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association classification</td>
</tr>
<tr>
<td>PEA</td>
<td>Peak Endocardial Acceleration</td>
</tr>
<tr>
<td>RV</td>
<td>Right ventricle/Right ventricular</td>
</tr>
<tr>
<td>RV dP/dt</td>
<td>Rate of systolic right ventricular pressure rise</td>
</tr>
<tr>
<td>SV</td>
<td>Stroke Volume</td>
</tr>
<tr>
<td>TIC</td>
<td>Trans-thoracic Impedance Cardiography</td>
</tr>
<tr>
<td>VTI</td>
<td>Velocity Time Integral</td>
</tr>
<tr>
<td>VV</td>
<td>Interventricular</td>
</tr>
</tbody>
</table>
Introduction

Heart failure is a syndrome characterised by a structural or functional cardiac disorder that impairs the ability of the ventricles to fill with or eject enough blood to meet the peripheral tissues needs or can do so only at the cost of increasing filling pressures.

This syndrome manifests itself primarily as fatigue and reduced exercise tolerance, dyspnoea and fluid retention.

Heart failure can be caused by rhythm disturbances, great vessels disorders, valvular heart diseases, pericardial disorders or myocardial dysfunction; the latter of which is more commonly the cause of heart failure syndrome since all the other causes listed above are usually easily treated with either effective surgical correction or appropriate medical treatment.

Epidemiological studies have shown that the prevalence of heart failure increases steadily over the age of 60 and that the hospital discharges for heart failure have tripled in the last 20 years of the 20th century1 2.

Recent advances in the treatment of heart failure have resulted in a definite improvement in mortality rates in this group of patients3 but despite that the prognosis remains poor with a five-year mortality rate in the range of 50% and a vast impact on the economical health budget in the western world4.
Background

Cardiac resynchronization therapy

Electrical and mechanical dyssynchrony

Despite optimal medical treatment many heart failure patients deteriorate over the years and become more symptomatic.

In the last decade more interest has been focused on electro-mechanical activation patterns in the failing heart. About one third of the patients suffering from heart failure have a widened QRS on the ECG and already in the Framingham study a significant correlation was found between the presence of left bundle branch block (LBBB) and increased mortality. The Framingham study also showed that subjects with LBBB had a cardiovascular mortality of approximately 50% within 10 years of onset of LBBB compared with only 11.6% in an age matched control group.

Modern technology has allowed us to investigate more in detail the sequence of electrical activation in LBBB and the asynchronous contraction that follows. In animal models, by using right ventricular pacing to induce LBBB, it has been observed that while early activated regions can shorten rapidly even before the onset of the ejection phase, their shortening is minimal during the systolic phase which can result in holo-systolic stretch and premature relaxation. In contrast late activated regions are stretched in early systole which results in accentuated net systolic shortening and delayed relaxation. This asynchronous contraction pattern implies that opposite regions of the ventricular wall are “out of phase” and that the energy generated by one region is dissipated in the opposite one thus affecting the efficiency of the entire contraction.

An abnormality observed in heart failure patients with sinus rhythm and prolonged PR interval and also occurring with right ventricular pacing is uncoupling between atrial and ventricular contraction. This is known as atrioventricular dyssynchrony. The delayed onset of ventricular activation in relation to atrial filling has a negative impact on ventricular performance due to a suboptimal preload and it results in a prolonged “isovolumic” contraction that causes diastolic mitral regurgitation.

The asynchronous activation associated with LBBB leads to inter- and intraventricular dyssynchrony. Interventricular dyssynchrony is the result of delayed left ventricular activation and altered trans-septal pressure leading to
pre-systolic posterior-septal wall motion; intraventricular dyssynchrony is caused by delayed activation of some left ventricular segments during the ejection phase and prolonged contraction after aortic valve closure which gives rise to prolonged isovolumetric contraction and relaxation phases without an increase in the total duration of systole\textsuperscript{13 14}.

The effects of dyssynchronous activation on left ventricular pump function are independent of changes in pre- and afterload\textsuperscript{15 16}. In invasive hemodynamic studies in animals as well as in humans the maximal rate of rise of left ventricular pressure (LV \(dP/dt_{\text{max}}\)) has shown to be a sensitive marker of reduced systolic function due to dyssynchrony. The LV \(dP/dt_{\text{max}}\) is dependent on preload but hardly changes with changing pacing site or mode which made it the choice of preference for evaluation of dyssynchrony-induced changes in left ventricular contractility\textsuperscript{17}.

It is now well established that prolonged right ventricular pacing and LBBB reduce left ventricular contractility and lead to major structural changes such as ventricular dilatation and asymmetric hypertrophy\textsuperscript{18}. However, while in the case of heart failure related to post-myocardial infarction and hypertension ventricular remodeling appears, at least initially, to play a compensating role for the loss of function and the increased load respectively, in the case of LBBB, dilatation and hypertrophy do not reduce the dyssynchrony but rather increase it\textsuperscript{19 20}.

Cardiac resynchronization therapy indications and effects

In the middle of 1990s a few publications described the use of multisite pacing in advanced heart failure patients and reported a substantial improvement in clinical status and hemodynamic parameters\textsuperscript{21 22 23}.

This new pacing modality known as biventricular pacing or cardiac resynchronization therapy (CRT) is based on simultaneous right and left ventricular pacing achieved through a conventional endocardial right ventricular lead and an epicardial left ventricular lead placed preferably in a posterolateral branch of the coronary sinus.

Biventricular pacing can be delivered by a pacemaker or by a cardioverter-defibrillator, these systems are respectively known as CRT-P and CRT-D.

In the early days of CRT some concern was expressed since it seemed that this new therapy was enthusiastically embraced despite a substantial lack of randomized clinical trials to justify its use. Since then the body of evidence supporting CRT has grown tremendously and counts now a population of over 6000 patients included in completed randomized trials.

The initial trials included only patients with advanced heart failure and left ventricular ejection fraction \(\leq 35\%\), in New York Heart Association (NYHA) functional class III or IV, sinus rhythm and LBBB pattern on the surface ECG\textsuperscript{24 25 26 27 28}.  

9
All those trials demonstrated an improvement in quality of life, exercise tolerance and decreased need for hospitalization but it was only in 2004-2005 that the COMPANION\textsuperscript{29} and CARE-HF\textsuperscript{30} trials could demonstrate a reduction in mortality for patients treated with CRT compared with medical therapy only. Accordingly international guidelines\textsuperscript{31-32} advocated the use of CRT as a tool to reduce symptoms and improve survival but only in patients in NYHA class III and IV.

A major change in those recommendations has been introduced in 2010 when the compelling evidence of the REVERSE\textsuperscript{33} study and MADIT-CRT\textsuperscript{34} trial were taken into account. Both these studies demonstrated that the already known positive effects of CRT observed in patients with advanced heart failure could also be demonstrated in less symptomatic patients (NYHA I and II) and that CRT could play an important role in slowing down the disease progression.

The recently updated guidelines of the European Society of Cardiology (ESC)\textsuperscript{35} recommend the use of CRT as a class I recommendation with level of evidence A in patients with LBBB on the ECG and in NYHA class II to IV.

The beneficial effects of CRT are due to the restored homogeneous ventricular contraction and decreased intra- and interventricular dyssynchrony\textsuperscript{36-37}. The more uniform cardiac contraction during CRT ultimately leads to a higher efficiency of the entire left ventricular chamber and it has been demonstrated that resynchronization increases LV dP/dt\textsubscript{max} without any increase in myocardial metabolic demands\textsuperscript{38}. Positron emission tomography studies have also shown a more uniform distribution of blood flow and glucose uptake in the myocardium within 2 weeks upon initiation of CRT\textsuperscript{39-41}.

The correction of intraventricular dyssynchrony results also in a reduction of functional mitral regurgitation\textsuperscript{42} that can be observed immediately after the onset of successful resynchronization\textsuperscript{37-43} and is dependent on the improved coordination of the papillary muscles and the surrounding segments in combination with the simultaneous improvement in the left ventricular rate of pressure rise (dP/dt)\textsuperscript{42-44}. The reduction in mitral regurgitation contributes to decrease left atrial pressure which in its turn further decreases left ventricular end-diastolic pressure and volume.

The benefits of resynchronization therapy on cardiac function are progressive and additive\textsuperscript{37} and start a positive feedback loop that culminates in reverse remodeling\textsuperscript{45-46}. 
Non-responders to CRT

Although the clinical benefits of CRT have been well proved there still is a consistent 20-30% of patients that do not seem to respond to this therapy.

Among the various methods used to characterize non-responders to CRT, the lack of acute hemodynamic improvement measured invasively by LV $dP/dt_{max}$ is one although it has not shown to predict any long-term benefit and it is not always feasible after CRT implantation.

In two recent retrospective observational studies$^{47,48}$ patients undergoing LV $dP/dt_{max}$ measurements after successful CRT implantation were followed up for a minimum period of 17 months$^{47}$ respectively 1 year$^{48}$. Both studies showed that LV $dP/dt_{max}$ at baseline and during CRT was correlated to survival but the degree of improvement in LV $dP/dt_{max}$ achieved by initiation of CRT had no relation with clinical outcome.

In another study evaluating a small number of patients (n=32) Duckett et al.$^{49}$ reported that the acute hemodynamic response assessed by LV $dP/dt_{max}$ could predict reverse remodeling in CRT recipients, however in this study LV $dP/dt_{max}$ was used in order to guide left ventricular lead placement and not only measured post implantation.

Evaluation of the patients’ clinical status by lack of improvement in NYHA functional class is another suggested definition of non-responder to CRT. The obvious limitation with this definition is the placebo effect that has been well described by evaluating patients in the control group of some of the major CRT trials$^{27,28}$.

Assessing left ventricular reverse remodeling with echocardiography is currently the most commonly used technique to evaluate response to CRT since it reflects the improvement in cardiac structure and function, it is not prone to placebo effect and can be repeated in time. In some studies CRT response assessed by echocardiography was predictive of long-term outcome$^{50,51}$.

The role of echocardiography for the evaluation of response to CRT has generated the hypothesis that non-responders were at least to some extent the result of suboptimal patient selection criteria since the presence of LBBB was the only marker of intraventricular delayed conduction used to select candidates for CRT.

The PROSPECT$^{52}$ study was designed to evaluate the possible role of multiple echocardiographic measures of dyssynchrony for the identification of responders to CRT; the results were disappointing with low reproducibility of dyssynchrony variables and no measurement was able to predict the response to CRT.

At present there are no other data supporting the concept that echocardiographic assessment of dyssynchrony before CRT implantation increases the likelihood of a positive response. On the contrary, recent trials$^{33,34}$ seem to
emphasize that the presence of LBBB and the QRS duration are the best predictors of a favorable response to CRT.

**CRT optimization**

Modern CRT devices have programmable atrioventricular (AV) and interventricular (VV) delays to further tailor the settings of resynchronization whenever needed.

In patients treated with CRT intra-atrial and interventricular conduction directly affect ventricular filling and activation, an appropriate programming of AV and VV timings allows to coordinate the different activation fronts in order to achieve resynchronization. Moreover the position of the atrial, right ventricular and left ventricular leads differs in each patient which makes it more difficult to predict the optimal AV and VV setting and supports the concept of an individualized programming.

There are several invasive and non-invasive methods available to optimize both the AV and VV delay. The ideal optimization method should be able to measure changes in left ventricular systolic function in a reproducible and possibly non-invasive way.

A measure of left ventricular contractility that is often used as an invasive reference for other methods is the rate of left ventricular pressure rise or LV dP/dt.

This method is well established as a reliable and reproducible measure of left ventricular contractility. Changes in contractility alter the slope of the pressure curve resulting in an increased or decreased peak rise in intraventricular pressure (dP/dt$_{\text{max}}$) during isovolumetric contraction. It has to be mentioned that LV dP/dt is a complex function that depends not only on contractility but also on preload, afterload and heart rate. However, within physiological limits, LV dP/dt$_{\text{max}}$ is mainly dependent on contractility and preload which makes it a useful tool to evaluate the effect of changes in AV and VV delay programming on myocardial performance.

Some early studies have derived LV dP/dt from a left ventricular pressure curve obtained by a micromanometer introduced in the left ventricle but in later studies high-fidelity pressure wires have been successfully used and are now preferred.

Optimization of the AV and VV delays guided by LV dP/dt$_{\text{max}}$ can be performed directly after implantation and data interpretation is not dependent on the operator or limited by technical factors. The disadvantage is, however, the invasive nature of this method which makes it contraindicated in some patients.

In PATH-CHF and PATH CHF II trials invasive measurements of LV dP/dt$_{\text{max}}$ were used to optimize the AV delay.

A tailored programming of the AV delay not only ensures biventricular capture (particularly in those patients with normal AV conduction) but also
guarantees an optimal left ventricular filling time with a maximized atrial contribution.

Several studies demonstrated that optimizing the AV delay results in acute hemodynamic improvement\textsuperscript{61,62} and Doppler echocardiography is the most commonly used and feasible technique to evaluate the ventricular diastolic filling phase\textsuperscript{63}. Some of the major CRT trials used the echocardiographic technique known as “Ritter’s method”\textsuperscript{64} to optimize the AV delay although it was originally described for DDD paced patients with high degree AV block and never validated in the CRT population. Recent data question the value of the Ritter’s method in AV delay optimization for CRT\textsuperscript{65}.

Some prospective and/or randomized studies have compared an empirically set AV delay to an optimized one. Despite the small number of patients included in these studies and the use of different optimization techniques it has been showed that AV delay optimization has a positive effect on acute hemodynamic response, left ventricular function and NYHA class\textsuperscript{66,67,68}.

Optimizing the VV delay offers multiple configurations of ventricular activation sequences.

The rational for optimizing the VV delay is that even in healthy hearts the ventricular contraction is not simultaneous and in dyssynchronous hearts the interaction between right and left ventricle is highly impaired (interventricular dyssynchrony).

Moreover the left ventricular activation during CRT starts from the epicardial side and the position of the left ventricular lead might be suboptimal due to the limitation of the coronary sinus venous system anatomy.

Acute hemodynamic studies have reported significant improvement in contractility due to VV delay optimization\textsuperscript{69,70} and several non-invasive techniques including echocardiography\textsuperscript{71,72}, impedance cardiography\textsuperscript{73} and finger plethysmography\textsuperscript{74} have been proposed to achieve optimal CRT programming.

No consensus has, however, yet been reached on which technique should be used to optimize the VV delay in CRT patients.

Moreover the long-term effects of VV delay optimization have been questioned.

The RHYTHM II ICD study\textsuperscript{75} included 121 CRT-D treated patients and randomized them to either simultaneous or sequential biventricular pacing. The VV delay optimization was carried out by echocardiographic measurements of left ventricular outflow tract velocity time integral (LVOT-VTI) and at 6-months follow-up the group receiving sequential biventricular pacing showed no clinical benefit as compared to the group receiving simultaneous biventricular pacing. The DECREASE-HF trial\textsuperscript{76} held similar results showing no significant improvement in LV systolic function and remodeling with sequential versus simultaneous biventricular pacing.

The RESPONSE-HF trial\textsuperscript{77} evaluated patients that 3 months after CRT implantation were non-responders on the basis of NYHA class and 6-
minutes hall walk test. Patients were randomized to either sequential or simultaneous biventricular pacing. The VV delay optimization was performed using an algorithm based on the intracardiac electrograms. At 9 months follow-up response rate in the sequential group was considerably higher compared to the simultaneous group.

Some other studies have also reported an improvement in exercise tolerance in patients undergoing VV delay optimization\(^7\)\(^8\)\(^9\) even though no other clinical benefits were described. Currently there is no evidence supporting the hypothesis that CRT optimization can have an impact on long-term prognosis.

These negative results might be explained by the inadequate statistical power of the studies that evaluated the effect of VV delay optimization. Some data suggest that the optimal AV and VV delays vary over time\(^8\)\(^0\)\(^1\) as a consequence of reverse remodeling and that the optimal settings identified at rest and programmed in the device do not correspond to the optimal settings during physical exercise\(^8\)\(^2\)\(^8\)\(^3\)\(^8\)\(^4\) due to change in the ventricular activation pattern.

In this respect a rather attractive optimization tool would be an automated algorithm integrated in the device and able to adapt the CRT settings to the patients needs.

In the last few years CRT devices manufacturers have developed automated algorithms to optimize the AV and/or VV delay.

The SmartDelay (Boston Scientific Corporation, St Paul MN, USA) and the QuickOpt (St Jude Medical, St Paul MN, USA) are optimization algorithms that use intracardiac electrograms.

The SmartDelay algorithm has been compared to two echocardiographic optimization methods for the AV delay (Ritter’s and aortic velocity time integral) with positive results\(^8\)\(^5\). This algorithm has been also evaluated in a large randomized trial\(^8\)\(^6\) where 980 CRT-D recipients were assigned to one of three arms: fixed AV delay, echocardiography optimized AV delay, and SmartDelay optimized AV delay. The results showed no difference among the three groups of patients in end-systolic volume at 6 months follow-up.

Also the QuickOpt algorithm has shown a strong correlation with echocardiographic measurements of aortic velocity time integral\(^8\)\(^7\) but invasive measurements have shown no correlation with the optimal VV delay determined by LV dP/dt\(_{max}\)\(^8\)\(^8\). Moreover the recent FREEDOM trial\(^8\)\(^9\) has shown that frequent optimization using QuickOpt had no significant influence on clinical outcome.

An alternative approach for the optimization of the AV and VV intervals is the use of a hemodynamic sensor.

The Peak Endocardial Acceleration (PEA) sensor (SonR®, Sorin CRM SAS, Clamart France) detects cardiac muscle vibrations that reflects the first heart sound and has been demonstrated to correlate well with left ventricular contractility measured by LV dP/dt\(_{max}\)\(^9\)\(^0\)\(^9\)\(^1\).
An algorithm for CRT optimization based on the PEA sensor has been described with encouraging early results. The recently published CLEAR trial evaluated the long-term outcome in patients receiving a CRT device capable of PEA measurements.

The study was a single-blind randomized trial and included 238 patients that were randomized to either a PEA group or a control group. For the patients in the PEA group the AV delay was optimized by the device on a weekly basis and the VV delay was optimized at each follow-up visit, for the patients in the control group optimization was left to the treating center routine procedures.

At 1 year follow-up a significant greater proportion of patients in the PEA group improved according to the primary clinical endpoint (death from any cause, hospitalization for HF treatment, NYHA class, quality of life) compared to the patients in the control group.

The results of the CLEAR trial will probably increase interest for this form of automated optimization, however, it has to be pointed out that the assessment of NYHA class in this study was not blinded and that the positive effect of PEA guided optimization on the primary endpoint was mainly driven by changes in NYHA class.
Aims

The general purpose of this thesis was to investigate new CRT optimization techniques and to assess their reliability when compared to invasive measurements of left ventricular contractility.

The specific aims were:

- To assess whether non-invasive measurements of cardiac output by means of trans-thoracic impedance cardiography could correctly identify the optimal VV delay
- To test whether measurements of right ventricular dP/dt_{max} could be used to guide CRT optimization
- To evaluate whether cardiogenic impedance (CI) measurements obtained from a CRT-D device at implantation correlate with invasive hemodynamic measurements
- To investigate CI as a tool for AV and VV delay optimization at the time of CRT implantation
- To evaluate the stability of CI signals obtained from a CRT-D device 24 hours post-implantation
- To investigate whether a correlation is present between CI measurements and echocardiographic measurements 24 hours post implantation
Materials and methods

Patient selection

The study population included patients that received a CRT-P or CRT-D device. Almost all patients were in NYHA class III or IV heart failure despite optimal medical treatment, had a wide QRS complex (>120ms) and low LVEF (<35%).

The study population for Study I and Study II included 27 consecutive patients referred to Uppsala University Hospital, Uppsala, Sweden for implantation of a CRT device. Among those patients one had a narrow QRS (96ms) but had biventricular dysfunction and LVEF < 30% and one was in NYHA function class II and had developed dilated cardiomyopathy due to continuous right ventricular pacing and sarcoidosis.

Patients with mechanic aortic valve or other contra-indication for heart catheterization were not included in the studies, high degree AV block was not an exclusion criteria.

For Study III and IV a total of 17 patients were enrolled in two separate centers: St Thomas’ Hospital, London, UK and Uppsala University Hospital, Uppsala, Sweden.

All 17 patients fulfilled criteria for implantation of a CRT-D device, exclusion criteria were contra-indication for left heart catheterization or anticoagulation, third degree AV-block and indication for cardiac transplantation.

The studies were approved by the local ethics committees and all patients gave written informed consent prior to enrollment in any of the studies.

An overview of the patients’ demographics is shown in table 1.
Table 1. Patients’ demographics

<table>
<thead>
<tr>
<th></th>
<th>Study I and II</th>
<th>Study III and IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>22/5</td>
<td>14/3</td>
</tr>
<tr>
<td>Ischemic CM</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Dilated CM</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Prolonged RV pacing</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Unspecified CM</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>NYHA II</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>NYHA III</td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>AV block</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

CM: cardiomyopathy, RV: right ventricular, NYHA: New York Heart Association class.

Study design

In study I and II patients underwent right and left heart catheterization after successful implantation of a CRT-P or CRT-D system in order to identify the optimal AV and VV delay according to the respective measurement.

Patients were then evaluated with trans-thoracic impedance cardiography (TIC) which provided a non-invasive measurement of cardiac output (CO), the VV delay that resulted in the highest CO was considered optimal.

In study I we compared the optimal VV setting according to the TIC measurements to the one according to the left ventricular (LV) dP/dt measurements.

In study II we evaluated the effect of changing the VV delay on right ventricular (RV) dP/dt and compared the optimal settings obtained during RV catheterization with those obtained during LV catheterization.

In study III patients were evaluated directly after successful implantation of a CRT-D system and AV and VV delay optimization was performed. All patients underwent LV catheterization and simultaneously cardiogenic impedance (CI) signals were obtained from the CRT-D device, we assessed the ability of the CI based models to predict the optimal CRT setting.

In study IV we re-evaluated the same patients from study III 24 hours post implantation. In this study we assessed the stability of the CI signal, the possibility to calibrate the CI based models with non-invasive measurements (finger plethysmography) and compared the CI based models to echocardiographic measurements when the AV and VV delays were changed around their optimal values.
CRT implantation

The implantation of CRT-P and CRT-D devices took place for all patients in the electrophysiology laboratory.

A standard technique for CRT implantation was followed: venous access was established via the cephalic or the subclavian vein, the RV lead was placed in the RV apex or in a mid-septal position, the atrial lead was placed in the right atrial appendage and the coronary sinus lead was placed in a postero-lateral or posterior coronary sinus branch.

Prior to discharge all patients were evaluated with fluoroscopy to ensure appropriate and stable leads’ position and the devices were programmed according to clinical considerations.

After discharge all patients underwent regular follow-ups for evaluation of clinical status and device control.

LV dP/dt\text{max} and RV dP/dt\text{max} measurements

In study I, II and III invasive measurements of LV contractility were performed after successful CRT implantation using a high-fidelity wire that has a pressure sensor located at 30mm from its tip.

In study I and II a 0.014in wire with a 500Hz frequency response (PW-4, Radi Medical Systems, Uppsala, Sweden) was used, arterial access was obtained from the right femoral artery where a 5 Fr pigtail catheter was introduced and then advanced into the LV cavity. The pressure wire was introduced in the catheter and once a stable position was obtained LV pressure and LV dP/dt\text{max} were recorded and electronically calculated via a Radi analyzer® and a computer equipped with a PhysioMon® software that shows real time blood pressure and LV dP/dt\text{max} curves.

The invasive LV measurements were performed in a similar way in study III with the only differences being the pressure wire model (Radi™ wire, Radi Medical Systems, Uppsala, Sweden) with a frequency response of 400Hz and the arterial access that in this case was obtained from either the radial or the femoral artery.

In study II, once the LV pressure measurements were completed, the same pressure wire (PW-4, Radi Medical Systems, Uppsala, Sweden) was introduced in the right femoral vein and then advanced in the RV where RV pressure and RV dP/dt\text{max} were recorded and electronically calculated using the same software mentioned above.
Trans-thoracic impedance measurements

In study I all patients underwent measurements of CO by trans-thoracic impedance cardiography (TIC) after invasive measurements of LV pressure.

The measurements were performed using a commercially available system (Task Force Monitor Systems, CNSystems, Graz, Austria) that records changes in impedance to a current flow through the chest. A low amplitude (1mA) high frequency (100KHz) current is delivered via three surface electrodes placed behind the neck and bilaterally on the lower chest while the resistance to this current flow is measured by four other electrodes placed on each side of the sternum and on the abdomen.

The rationale is that changes in thoracic impedance are caused by the systolic aortic flow and on this basis the system calculates stroke volume and CO on a beat-to-beat basis from the TIC signal.

Cardiogenic impedance measurements

All patients in study III and IV received a Promote™ CRT-D device (St Jude Medical, Sylmar, CA, USA) which includes an impedance sensor capable of measuring the impedance between several electrode surface (device case, tip electrodes, ring electrodes and coils of the high voltage lead) within the pulse generator system.

To obtain an impedance measurement, the device delivers a continuous sequence of sub-threshold current impulses between two selected electrodes. It is a triphasic, charge balanced pulse with +850/-125µA and a pulse duration of 19 µs. These pulses are emitted at 128Hz.

In both studies two different impedance vectors were evaluated: V1 with injection of the measurement current from RV ring to LV ring and voltage sensing from RV tip to LV tip, V3 with injection of the measurement current from RV ring to RV tip and voltage sensing from RV ring to RV tip.

In study IV two additional vectors were also used: V5 (current delivered from RA ring to case and voltage sensing from RA tip to case) and V6 (current delivered from RV ring to case and voltage sensing from RV tip to case).

The pacing function and pacing vectors of the device are not affected by the use of impedance monitoring.

In study III V1 and V3 signals were recorded after successful CRT implantation in all patients, simultaneously LV dP/dt_{max} measurements were obtained as described above.

In study IV the four mentioned impedance vectors were evaluated 24 hours post-implantation and simultaneous echocardiographic measurements were performed.
Finger plethysmography and echocardiography

In study IV non-invasive measurements of arterial pressure were obtained in all patients after successful CRT implantation, at the same time LV dP/dt_{max} and cardiogenic impedance were measured as described above.

The system used to measure arterial pressure non-invasively is a finger plethysmograph (Finometer®, Finapres Medical Systems BV) which utilizes a volume clamp method based on a finger cuff applied to one of the patient’s fingers. The cuff is inflated dynamically to produce a pressure over the finger that equalizes the pressure within the artery and through the arterial wall. To monitor the unloading of the arterial wall calibration checks are performed with tenths of seconds in between, in this way the finger cuff mirrors the finger arterial pressure.

A reconstructed brachial artery pressure signal is obtained by letting the finger arterial pressure signal pass through a brachial waveform filter and correcting for the height difference between the heart and the cuff. A number of beat to beat parameters can be calculated based on the brachial artery pressure signal and the ones we used in our analysis were stroke volume (SV) and LV dP/dt.

In study IV all patients also underwent echocardiographic evaluation 24 hours after CRT implantation, cardiogenic impedance was measured simultaneously and a dedicated echocardiographer in each clinic performed the study.

A list of the echocardiographic measurements is shown in table 2; further details are described in the following paragraph.
Table 2. Echocardiographic measurements performed in study IV

<table>
<thead>
<tr>
<th>During intrinsic rhythm</th>
<th>At each AV/VV setting</th>
<th>Echocardiographic measurement</th>
<th>Short name</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>√</td>
<td></td>
<td>LA diameter</td>
<td>LAD</td>
<td>mm</td>
</tr>
<tr>
<td>√</td>
<td>√</td>
<td>LV end-diastolic diameter</td>
<td>LVEDD</td>
<td>mm</td>
</tr>
<tr>
<td>√</td>
<td>√</td>
<td>LV end-systolic diameter</td>
<td>LVESD</td>
<td>mm</td>
</tr>
<tr>
<td>√</td>
<td></td>
<td>Interventricular septum thickness (end-diastolic)</td>
<td>IVSD</td>
<td>mm</td>
</tr>
<tr>
<td>√</td>
<td></td>
<td>LV posterior wall thickness (end-diastolic)</td>
<td>LVPWD</td>
<td>mm</td>
</tr>
<tr>
<td>√</td>
<td>√</td>
<td>Time from onset of QRS complex to peak systolic movement of the LV posterior wall</td>
<td>LVPW_PSMP</td>
<td>msec</td>
</tr>
<tr>
<td>√</td>
<td>√</td>
<td>LV fractional shortening</td>
<td>LVFS</td>
<td>%</td>
</tr>
<tr>
<td>√</td>
<td>√</td>
<td>RV pre-ejection period</td>
<td>RVPEP</td>
<td>msec</td>
</tr>
<tr>
<td>√</td>
<td></td>
<td>LV end-diastolic volume (A4C)</td>
<td>LVEDV_MOD_A4C</td>
<td>mL</td>
</tr>
<tr>
<td>√</td>
<td></td>
<td>LV end-systolic volume (A4C)</td>
<td>LVESV_MOD_A4C</td>
<td>mL</td>
</tr>
<tr>
<td>√</td>
<td>√</td>
<td>Mitral regurgitation jet width</td>
<td>MRJD</td>
<td>mm</td>
</tr>
<tr>
<td>√</td>
<td>√</td>
<td>Max LV dp/dt</td>
<td>LV_DPDT_MAX</td>
<td>mmHg/sec</td>
</tr>
<tr>
<td>√</td>
<td>√</td>
<td>Mitral valve VTI</td>
<td>MV_VTI</td>
<td>cm</td>
</tr>
<tr>
<td>√</td>
<td>√</td>
<td>LV filling time</td>
<td>LVFT</td>
<td>msec</td>
</tr>
<tr>
<td>√</td>
<td>√</td>
<td>RR interval at mitral flow measurement</td>
<td>RR_MV</td>
<td>msec</td>
</tr>
<tr>
<td>√</td>
<td>√</td>
<td>LV pre-ejection period</td>
<td>LVPEP</td>
<td>msec</td>
</tr>
<tr>
<td>√</td>
<td>√</td>
<td>Isovolumic contraction time</td>
<td>IVCT</td>
<td>msec</td>
</tr>
<tr>
<td>√</td>
<td>√</td>
<td>Isovolumic relaxation time</td>
<td>IVRT</td>
<td>msec</td>
</tr>
<tr>
<td>√</td>
<td>√</td>
<td>LV ejection time</td>
<td>LVET</td>
<td>msec</td>
</tr>
<tr>
<td>√</td>
<td>√</td>
<td>Aortic VTI</td>
<td>AO_VTI</td>
<td>cm</td>
</tr>
<tr>
<td>√</td>
<td></td>
<td>LV end-diastolic volume (A2C)</td>
<td>LVEDV_MOD_A2C</td>
<td>mL</td>
</tr>
<tr>
<td>√</td>
<td></td>
<td>LV end-systolic volume (A2C)</td>
<td>LVESV_MOD_A2C</td>
<td>mL</td>
</tr>
<tr>
<td>√</td>
<td>From calculations</td>
<td>LV ejection fraction (Simpson’s model)</td>
<td>LVEF</td>
<td>%</td>
</tr>
<tr>
<td>√</td>
<td></td>
<td>Tei index</td>
<td>TEI_INDEX</td>
<td></td>
</tr>
</tbody>
</table>

LA: left atrium, LV: left ventricular, RV: right ventricular, VTI: velocity time integral.

**CRT optimization**

In study I and II, LV dP/dt_{max}, RV dP/dt_{max}, and TIC were measured during intrinsic rhythm and then during biventricular pacing at a rate of either 80 beats per minute (bpm) or at ten beats above the intrinsic rhythm in order to ensure continuous biventricular pacing.

First, the AV delay was optimized in patients with sinus rhythm during simultaneous RV-LV pacing. Four different AV intervals were tested (90ms, 110ms, 130ms, 150ms), the optimal AV delay was defined as the one that produced the highest LV dP/dt_{max} value and was then programmed in the device. The AV delay remained fixed during RV dP/dt_{max} and TIC measurements.
The following step was VV delay optimization which was performed according to the same protocol during all three measurements. Eight different VV intervals ranging from +80ms (LV pre-excitation) to -80ms (RV pre-excitation) were tested using 20ms steps.

Left ventricular pressure and LV dP/dt max were recorded for at least two respiratory cycles at each given device setting and a steady state pause of at least one minute was used after each change of setting in order to ensure hemodynamic stabilization.

Right ventricular pressure and RV dP/dt max were measured for at least 20 seconds with each VV setting in order to minimize respiratory variations and a one minute pause was used after each device setting change as described for the LV measurements.

Cardiac output was assessed by TIC with the same VV delay optimization protocol used for the other two measurements, the CO was recorded for one minute at each pacing setting and the average value was reported. A one minute stabilization period was used to reach steady state after any setting change. Telemetry between the device and the programmer was always discontinued during TIC measurements in order to avoid interferences.

In study III and IV the AV (in patients implanted with an atrial lead) and VV delays were varied according to the protocol shown in figure 1. The protocol was designed to mainly cause variation in hemodynamics rather than to reflect a typical optimization procedure. This was done so that comparison could be made across a larger spectrum of invasive hemodynamic data along with the CI and finger plethysmography data acquired.

At each device setting recordings were made after one minute in intrinsic rhythm, atrial pacing and ventricular sensing and dual response mode (DDD) at a rate of 10bpm above intrinsic rhythm once steady state was achieved. Left ventricular dP/dt max and non-invasive arterial pressure were recorded beat by beat for one minute and two separate sets of cardiogenic impedance parameters were recorded beat by beat for ≥ 20 seconds each.

In study IV echocardiographic measurements and CI measurements according to four different vectors were performed 24 hours post implantation during intrinsic rhythm and during biventricular pacing at the optimal AV and VV setting identified on the previous day with invasive measurements. The AV and VV delays were then changed by ±40ms around their optimal value in order to cause a significant change in hemodynamic.

As shown in table 2 a slightly reduced list of echocardiographic measurements was obtained at each AV and VV setting.
Figure 1. Protocol for atrioventricular and interventricular delay optimization used in study III.

AV: atrioventricular, VV: interventricular, LV: left ventricular, RV: right ventricular, Biv: biventricular

Statistical methods

In all studies continuous variables are presented as mean plus/minus standard deviation and a $P$ value of $< 0.05$ was considered statistically significant.

In study I and II the LV $dP/dt_{\text{max}}$ and TIC measurements and respectively the left and right ventricular $dP/dt_{\text{max}}$ measurements were subject to cross spectral analysis in order to study the within-patient correlation for the respective couple of measurements during VV interval optimization.

In order to calculate the overall correlation between the two methods in each study the intervals were combined into three broader interval ranges: -80 to -40 ms, -20 to +20 ms and +40 to +80 ms and coded -1, 0 and +1 respectively. As a measure of association for ordinal data, where ties are abundant, the gamma correlation was used.
In study III and IV patient-specific models were developed since we noticed that the CI waveform varied between patients but its characteristics were remarkably reproducible in each patient.

The impedance waveform characteristics analyzed were: peak-to-peak, slope, fractionation, diastolic dispersion and the average value of the impedance containing the DC frequency $Z_0$.

The patient specific model was developed by weighting the various impedance characteristics for each patient according to their relative contribution to explain the variation in LV $dP/dt_{max}$. This was calculated using a multivariate partial least square regression using the software SIMCA P+ (Umetrics AB, Umeå, Sweden).

Both patient-specific as well as generic impedance-based prediction models for predicting LV $dP/dt_{max}$ values were built. For the patient-specific models the contribution of different impedance characteristics in predicting LV $dP/dt_{max}$ varied, therefore the regression coefficient differed between patients. For the generic impedance-based model data were centred patient by patient in order to minimize inter-patient variability and the same coefficient values were used for all patients. The generic model did not require patient-specific calibration to a hemodynamic reference.

In order to compare measurements taken at different time points and device settings and to suppress variation due to respiratory motion, the recordings were averaged into waveform templates that are representative of one cardiac cycle. The waveform templates were normalized for time and amplitude due to intra- and interpatient variation of the R-R interval.

In study III the patient-specific and generic models were applied to predict a value of LV $dP/dt_{max}$ at each AV and VV setting. The LV $dP/dt_{max}$ was predicted on the basis of impedance values and waveform characteristics and this was compared to the invasively measured LV $dP/dt_{max}$.

In study IV non-invasive measurements of SV and $dP/dt$ were evaluated as a potential reference for calibration of the patient-specific impedance-based model. The evaluation was carried out for both SV and the non-invasive $dP/dt$ in two phases where the first phase aimed to investigate to which extent a non-invasive reference optimization correlated to the invasive reference LV$dP/dt_{max}$ optimization and the second phase assessed whether the impedance-based prediction model can describe the non-invasive measurements.

In study III and IV statistical analysis was performed using paired $t$-tests; in study IV the effect of varying the AV and VV delay on each echocardiographic parameter was analyzed using analysis of variance (ANOVA) models. Data were centered patient by patient as percentage change from average in order to normalize inter-patient variation.
Results

Study I

In this study we assessed whether CO measured by TIC could correctly identify the optimal VV delay for biventricular pacing, invasive measurements of LV contractility were used as reference.

Of the 27 patients that underwent invasive measurements of LV dP/dt\text{max} for identification of optimal CRT settings post implantation only 24 could also be evaluated with TIC.

According to the LV dP/dt\text{max} measurements, simultaneous RV-LV pacing was the optimal setting in nine cases (37.5%), LV pre-excitation was optimal in nine patients (37.5%) while RV pre-excitation was optimal in six patients (25%). The optimal VV interval value were: +80ms in 2 patients, +60ms in 1 patient, +40ms in 2 patients, +20ms in 4 pat, -20ms in 5 pat, -40ms in 1 pat.

Left ventricular pacing alone did not show any hemodynamic improvement (LV dP/dt\text{max} 821±145mmHg/s) if compared to both simultaneous and sequential pacing.

No complication occurred during the left heart catheterization.

The measured LV dP/dt\text{max} during intrinsic rhythm, simultaneous RV-LV pacing and during pacing with optimal VV interval settings are shown in tables 3 and 4.

The highest CO measured by TIC was achieved by LV pre-excitation in fourteen patients (58%), by simultaneous pacing in five patients (21%) and by RV pre-excitation in five patients (21%). The mean CO obtained by TIC during intrinsic rhythm, simultaneous pacing and pacing with optimal VV interval settings are shown in tables 3 and 4.

In only six cases (25%) were the optimal VV intervals identical, as defined by both the CO and LV dP/dt\text{max} measurements. In eleven cases (46%) the two methods agreed with regard to which chamber to be paced first, while in the remaining patients the defined optimal VV interval differed more than 40 ms between the techniques. The optimal VV interval settings differed with a mean of 52±36ms between the two methods. The LV dP/dt\text{max} was on average 79.6±51.6 mmHg/s lower when the optimal VV interval as defined by the TIC measurements was programmed in the device.

No significant statistical correlation was found between the two optimizing methods when their corresponding optimal VV intervals were compared (p > 0.05). A statistically significant correlation was, however, found if a
broader (40ms) optimal VV interval range was constructed (-80 to -40ms, -20 to +20ms, +40 to +80ms respectively coded -1, 0 and +1) and the two ternary variables so obtained were compared (p=0.0166).
Table 3. Hemodynamic measurements in patients who were not pacemaker dependant (n=17) during intrinsic rhythm and biventricular pacing.

<table>
<thead>
<tr>
<th>Method of measurement</th>
<th>LV $dP/dt_{max}$ mmHg/s</th>
<th>CO liter/minute, by TIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacing setting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrinsic rhythm</td>
<td>753±163</td>
<td>4.3±0.9</td>
</tr>
<tr>
<td>Simultaneous RV-LV pacing</td>
<td>878±156 (16.6%)$^1$</td>
<td>5.0±0.9 (16.2%)$^1$</td>
</tr>
<tr>
<td>Pacing with optimal VV interval</td>
<td>911±150 (3.8%)$^2$</td>
<td>6.5±1.9 (30%)$^2$</td>
</tr>
</tbody>
</table>

Figures in brackets indicate the absolute increase of LV $dP/dt_{max}$ and CO compared with intrinsic rhythm$^1$ and simultaneous RV-LV pacing$^2$. Abbreviations: RV: right ventricular, LV: left ventricular, s: second, CO: cardiac output, TIC: trans-thoracic impedance cardiography.

Table 4. Hemodynamic measurements during simultaneous RV-LV pacing and pacing with optimal VV interval in patients who improved by VV optimization (i.e. simultaneous biventricular pacing was not their optimal setting).

<table>
<thead>
<tr>
<th>Method of measurement</th>
<th>LV $dP/dt_{max}$ mmHg/s</th>
<th>CO liter/minute, by TIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacing setting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simultaneous RV-LV pacing</td>
<td>819±121</td>
<td>4.6±1.0</td>
</tr>
<tr>
<td>Pacing with optimal VV interval</td>
<td>865±130 (5.6%)$^*$</td>
<td>6.5±2.0 (41.3%)$^*$</td>
</tr>
</tbody>
</table>

Figures in brackets indicate the absolute increase of LV $dP/dt_{max}$ and CO compared with simultaneous RV-LV pacing$^*$. Abbreviations: RV: right ventricular, LV: left ventricular, s: second, CO: cardiac output, TIC: trans-thoracic impedance cardiography.
Study II

In this study we assessed whether measurements of RV $dP/dt_{\text{max}}$ could be used to guide VV interval optimization in CRT devices, with LV $dP/dt_{\text{max}}$ measurements as reference, and we evaluated the effect of biventricular pacing with different settings on RV function.

Of the 27 patients that underwent invasive measurements of LV $dP/dt_{\text{max}}$ directly after successful CRT implantation 26 were also evaluated with invasive right ventricular measurements, in one case the operator decided against right ventricular catheterization due to prolonged procedure time.

The measured value of LV $dP/dt_{\text{max}}$ during intrinsic rhythm, simultaneous RV-LV pacing and pacing with optimal VV interval are presented in table 5 and 6. The measurements during intrinsic rhythm could not be performed in the 6 patients who were pacemaker dependant and was missed in one patient.

The optimal VV interval setting was simultaneous RV-LV pacing in 11 patients (42.3%), LV pre-excitation in 9 patients (34.6%) and RV pre-excitation in the remaining 6 patients (23.1%) according to the LV $dP/dt_{\text{max}}$ measurements. Among the 15 patients in whom LV or RV pre-excitation gave the optimal setting, the optimal VV intervals were: +20ms in 4 patients, -20ms in 4, +40ms in 3, -40ms in 2, +60ms in 1 and +80ms in 1 patient.

The values of RV $dP/dt_{\text{max}}$ during simultaneous pacing and pacing with the VV interval optimized according to the RV contractility measurements are presented in table 5 and 6.

The optimal VV interval setting according to the RV $dP/dt_{\text{max}}$ was simultaneous pacing in only 4 patients (15%), LV pre-excitation in 7 cases (27%) and RV pre-excitation in the remaining 15 cases (58%). The comparison of optimal VV intervals obtained from the left and right ventricular $dP/dt_{\text{max}}$ respectively, showed identical values in 7 cases (27%) while in the remaining 19 patients they differed by: 20ms in 3 cases, 40ms in 7 cases and 60ms or more in 9 cases. The mean difference between the identified optimal VV intervals was 60.0±27.3ms ranging between 20ms and 140ms.

In the 19 patients for whom the LV and RV $dP/dt_{\text{max}}$ measurements resulted in divergent optimal VV intervals the average decrease in RV $dP/dt_{\text{max}}$ was 30.2±17.5mmHg/s (range from 3 to 81mmHg/s) when the VV interval was programmed according to the LV measurements whereas the decrease in LV $dP/dt_{\text{max}}$ was 85.3±52.8mmHg/s (range from 12 to 205mmHg/s) when the VV interval was optimized according to the RV measurements.

Among the 8 patients with RV dysfunction the optimal VV interval setting according to both LV and RV $dP/dt_{\text{max}}$ measurements was identical in 2 patients and in both cases it was simultaneous pacing whereas in the remaining cases the mean difference between the identified optimal VV intervals was 56.6±22.2ms which did not differ substantially from the mean difference recorded in the whole study group (60.0±27.3ms) or in those patients without RV dysfunction (61.5±29.3ms).
No statistically significant correlation was found between LV and RV \( \frac{dP}{dt_{\text{max}}} \) when the optimal VV intervals identified by each measurement were compared (\( p > 0.05 \)). However, using a broader optimal VV interval range of 40ms (-80 to -40ms, -20 to +20ms, +40 to +80ms, respectively coded -1, 0 and +1) and comparing the two ternary variables so obtained, a statistically significant correlation was found (\( P=0.037 \)) as illustrated in figure 2. Still in nine cases (35%) the optimal intervals differed 60ms or more.

No complication occurred during invasive measurements of LV and RV \( \frac{dP}{dt_{\text{max}}} \).

*Table 5.* Hemodynamic measurements in patients who were not pacemaker dependant (n=19) during intrinsic rhythm and biventricular pacing.

<table>
<thead>
<tr>
<th>Method of measurement</th>
<th>LV ( \frac{dP}{dt_{\text{max}}} ) mmHg/s</th>
<th>RV ( \frac{dP}{dt_{\text{max}}} ) mmHg/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrinsic rhythm</td>
<td>767.5±200.1</td>
<td>(not done)</td>
</tr>
<tr>
<td>Simultaneous RV-LV pacing</td>
<td>908.9±188.7 (18.3%)</td>
<td>306.9±74.2</td>
</tr>
<tr>
<td>Pacing with optimal VV interval</td>
<td>937.5±189.1 (3.1%)</td>
<td>329.0±73.5 (7.2%)</td>
</tr>
<tr>
<td>(according to respective method)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figures in brackets indicate the absolute increase of LV \( \frac{dP}{dt_{\text{max}}} \) and RV \( \frac{dP}{dt_{\text{max}}} \) compared with intrinsic rhythm\(^1\) and simultaneous RV-LV pacing\(^2\). Abbreviations: RV: right ventricular, LV: left ventricular, s: second.

*Table 6.* Hemodynamic measurements during simultaneous RV-LV pacing and pacing with optimal VV interval in patients who improved by VV optimization (i.e. simultaneous biventricular pacing was not their optimal setting).

<table>
<thead>
<tr>
<th>Method of measurement</th>
<th>LV ( \frac{dP}{dt_{\text{max}}} ) mmHg/s</th>
<th>RV ( \frac{dP}{dt_{\text{max}}} ) mmHg/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simultaneous RV-LV pacing</td>
<td>816.4±126.5</td>
<td>286.3±60.7</td>
</tr>
<tr>
<td>Pacing with optimal VV interval</td>
<td>865.5±140.0 (6%)</td>
<td>321.4±67.3 (9%)</td>
</tr>
<tr>
<td>(according to respective method)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figures in brackets indicate the absolute increase of LV \( \frac{dP}{dt_{\text{max}}} \) and RV \( \frac{dP}{dt_{\text{max}}} \) compared with simultaneous RV-LV pacing\(^*\). Abbreviations: RV: right ventricular, LV: left ventricular, s: second.
Figure 2. A bivariate histogram of the two ternary variables obtained by constructing broader interventricular intervals (-80 to -40ms= -1, -20 to +20ms=0, +40 to +80ms=1). The left hand bottom axis (LV dP/dt) represents the three variables from the left ventricular measurements and the right hand bottom axis (RV dP/dt) represents the three variables for the right ventricular measurements. The vertical axis represents the number of observations. This figure can be regarded as a three dimensional plot of a 3x3 cross table.

Study III

In this study we evaluated the feasibility of using CI as a marker for acute hemodynamic response to CRT and investigated its use for CRT optimization with invasive measurements of LV dP/dtmax as a reference.

Of the seventeen patients initially enrolled in the study two were excluded from further analysis due to unsuccessful LV lead implantation at first attempt and other two were excluded due to unsuccessful LV catheterization.

Among the remaining 13 patients 3 had atrial fibrillation and were therefore not included in the AV delay protocol. The optimal AV delay in the remaining 10 patients was 141±41ms, biventricular pacing with optimization of the AV delay improved hemodynamics from 935±186mmHg/s at baseline to 1150±248mmHg/s (P<0.05).

The optimal VV delay in the 13 patients analyzed was LV first by 35±33ms.
As a result of VV delay optimization a positive change in LV $dP/dt_{max}$ was observed, from $1106\pm236\text{mmHg/s}$ with simultaneous biventricular pacing to $1121\pm226\text{mmHg/s}$ with sequential pacing. However, this slight improvement was not statistically significant.

The patient-specific impedance-based prediction model identified the optimal setting for the AV delay in 9 of 10 patients to within 5% points (of change in $dP/dt_{max}$ from intrinsic rhythm). In patient 14 the difference between impedance predicted LV $dP/dt_{max}$ and the measured LV $dP/dt_{max}$ was $56\text{mmHg/s (7%)}$ and the discrepancy from optimal AV delay was one interval in the protocol. These results are shown in figure 3A.

For the VV optimization the patient-specific impedance-based prediction model correctly identified the optimal VV delay in 12 of 13 patients to within 5% points. In the remaining patient (Patient 9) the discrepancy between the impedance-predicted LV $dP/dt_{max}$ and the measured value was $40\text{mmHg/s (6%)}$. The difference between the optimal VV delay value and the one predicted by the model was 20ms, one increment in the VV delay optimization protocol. These results are shown in figure 3B.

The generic impedance-based prediction model developed for the whole patient group yielded results that were far less accurate than the patient-specific model; this approach identified the optimal VV delay in only 2 of 13 patients.
Figure 3. (A) Graph of the AV delay optimization based on patient-specific impedance-based prediction models (green diamonds) and comparison with the range of measured values across all settings (solid colored bars). (B) Graph of the VV delay optimization based on patient-specific impedance-based prediction models (green diamonds) and comparison with measured values (solid colored bars).
Study IV

In this study we wanted to: evaluate the reliability of the impedance-based patient-specific prediction model based upon pre-specified impedance vectors 24 hours post implantation, investigate whether a correlation is present between these CI signals and certain echocardiographic parameters acquired 24 hours post implantation and examine the possibility of a non-invasive calibration of the impedance-based model using parameters derived by non-invasive measurements of arterial pressure obtained by finger plethysmography at implantation.

The hemodynamic benefit for a VV delay optimization based on the patient-specific impedance-based prediction model created at implantation and then applied on the data from implantation and on the data from follow-up is shown in figure 4.

Within the range of LV dP/dt\textsubscript{max} observed during the implantation testing the hemodynamic benefit achieved by optimal VV setting according to the patient-specific impedance-based prediction model at follow-up is not as large as that obtained at implantation.

The impedance-based prediction models likely performed better on the data from implantation since the models were based upon these data. However, assuming that the response in reference LV dP/dt\textsubscript{max} to different VV delays is similar during both implantation and at follow-up day, most of the patients would be set within the upper half of their hemodynamic range as shown in figure 4.

The effect on echocardiographic parameters of varying the AV delay around the invasively optimized value resulted in a statistically significant effect in ANOVA models for mitral valve VTI and Tei index which were respectively maximized and minimized at the optimal AV delay. Further meaningful analysis of these data was not possible due to the limited number of data points per patient.

Varying the VV delay by 40 ms around the LV dP/dt\textsubscript{max} optimized value obtained at implantation resulted in a hemodynamic change that was statistically significant for the ANOVA models for two of the evaluated echocardiographic parameters: aortic velocity time integral (Ao-VTI) and LV filling time (LVFT).

We therefore further analyzed the relationship between CI features and Ao-VTI in a multivariate partial least square regression analysis and found a weak but significant correlation between the Ao-VTI and a generic linear combination of impedance features from the measured impedance vectors. The cross-validated correlation coefficient obtained was 0.42 (P<0.005).

Unfortunately patient-specific models to further analyze the correlation between CI features and echocardiographic parameters could not be performed due to limited number of data points per patient.
The non-invasive SV and dP/dt\textsubscript{max} values obtained by finger plethysmography during CRT optimization on implantation day were evaluated as an alternative calibration method for the impedance-based prediction model.

The non-invasive SV and dP/dt\textsubscript{max} optimization seem to have some similarities with the invasive LVdP/dt\textsubscript{max} optimization of the AV and VV delay, however, over the entire patient cohort, the impedance-based prediction model seemed to correlate poorly to both the non-invasive SV and dP/dt\textsubscript{max} references.

**Figure 4.** Clinical benefit plot from the VV delay optimization using the patient-specific impedance-based prediction models at both the implantation (day 1) and at the follow-up (day 2). The reference LV dP/dt\textsubscript{max} was only measured at implantation (day 1).
Discussion

CRT is a valuable treatment for patients with heart failure and electromechanical dyssynchrony whose symptoms persist despite optimal medical treatment.

Several randomized trials have demonstrated that CRT improves left ventricular function and exercise tolerance, reduces mortality and alleviates heart failure symptoms $^{26,27,29,30,33,34}$. Despite these encouraging data about 30% of the patients treated with CRT do not seem to experience any improvement; the reasons for this lack of response are yet not fully understood $^{94}$, however suboptimal LV lead position $^{95,96}$, presence of scar tissue in the area of stimulated myocardium $^{97}$ or inappropriate programming of the AV and VV delays $^{93}$ seem to be among the treatable causes.

A tailored programming of the AV and VV delays has been reported to further improve the hemodynamic effect of CRT $^{69,70}$, but up to date no consensus has been reached regarding the method that should be used to identify the optimal CRT setting in the individual patient.

The present thesis focuses on the evaluation of novel non-invasive methods for CRT optimization.

Trans-thoracic impedance cardiography and CRT optimization

Trans-thoracic impedance cardiography (TIC) has been described as a reliable non-invasive technique to measure hemodynamic variables such as stroke volume and cardiac output (CO) on a beat to beat basis.

Previous studies in non-CRT patients have demonstrated that CO measurements obtained by TIC are highly reproducible, correlate well with invasive CO determination methods such as thermodilution and Fick’s principle $^{98,99}$ and could be used to optimize the AV delay in pacemaker recipients with high degree AV block $^{100}$. In CRT recipients TIC has been described as a useful tool to optimize the AV delay (using Doppler echocardiography as a reference) $^{101}$ and the VV delay $^{73}$. 
These reports contradict our results in study I which showed that the optimal VV intervals identified by TIC correlated poorly with those obtained by LV dP/dt\textsubscript{max}.

The reason for these divergent results might be mainly of methodological nature since Heinroth et al\textsuperscript{73} performed AV and VV delay optimization by TIC without performing any comparison with invasive or non-invasive measurements. Moreover in their study they used a cut-off of 10\% increase in CO to define patients as responder to CRT but they reported that the mean variation between recordings in each patient was very close to this cut-off value (10.1\% during intrinsic rhythm and 11.8\% during pacing)\textsuperscript{73}.

In our study we also observed a decrease in left ventricular contractility when the optimal VV interval according to TIC was programmed in the device. This is particularly interesting if we consider that the increase in LV dP/dt\textsubscript{max} and CO observed upon initiation of biventricular pacing (16\%) was in the same order of magnitude while a much greater increase in CO (41.3\%) then in LV dP/dt\textsubscript{max} (5.3\%) was observed during sequential pacing. It can be speculated that smaller changes in contractility could result in larger changes in CO, however a change of this magnitude observed at rest is questionable particularly in patients with advanced heart failure.

The increase in LV dP/dt\textsubscript{max} measured in our study upon initiation of simultaneous biventricular pacing and after VV delay optimization was not greater than expected and was comparable with the increase measured in similar invasive studies\textsuperscript{69,70}.

We also observed a substantial variation in the optimal CRT setting among our patients and could not identify any optimal VV setting that could suit the majority of our population. Moreover in only 37.5\% of our patients simultaneous pacing was the optimal setting. Considering that simultaneous pacing is the most common programming in clinical practice when VV delay optimization cannot be performed, it is clear that some patients could derive a further hemodynamic improvement from sequential pacing.

It is well known that TIC measurements can be affected by several factors such as changes of respiration pattern, difference in body weight and thoracic anatomy, variation of surface electrode configuration. In our study repetitive CO measurements for the evaluation of variability were not performed in order not to lengthen the study.

Other limitations of this study are the relatively small amount of patients evaluated and the lack systematic follow-up in order to evaluate clinical response to CRT and echocardiographic reverse remodeling.
CRT optimization and right ventricular contractility

Right ventricular function is well known for being an independent prognostic factor in heart failure patients\textsuperscript{102,103}, however very little is known about the effect of CRT and AV and VV delay optimization on RV function.

In study II we hypothesized that the RV electrode could be used as a constant hemodynamic “monitor” for long-term VV interval optimization and that measurements of RV $dP/dt_{\text{max}}$ could be used to guide VV interval optimization in CRT devices, with LV $dP/dt_{\text{max}}$ measurements as reference.

To our knowledge no other study in the CRT population has invasively evaluated RV function. Echocardiographic studies have shown that CRT results in an acute improvement of RV function\textsuperscript{104} and that the same positive effect can be observed at follow-up\textsuperscript{105}, in both ischemic and non-ischemic patients and is independent of the increase in LV ejection fraction\textsuperscript{106}.

Other studies have evaluated the possibility of CRT optimization using a RV sensor capable of monitoring peak endocardial acceleration and this approach has shown positive results both in early studies\textsuperscript{90,92} and in a more recent randomized trial\textsuperscript{93}.

Our results showed that the optimal VV intervals identified by LV $dP/dt_{\text{max}}$ and RV $dP/dt_{\text{max}}$ were poorly correlated and were concordant in only a minority (27%) of the patients.

Possible explanations for this finding include variation in preload and breathing cycle variability which may affect RV more than LV function. Suboptimal RV filling pressures may result in shallow contractility curves irrespective of the used VV interval. Whether the pattern of a ”flat” $dP/dt$ response curves observed in some patients can be explained by low RV filling pressure, was difficult to evaluate.

Our study population included 8 patients with right ventricular dysfunction and no specific VV setting seemed to prevail among them. It is also important to notice that the mean difference in the optimal VV interval identified by RV and LV $dP/dt_{\text{max}}$ measurements respectively in this subpopulation did not differ substantially from the mean difference recorded in the whole study group and among the patients without RV dysfunction which might indicate that RV function does not strongly affect interventricular dyssynchrony.

Despite the lack of correlation between the RV and the LV $dP/dt_{\text{max}}$ optimized VV delays a statistically significant correlation was found when broader VV interval settings were compared.

Limitations of this study are the small number of patients evaluated and the fact that RV and LV pressures were not recorded simultaneously.
Cardiogenic impedance for CRT optimization

Cardiogenic impedance (CI) measurements obtained at epicardial or endocardial sites have been evaluated in animal models of heart failure and showed a good correlation with hemodynamic variables \(^{107,108}\).

More recently studies in patients with non-ischemic cardiomyopathy investigated the feasibility of CI measurements, using an external device, at CRT implantation or during an electrophysiologic study and demonstrated a strong correlation with invasive measured stroke volume \(^{109}\). The same CI measurements have also demonstrated to be a useful tool for optimizing LV lead site and AV and VV delays \(^{110}\).

In study III we evaluated the possibility of measuring CI through a CRT-D device at the time of implantation and evaluated its correlation with invasive measurements of LV dP/dt\(_{\text{max}}\).

Our results demonstrated that it is feasible to derive CI measurements from the lead impedance measurements using a CRT-D device.

We also demonstrated that impedance parameters can be used to predict the optimal AV and VV delays; although it seems that a patient-specific impedance-based prediction model based on several characteristics of the impedance waveform is needed for accurate prediction. A limitation with this model is that it relies on an invasive reference value.

In study IV we evaluated the reliability of the impedance-based patient-specific prediction model based upon pre-specified impedance vectors 24 hours post implantation, investigated whether a correlation was present between these CI signals and certain echocardiographic parameters acquired 24 hours post implantation and examined the possibility of a non-invasive calibration of the impedance-based model using parameters derived by non-invasive measurements of arterial pressure obtained by finger plethysmography at implantation.

Our results showed that, while the patient-specific impedance-based prediction models did not perform as well on the follow-up data as they did on the data from the implantation day, the impedance-based choice for the VV delays still provided a hemodynamic benefit in a majority of the patients.

It should be emphasized, though, that the patient-specific impedance-based prediction models were based on the invasively measured LV dP/dt\(_{\text{max}}\) values at implantation and that on the follow-up day one can only assume that varying the VV delay still held the same variation in LV dP/dt\(_{\text{max}}\) as observed at implantation.

We also compared CI features to several echocardiographic parameters acquired at follow-up with the optimal CRT setting according to the invasive measurements and when the VV delay was varied by 40ms around its optimal value. The parameter showing a statistically significant hemodynamic change was Ao-VTI and a correlation was found between the Ao-VTI measurements and a generic linear combination of CI features.
Unfortunately patient-specific models to further analyze the correlation between CI features and echocardiographic parameters could not be performed due to limited number of data points per patient.

Our attempt to calibrate the patient-specific impedance-based prediction model using non-invasive measurements of stroke volume and dP/dt max obtained by finger plethysmography at implantation was unfortunately unsuccessful since the correlation between the two was poor.

These negative findings might be, at least in part, explained by the small amount of patients evaluated which did not allow further analysis. Moreover, our population was relatively heterogeneous compared to the one evaluated in similar studies\textsuperscript{109,110} which might have affected the data collected.

Further studies evaluating a larger patient population might be useful to assess the potential value of CI as a hemodynamic monitor and possibly an optimization tool for CRT during follow-up.

Based on the data collected in our studies we concluded that recording CI measurements through the CRT-D device is feasible and that CI could be used to optimize the CRT settings but since it seems to require calibration it cannot yet be suggested as a tool for ambulatory use.
Conclusions

Based on this work the following conclusions can be made:

- Measurements of cardiac output by trans-thoracic impedance cardio-gram could not correctly identify the optimal VV interval and therefore this method can not be recommended as an ambulatory tool for VV delay optimization in CRT

- Right and left ventricular $\frac{dP}{dt_{\text{max}}}$ are not correlated in a linear and predictable fashion at different VV interval settings and the use of RV $\frac{dP}{dt}$ can not be recommended as a reliable method for VV delay optimization in CRT

- Cardiogenic impedance measurements can be obtained from a CRT-D device at the time of implantation and a patient-specific impedance-based prediction model can predict the optimal AV and VV delays

- The use of cardiogenic impedance as an optimization tool during CRT follow-up seems questionable at the moment since it requires a prediction model that can not be calibrated on a non-invasive reference.
Clinical implications and future perspectives

In patients with symptomatic heart failure despite optimal medical treatment and prolonged QRS duration on the surface ECG, CRT has proven to alleviate symptoms, slow disease progression and reduce mortality. Nevertheless, lack of response to this therapy is still observed in about one third of the treated patients.

Optimization of the AV and VV delays after CRT implantation has shown to result in a further improvement of the acute hemodynamic response which has generated the hypothesis that this approach could increase the clinical benefit derived from CRT.

Numerous invasive and non-invasive methods have been proposed for CRT optimization, but, at present, no single method can be recommended for standard practice.

Our findings highlighted the need for further evaluation of novel optimization techniques prior to their introduction into clinical practice.

The magnitude of contribution of AV and VV delay optimization to CRT response is difficult to ascertain. Most of the major randomized trials incorporated echocardiographic AV delay optimization using the Ritter’s method, but further evaluation has shown no correlation between this method and other invasive and non-invasive measures of acute hemodynamic improvement in CRT patients.

The VV delay has not been optimized in any of the major CRT trials. In some randomized trials VV delay optimization did not result in any significant clinical benefit, in some other studies an increased exercise tolerance was observed.

The acute hemodynamic benefit derived from VV optimization is relatively small and probably is relevant only in a minority of patients. Large scale studies with prolonged follow-up might help to better characterize the subset of CRT patients that is likely to benefit the most from VV delay optimization.

The majority of the available data on the effect of CRT optimization have been obtained directly after device implantation and at resting conditions. Automated algorithms integrated in the CRT device may allow to implement dynamic optimization in order to adapt to physiological alterations during exercise and after anatomical remodeling.

So far the existing algorithms for CRT optimization based on intracardiac electrograms have not shown any positive effect on long-term outcome.
The use of cardiogenic impedance to optimize CRT has been tested in our pilot studies with mixed results, further investigation is needed to evaluate this technique in a larger population and to assess its performance during long-term follow-up.

An alternative approach to CRT optimization can be based on a hemodynamic sensor integrated in the right atrial or ventricular lead. Our study investigating right ventricular contractility did not have positive results but encouraging results have been recently reported on the Peak Endocardial Acceleration (PEA) sensor\textsuperscript{92--93}. It remains to be seen if these initial positive data can translate in an improvement of long-term prognosis, but at the moment the PEA sensor seems to be a promising tool for CRT optimization.
Aknowledgements

I wish to express my sincere gratitude to all those who have contributed in different ways to this thesis. In particular I wish to thank:

**Carina Blomström Lundqvist**, my supervisor, for being my mentor and for guiding my research with her knowledge in cardiac pacing and electrophysiology, for all the fruitful discussions and helpful advice that have made this thesis possible and for the trust and support I received during these years.

**Stefan Lönnerholm**, my co-supervisor, for all valuable advice and fruitful discussions, for the energy and time invested in the electrophysiology laboratory recruiting patients for our studies and for encouraging my research activity.

**Per Blomström**, my co-author and colleague, for sharing his vast knowledge in cardiac pacing and electrophysiology and for his support over the years.

My co-authors **Helena Malmborg, John Gustafsson and Andreas Karlsson** for valuable scientific input and friendly support.

**David Mörtsell, Priit Teder, Bozena Ostrowska, Panagiotis Arvanitis, Johan Probst** my colleagues and members of the research group on cardiac arrhythmias and electrophysiology, for support and encouragement throughout the years.

The medical staff at the electrophysiology laboratory for cooperation and support during all phases of our studies.

All the patients that willingly participated in the studies.

My parents **Michele and Teresa** for their unconditional love and for trusting and supporting me in all my choices.

**Gerriet**, my wonderful husband for bringing sunshine in my life each and every day!
References


5 Baldasseroni S, Opasich C, Gorin M et al. Left bundle branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: A report from the Italian Network on Congestive Heart Failure. Am Heart J 2002; 143: 398-405


9 Delhaas T, Arts T, Prinzen FW et al. Relation between regional electrical activation time and subepicardial fiber strain in the canine left ventricle Eur J Physiol 1993; 423: 78-87

10 Chevalier S, Basta M, Leitch JW. The importance of the left atrioventricular interval during atrioventricular sequential pacing. Pacing Clin Electrophysiol 1997; 20: 2958-2966

11 Auricchio A, Ding J, Spinelli JC et al. Cardiac resynchronization therapy restores optimal atrioventricular mechanical timing in heart failure patients with ventricular conduction delay. J am Coll Cardiol 2002; 39: 1163-1169


14 Zhou Q, Henein M, Coats A et al. Different effects of abnormal activation and myocardial disease on left ventricular ejection and filling times. Heart 2000; 84: 272-276
15 Park RC, Little WC, O'Rourke RA. Effect of alteration of left ventricular activation sequence on left ventricular end-systolic pressure-volume relationship in closed-chest dogs. Circ Res 1985; 57: 706-717
31 Dickstein K, Cohen-Solal A, Flippatos G, McMurray JJ et al. ESC guidelines for diagnosis and treatment of acute and chronic heart failure 2008 : the Task Force
for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008; 29: 2388-2442


33 Linde C, Abraham WT, Gold MR et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008; 52: 1834-1843


Guidelines for cardiac resynchronization therapy. Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. Europace 2010; 12: 1526-1536


43 Breithardt OA, Kuhl HP, Stellbrink C. Acute effects of resynchronization treatment on functional mitral regurgitation in dilated cardiomyopathy. Heart 2002; 88: 440

45 Bax JJ, Molhoek SG, Van Erven L et al. Usefulness of myocardial tissue Doppler echocardiography to evaluate left ventricular dyssynchrony before and after biventricular pacing in patients with idiopathic dilated cardiomyopathy. Am J Cardiol 2003; 91: 94-97

46 Vernooy K, Verbeek XAAM, Crijns HJGM et al. Non-uniform workload and remodeling of the left ventricle, induced by left bundle branch block, is reversed by biventricular pacing. Circulation 2004; 110: III-481


48 Bogaard MD, Houthuizen P, Bracke FA et al. Baseline left ventricular dP/dt_{max} rather than the acute improvement in dP/dt_{max} predicts clinical outcome in patients with cardiac resynchronization therapy. Eur J Heart Fail 2011; 13: 1126-1132


50 Yu CM, Bleecker GB, Fung JWH et al. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. Circulation 2005; 112: 1580-1586


52 Chung ES, Leon AR, Tavazzi L et al. Results of the Predictors of Response to CRT (PROSPECT) trial. Circulation 2008; 117: 2608-2616


54 Mason DT, Braunwald E, Covell JW, Sonnenblick EH, Ross J Jr. Assessment of cardiac contractility. The relation between the rate of pressure rise and ventricular pressure during isovolumic systole. Circulation 1971; 44: 47-58


56 Reeves T, Hefner L, Jones W et al. The hemodynamic determinants of the rate of change in pressure in the left ventricle during isometric contraction. Am Heart J 1960; 74-761


Jansen AHM, Bracke FA, Van Dantzig JM et al. Correlation of echo-doppler optimization of atrioventricular delay in cardiac resynchronization therapy with invasive hemodynamics in patients with heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 2006; 97: 552-557


Van Gelder BM, Bracke FA, Meijer A et al. Effect of optimizing the VV interval on left ventricular contractility in cardiac resynchronization therapy. Am J Cardiol 2004; 93: 1500-1503


Boriani G, Muller CP, Seidl KH et al. Randomized comparison of simultaneous biventricular stimulation versus optimized interventricular delay in cardiac resynchronization therapy. The Resynchronization for the HemodYnamic Treat-
ment for Heart Failure Management II implantable cardioverter defibrillator (RHYTHM II ICD) study. Am Heart J 2006; 151: 1050-1058

76 Rao RK, Kumar UN, Shafer J et al. Reduced ventricular volumes and improved systolic function with cardiac resynchronization therapy: a randomized trial comparing simultaneous biventricular pacing, sequential biventricular pacing, and left ventricular pacing. Circulation 2007; 115: 2136-2144


84 Van Gelder BM, Meijer A, Bracke FA. Stimulation rate and the optimal interventricular interval during cardiac resynchronization therapy in patients with chronic atrial fibrillation. Pacing Clin Electrophysiol 2008; 31: 569-574


86 Ellenbogen KA, Gold MR, Meyer TE et al. Primary results from the SmartDelay determined AV optimization: a comparison to other AV delay methods used in cardiac resynchronization therapy (SMART-AV) trial: a randomized trial comparing empirical, echocardiographic-guided, and algorithmic atrioventricular delay programming in cardiac resynchronization therapy. Circulation 2010; 122: 2660-2668


89 Abraham WT, Gras D, Yu Cm et al. Results from the FREEDOM trial - assess the safety and efficacy of frequent optimization of cardiac resynchronization therapy. Heart Rhythm 2010; Late Breaking Clinical Trial insert: 2-3
93 Ritter P, Delnoy PP, Padelletti L, Lunati M et al. A randomized pilot study of optimization of cardiac resynchronization therapy in sinus rhythm patients using a peak endocardial acceleration sensor vs standard methods. Europace, published online May 1st 2012
96 Ypenburg C, van Bommel RG, Delgado V, Mollema SA et al. Optimal left ventricular lead position predicts reverse remodeling and survival after cardiac resynchronization therapy. Am Coll Cardiol 2008; 52: 1402-1409
97 Bleeker GB, Kaandorp TA, Lamb HJ, Boersma E et al. Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy. Circulation 2006; 113: 969-976
100 Kindermann M, Frohlig G, Doerr T, Schieffer H. Optimizing the AV delay in DDD pacemaker patients with high degree AV block: mitral valve doppler versus impedance cardiography. PACE 1997; 20: 2453-2462

Rajagopalan N, Suffoletto MS, Tanabe M, Miske G et al. Right ventricular function following cardiac resynchronization therapy. Am J Cardiol 2007; 100: 1434-1436


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine.