Electromechanical effects and optimization modalities of cardiac resynchronization therapy

Cinzia Valzania
Write on the sand
what you give,
write on the rock
what you receive

M. Lauritano
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Abstract

Background and aims
Heart failure is a major health care problem, with high morbidity and mortality rates. In recent years, cardiac resynchronization therapy (CRT) has become an established additive treatment for patients with advanced heart failure, left ventricular (LV) dysfunction, and wide QRS complex. CRT is a stimulation technique based on right ventricular (RV) and LV pacing, usually in synchrony, delivered by a pacemaker or a cardioverter-defibrillator. Significant improvements in heart failure symptoms, hospitalization rates and mortality have been documented after initiation of CRT treatment. However, to date, 20% to 30% of patients do not respond to CRT (non responders), and improved management strategies are important. This thesis explores the acute and long-term electromechanical effects of CRT at rest and during stress, and investigates novel methods for CRT optimization.

Study I
Twenty-one heart failure patients, responders to CRT, were assessed by low-dose dobutamine stress echocardiography, clinical evaluation and analysis of brain natriuretic peptide at two times: during active CRT (“on”) and after withholding of CRT for two weeks (“off”). Clinical, neurohormonal and echocardiographic results were compared between “on” and “off” conditions. This short-term cessation of CRT was associated with a deterioration of LV performance and a slight clinical impairment.

Conclusion: The beneficial effects of CRT on LV systolic and diastolic function, observed at rest, were sustained during dobutamine stress, and this was mainly owing to maintained improvement in inter- and intraventricular synchrony.

Study II
Twenty-two heart failure patients with idiopathic dilated cardiomyopathy (without any evidence of significant coronary artery disease at previous angiography), who had successfully responded to CRT, underwent echocardiographic assessment of left anterior descending coronary artery (LAD) flow and intraventricular dysynchrony during different pacing modes. Changes in LAD flow variables were correlated with simultaneous variations in intraventricular dysynchrony. The mean coronary flow velocity increased by comparison with intrinsic conduction during simultaneous biventricular pacing (p = 0.0063) and biventricular pacing with LV preactivation (p < 0.0001), and was higher in the latter programming mode (p = 0.027).

Conclusion: In patients with idiopathic dilated cardiomyopathy, simultaneous biventricular pacing and biventricular pacing with LV preactivation increase LAD flow, and this is associated with a reduction in intraventricular dysynchrony.

Study III
Long-term variations in atrioventricular (AV) and interventricular (VV) delays were prospectively investigated in 37 heart failure patients subjected to echo-guided CRT optimization. All patients underwent CRT optimization within 48 hours of implantation and again after 6 months. Additionally, optimization at 12 months was performed in the first 14 patients enrolled.

Conclusion: Echocardiographic optimization of AV and VV delays is associated with broad intraindividual variability. A new assessment of optimized VV delays during long-term follow-up reveals nonconcordance with previous values and provides a further increase in forward stroke volume.

Study IV
Twenty-four CRT patients were assessed both by echocardiography and by an automated intracardiac electrogram (IEGM) method with regard to optimal AV and VV delays. In addition, the acute impact of exercise CRT optimization on hemodynamic variables was investigated. Significant rest-to-exercise changes in optimal VV delay, but not in AV delay, were observed. Reassessment of optimal device programming during ongoing exercise resulted in an improvement in LV dyssynchrony and hemodynamic parameters, giving an additional benefit to that provided by optimization performed at rest.

Conclusion: The IEGM method seems to be a promising alternative to the standard echocardiographic approach, both at rest and during exercise.

Study V
Twelve heart failure patients were evaluated for acute changes in multiple vector intracardiac impedance (ICZ) signals during implantation of a CRT device operating in different pacing modes. Bipolar (Z1) and quadripolar (Z2) impedance signals, recorded in the RV and between the LV and RV, respectively, were analyzed with respect to amplitude and systolic slope, and correlated with noninvasive hemodynamic and echocardiographic variables. The Z1 and Z2 variables correlated positively with all noninvasive hemodynamic variables and LV and RV ejection fractions, and inversely with LV and RV volumes. The Z2 systolic slope correlated with the interventricular conduction delay (r = 0.33, p < 0.05).

Conclusion: Multiple vector ICZ measurement may be a feasible tool for hemodynamic assessment in patients treated with biventricular pacing.

Summary
In heart failure patients, CRT has been shown to improve symptoms, exercise capacity and survival. Our findings suggest that in long-term responders, the benefits of CRT on LV synchrony and function that are observed at rest are sustained during pharmacological stress, thereby providing a link between pathophysiological mechanisms and clinical evidence of improved exercise capacity. The finding of increased LAD flow during biventricular pacing highlights a possible additional mechanism responsible for the beneficial effects of CRT. CRT optimization has been shown to provide acute hemodynamic benefits. The dynamic changes in optimal AV and VV delays during long-term follow-up and from rest to exercise suggest that reevaluations of CRT programming may be useful. Novel automated device-based algorithms seem to be a feasible alternative to echocardiography for CRT optimization. Furthermore, multiple vector ICZ measurement may be a promising tool for hemodynamic assessment and optimization in CRT patients.

Keywords: Cardiac resynchronization therapy; coronary blood flow; dyssynchrony; echocardiography; exercise; heart failure; hemodynamics; intracardiac electrogram; intracardiac impedance; optimization.
List of Original Papers

This thesis is based on the following studies, which will be referred to by their Roman numerals

I
Electromechanical effects of cardiac resynchronization therapy during rest and stress in patients with heart failure.

II
Effects of cardiac resynchronization therapy on coronary blood flow: evaluation by transthoracic Doppler echocardiography.

III
Cardiac resynchronization therapy: variations in echo-guided optimized atrioventricular and interventricular delays during follow-up.

IV
Valzania C, Eriksson MJ, Boriani G, Gadler F.
Cardiac resynchronization therapy during rest and exercise: comparison of two optimization methods.

V
Valzania C, Eriksson MJ, Holmström N, Järverud K, Gadler F.
Feasibility of multiple vector impedance measurements during biventricular pacing.
*(Submitted)*
List of abbreviations

A  Atrial transmitral peak flow velocity
Am Late diastolic tissue velocity
AV Atrioventricular
BNP Brain Natriuretic Peptide
CBF Coronary Blood Flow
CFG Coronary Flow Gradient
CFV Coronary Flow Velocity
CO Cardiac Output
CRT Cardiac Resynchronization Therapy
CRT-D Cardiac Resynchronization Therapy device with Defibrillation capabilities
CRT-P Cardiac Resynchronization Therapy device with Pacing capabilities
DSE Dobutamine Stress Echocardiography
E Early transmitral peak flow velocity
Em Early diastolic tissue velocity
IC Intrinsic Conduction
ICZ Intracardiac impedance
IEGM Intracardiac Electrogram
IVCD Interventricular Conduction Delay
IVMD Interventricular Mechanical Delay
LA Left Atrium/Left Atrial
LAD Left Anterior Descending coronary artery
LBBB Left Bundle Branch Block
LV Left Ventricles/Left Ventricular
LV dp/dt Rate of systolic left ventricular pressure rise
LVEDD Left Ventricular End-Diastolic Diameter
LVEDV Left Ventricular End-Diastolic Volume
LVEF Left Ventricular Ejection Fraction
LVEDS Left Ventricular End-Systolic Diameter
LVESV Left Ventricular End-Systolic Volume
LVOT Left Ventricular Outflow Tract
MR Mitral Regurgitation
NYHA New York Heart Association classification
PEA Peak Endocardial Acceleration
PET Positron Emission Tomography
QoL Quality of Life
RCT Randomized Controlled Trial
RV Right Ventricle/Right Ventricular
RVEF Right Ventricular Ejection Fraction
Sm Peak systolic tissue velocity
TDI Tissue Doppler Imaging
Ts time interval measured from the start of the QRS complex to peak systolic tissue velocity
TVI Tissue Velocity Imaging
VTI Velocity Time Integral
VO₂ Volume of Oxygen
VV Interventricular
Introduction

Heart failure

Heart failure is a syndrome characterized by symptoms such as shortness of breath at rest or during exertion, and/or fatigue, signs of fluid retention like pulmonary congestion or ankle swelling, and objective evidence of an abnormality of the structure or function of the heart at rest (1). Congestive heart failure is a major health care problem, and its incidence approaches 10 per 1000 population older than 65 years (2). Congestive heart failure is associated with frequent hospital admissions and represents the most common hospital discharge diagnosis in patients older than 65 years (3). Despite developments in drug treatment, morbidity and mortality rates remain high (2).

About two-thirds of patients with symptomatic heart failure have left ventricular (LV) systolic dysfunction, with LV ejection fraction (LVEF) <50% (3). Chronic systolic heart failure is characterized by LV remodeling, defined as the dynamic process of progressive LV dilatation, deterioration in ventricular systolic function, and distortion of both LV shape and mitral apparatus geometry, resulting in mitral regurgitation (3). LV remodeling may be triggered by prolonged pressure or volume overload, loss of contracting myocytes caused by myocardial infarction, cardiotoxic agents, or genetically determined abnormalities in the sarcomeric contractile proteins (3).

One-quarter to one-third of patients with heart failure have left bundle branch block (LBBB) (4, 5), which is a marker of poor prognosis (5). In patients with LBBB, LV electrical depolarization is altered markedly, and proceeds from the anterior septum to the inferior and lateral LV walls (see Figure 1). As a result, the interventricular septum is activated before the lateral wall, and the dysynchronous LV activation induces an inefficient mechanical contraction. Intraventricular dyssynchrony refers to these differences in the timing of contraction between the different myocardial segments (6), and can be assessed by echocardiography, nuclear imaging or magnetic resonance imaging (7, 8).

These observations led to the concept that simultaneous pacing of both ventricles to resynchronize ventricular contraction (i.e., cardiac resynchronization therapy, CRT) might be beneficial in patients with heart failure and conduction disturbances (4, 7).

Cardiac resynchronization therapy

CRT is a stimulation technique based on right and LV pacing, usually in synchrony, delivered by a pacemaker (CRT-P) or a cardioverter-defibrillator (CRT-D) (9). LV stimulation is obtained by positioning a lead into the coronary sinus, preferably in a lateral or postero-lateral vein (7, 10, 11). The first experiences with CRT in humans were reported in the 1990s (12-19), and showed acute hemodynamic benefits, that were reflected in an increase in cardiac index and a reduction in pulmonary capillary wedge pressure, during synchronous ventricular (RV) and LV pacing in patients with severe drug-refractory congestive heart failure and widened QRS complex. With encouraging results of subsequent invasive hemodynamic (20, 21) and clinical studies (22-27), the use of CRT spread rapidly, and it is currently established firmly as a valuable additive treatment for patients with advanced chronic heart failure and electro-mechanical dyssynchrony (1, 9).

Pathophysiological mechanisms

Heart failure patients with dilated cardiomyopathy and ventricular conduction disturbance display an asynchronous electro-mechanical activation pattern (28). Myocardial segments contract in an untimely manner,
Figure 1. The Cardiac Conduction System and Biventricular Pacing. Panel A shows the anatomy of the conduction system. With normal conduction, the left and right ventricles are depolarized simultaneously, with consequent simultaneous contraction (Panel B). In Panel B, yellow areas are the sites of earliest depolarization, with successive regions of depolarization shown in orange, red, and pink. In the setting of left bundle branch block, the right ventricular free wall and the interventricular septum are depolarized rapidly (Panel C). There is a clinically significant delay in the depolarization of the left ventricular free wall. As a result, left ventricular contraction is dyssynchronous. In Panel C, the sites of earliest depolarization are yellow and are all in the right ventricle; successive regions of depolarization are shown in orange, red, pink, purple, and blue. With CRT, pacemaker leads are situated to stimulate both ventricles, thus bypassing the conduction block in the left bundle branch (Panel D). Simultaneous depolarization and simultaneous contraction of the ventricles is restored. In Panel D, the sites of early depolarizations are yellow and are near the tip of both pacemaker leads as well as in the branches of the normally conducting right bundle branch system. Successive regions of depolarization are shown in orange, red, pink, and purple. From Jarcho JA, N Engl J Med 2006. Copyright © [2006] Massachusetts Medical Society. All rights reserved.
CRT effects and optimization

proves LV systolic function and therefore reduces LV end-systolic volume (LVESV). This is consistent with the finding that CRT improves ejection fraction not by increasing the energy consumption of the heart (21) but by restoring a more homogeneous contraction pattern. Mitral regurgitation, caused by distortion of the mitral apparatus in the presence of intraventricular dyssynchrony, is reduced by synchronous LV contraction. This decreases left atrial pressure and consequently decreases LV end-diastolic pressure and volume (LVEDV). In addition CRT improves LV diastolic filling by reducing the isovolumetric contraction time, thus increasing stroke volume further. The reduction in interventricular dyssynchrony improves right RV cardiac output. The common results of these mechanisms (i.e., reverse remodeling) also improve intraventricular synchrony and reduce secondary mitral regurgitation, giving a positive feedback loop (32).

Clinical effects and response to CRT

Several randomized CRT trials (22, 24, 33-36) have reported improvement in clinical end-points (symptoms, exercise capacity,

![Figure 2](image)

Figure 2. Chest x-ray of a patient with a bi-ventricular device (CRT-D). Leads are positioned in the right atrium, right ventricular apex, and in a lateral branch of the coronary sinus.

with contraction in one segment resulting in pre-stretching of another segment (28). Previous studies have reported that CRT can restore a homogeneous contraction, and result in LV reverse remodeling by several mechanisms (29-32), as shown in Figure 3. The major underlying mechanism is a decrease in intraventricular dyssynchrony, which im-

![Figure 3](image)

Figure 3. Proposed mechanisms underlying the beneficial effects of CRT. CO: cardiac output; dp/dt: rate of systolic left ventricular pressure rise; EF: ejection fraction; LA: left atrial; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; MR: mitral regurgitation. Modified from Yu CM et al., Circulation 2002.
The long-term response to CRT has been assessed usually 3-6 months after implantation and according to clinical or echocardiographic variables (39). Improvement in New York Heart Association (NYHA) functional class of at least one, increase in LVEF ≥5%, or reduction in LVESV ≥15% are the criteria used most frequently to define the response to CRT (39). Despite encouraging results, to date 20-30%

Table 1. Major randomized trials of CRT.

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<td>Improvement in 6MWT, QOL, NYHA class, hospitalizations</td>
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<td>MUSTIC 2002</td>
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<td>6MWT</td>
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<td>MIRACLE 2002</td>
<td>Parallel arms RCT 6 months</td>
<td>6MWT NYHA class QOL</td>
<td>Improvement in 6MWT, QOL, NYHA class, LVEF, LVEDD, MR</td>
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<tr>
<td>CONTAK-CD 2003</td>
<td>Crossover, parallel RCT 6 months</td>
<td>6MWT NYHA class QOL</td>
<td>Improvement in 6MWT, QOL, NYHA class, LVEF, LV volumes</td>
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<td>MIRACLE-ICD 2003</td>
<td>Parallel arms RCT 6 months</td>
<td>6MWT NYHA class QOL</td>
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<td>PATH-CHF II 2003</td>
<td>Crossover 3 months</td>
<td>Peak VO₂</td>
<td>Improvement in Peak VO₂, 6MWT, QOL</td>
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<tr>
<td>COMPANION 2004</td>
<td>Parallel arms RCT 12 months</td>
<td>All cause mortality or hospitalization</td>
<td>Reduced all cause mortality / hospitalization</td>
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<tr>
<td>CARE-HF 2005</td>
<td>Open label RCT 29.4 months</td>
<td>All cause mortality</td>
<td>Reduced all cause mortality and morbidity</td>
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CARE-HF (38): Cardiac Resynchronization in Heart Failure; CONTAK-CD (35): CONTAK-Cardiac Defibrillator; COMPANION (37): Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure; LV: left ventricular; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; MIRACLE (22): Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD (36): Multicenter InSync Implantable Cardioverter Defibrillator trial; MR: mitral regurgitation; MUSTIC (26): Multisite Stimulation in Cardiomyopathies; NYHA: New York Heart Association; PATH-CHF: Pacing Therapies in Congestive Heart Failure trial I (34) and II (33); QOL: quality of life; RCT: randomized controlled trials; VO₂: volume of oxygen; 6MWT: 6-min walk test.
of patients do not respond to CRT, and the reasons are currently not known completely (39). Inappropriate patient selection or LV lead positioning, and suboptimal device programming, are considered responsible for the lack of response to CRT (40). Initially, reduction in interventricular dyssynchrony, as reflected by QRS duration, was considered the most important mechanism underlying response to CRT (8). However, studies have shown that intraventricular, not interventricular, dyssynchrony is a strong predictor of a positive response to CRT (41, 42). Accordingly, the QRS width, which reflects mainly interventricular dyssynchrony, has become questionable as a selection criterion (8). Several echocardiographic methods, such as M-mode echocardiography, tissue velocity imaging (TVI), strain imaging and 3-D echocardiography, as well as echocardiographic indexes, have been proposed for the assessment of intraventricular dyssynchrony (7, 8, 43). However, no large prospective trial has proved the clinical utility of any of these indexes (43). Moreover, the methodology to derive the proposed dyssynchrony indexes has not been standardized (43). Interest has therefore focused on novel criteria for pre-implant patient selection, based mainly on mechanical dyssynchrony assessment (8), together with appropriate follow-up and optimization of device programming, to improve the individual response to CRT.

**Indications for CRT**

Based on the available trials, current guidelines support the use of CRT in patients with severe heart failure (NYHA class III or IV), LVEF ≤35%, and wide a QRS complex (≥120 ms) (1, 9). Of note, the role of dyssynchrony in patient selection has not been validated yet. The PROSPECT trial showed a low feasibility and high interlaboratory variability of dyssynchrony variables, suggesting that no single echocardiographic measure of dyssynchrony can be recommended to improve patient selection for CRT beyond current guidelines (44). At present, the American Society of Echocardiography does not recommend that CRT should be withheld from patients who meet the standard criteria because of negative results of an echocardiographic dyssynchrony study (45).

**Technical considerations**

Access to an appropriate coronary sinus tributary may be problematic. The reported initial success rate increases from about 50% to almost 90% with experience (46). The anatomic characteristics of the coronary sinus system and the skill of the operator account for this variability. Complications include lead displacement (in 5-10% of cases), increase in pacing threshold, coronary sinus dissection, cardiac tamponade, phrenic nerve stimulation, and a variety of sensing problems (46).

The optimal site for LV stimulation varies between patients and depends on the individual electromechanical LV activation pattern (47). Optimal sites are found commonly in the distal part of the lateral or posterolateral coronary sinus veins (46). Placement of the LV lead in these sites leads to significant hemodynamic improvement (48), and a greater increase in LV function compared with the anterior coronary sinus location (49). This is consistent with the results of Ansalone et al. (50), suggesting that pacing the area of latest ventricular activation results in the best clinical response. Recent observations show that scar tissue in the region of the LV pacing lead results in CRT failure (51). Despite these observations, in clinical practice anatomic constraints require using less favorable coronary venous sites in almost one-third of patients (46).

To improve ventricular resynchronization, interest focused on the possible stimulation of multiple LV sites. The TRIP-HF trial (52) demonstrated that in heart failure patients, with permanent atrial fibrillation and indications for permanent pacing, the degree of LV reverse remodeling was greater when CRT was delivered by means of one
RV and two LV leads (3-V configuration), than when delivered by one RV lead and one LV lead (standard 2-V configuration). In the 3-V configuration, the first LV lead was positioned in a lateral or posterolateral vein, and the second LV lead was positioned as far as possible from the first, in the anterior vein, high anterolateral vein, or middle cardiac vein. Of note, the implant of two LV leads was successful in 85% of patients (52).

To date, little is known about whether RV lead positioning provides additional benefit to CRT (53, 54). In an acute hemodynamic study (54), RV high septum stimulation showed no overall advantage for RV apical pacing during biventricular pacing. However, at long-term follow-up, midseptal positioning of the RV lead appears to promote reverse LV remodeling more than apical RV lead positioning (53).

In acute hemodynamic and echocardiographic studies (13, 18, 21, 29), LV pacing alone has provided similar benefits to biventricular pacing, by reversing intraventricular dyssynchrony to the same extent. However, the effects of LV pacing alone at mid-term follow-up are still under investigation (55).

**Current issues in CRT**

Although a prolongation in QRS interval identifies patients who are likely to respond to CRT, up to 30% of heart failure patients with mechanical dyssynchrony on echocardiography have a narrow QRS complex (56). Whether these patients may benefit from CRT has been debated. Recently, the RethinQ study (57) showed no significant difference in peak oxygen consumption at 6 months follow-up between controls and heart failure patients with mechanical dyssynchrony and QRS width \( \leq 130 \) ms receiving CRT, suggesting that heart failure patients with narrow QRS width may not benefit from CRT.

Another current issue in patient selection is whether NYHA class I-II heart failure patients should be considered candidates for CRT (58). In the REVERSE study (59), CRT reduced the risk for heart failure hospitalization and improved ventricular structure and function in NYHA functional class II and NYHA functional class I patients with previous heart failure symptoms. Further conclusions are expected from the MADIT-CRT trial (60). Whether patients with standard indication for permanent right ventricular pacing may benefit from CRT is being assessed in the ongoing BioPace study (61).

Much interest has focused on how to identify potential responders to CRT before implantation, or turning nonresponders into responders during follow-up. Although the initial studies on intraventricular dyssynchrony, assessed by echocardiography, have given promising results in predicting CRT response (8, 41), the PROSPECT trial has raised concerns regarding the widespread use of current echo methodologies before implantation (44). Further randomized, prospective studies using more specific myocardial imaging criteria are needed to determine the value of these techniques in selecting patients who are likely to respond to CRT.

Finally, whether to use CRT-P or CRT-D systems in different subsets of patients is still debated (62, 63). However, current guidelines recommend CRT-D for patients who fulfill the standard indications for CRT and have expectancy of survival with a good functional status for more than 1 year (9).

**CRT optimization**

Patients undergoing CRT display heterogeneity in chronic heart failure etiology, electrical activation, and myocardial contraction. Contemporary CRT devices permit the programming of both the atrioventricular (AV) and interventricular (VV) delay, thus allowing for an individually tailored ventricular activation sequence (40, 64-68). This provides further acute benefits in terms of reduction in intraventricular dyssynchrony.
and increase in stroke volume (40, 64-68). Several techniques have been proposed to optimize CRT (Figure 4), such as echocardiography (65, 69, 70), surface electrocardiography (71, 72), digital plethysmography (73, 74), intrathoracic impedance (75-77), acoustic cardiography (78), radionuclide ventriculography (79), automated device algorithms (80-82), and invasive hemodynamics (83). Although there is no general consensus on the gold standard for CRT optimization, echocardiography is the most widely adopted method at present.

**AV and VV delay optimization by echocardiography**

In heart failure patients, the pulsed Doppler profile of the trans-mitral inflow may be characterized by a fusion of E and A waves, because of long PR intervals or delayed LV relaxation (40). Shortening the AV delay by pacing may result in E wave anticipation and prolongation of LV filling time. However, an excessive AV delay shortening may produce A wave truncation, and should be avoided (40). The aim of AV delay optimization is to improve diastolic filling, which will in turn increase ejection, and minimize the isovolumetric contraction (65). Several echocardiographic methods can be used to determine the optimal AV delay. These can be grouped into Doppler-derived mitral inflow methods and aortic flow methods (84). The first category includes the Ritter method, which is used to calculate the time from the ventricular paced deflection to mitral valve closure at both a long (160-200 ms) and a short (50-60 ms) AV delay. The optimal AV delay is determined as the difference between the two time intervals subtracted from the “long” AV delay (84). Another approach is based on the separation of the peak mitral E and A waves to maximize LV diastolic filling. In this method, mitral inflow components (i.e., LV filling time, E

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**Figure 4.** Available techniques for CRT optimization. PEA: peak endocardial acceleration. TDI: tissue Doppler imaging. VTI: velocity time integral. Modified from Burri H et al., Pacing Clin Electrophysiol 2006.
wave, A wave) are measured at various AV delays, usually ranging from 0 to 200 ms in 20 ms steps, and the optimal AV delay is chosen according to the longest LV filling time and the best separation between E and A waves (see Figure 5) (84). The aortic flow methods are based on measurements of the systolic aortic velocity time integral (VTI) by either pulsed Doppler in the LV outflow tract (LVOT) or continuous Doppler at the aortic valve. Aortic VTI is measured at different AV delays, and the optimal AV is chosen according to the highest VTI (Figure 6) (84).

The aim of VV delay optimization is to enhance interventricular dynamics and to reduce ventricular delays (65). The most widely adopted method of VV delay optimization is based on measuring the LVOT or aortic VTI by using pulsed or continuous Doppler, respectively (65). Different VV delays, ranging from –80 ms (LV pacing first) to +80 ms (RV pacing first), can be tested in steps of 10 or 20 ms, and the optimal VV is chosen according to the highest LVOT or aortic VTI (65). Tissue Doppler

**Figure 5.** AV delay optimization according to filling time measurement. Before CRT (top panel) there is a fusion of E and A waves. Various AV delays during CRT affect LV filling time and the separation between E and A waves (lower panels). Maximal separation between E and A waves is reached at shorter AV delays. From Waggoner A et al, Echocardiography 2008. Copyright © [2008]. All rights reserved.

**Figure 6.** AV delay optimization based on aortic velocity time integral (VTI) measurement. The optimal AV is chosen according to the highest aortic VTI. From Waggoner A et al. Echocardiography 2008. Copyright © [2008]. All rights reserved.
CRT effects and optimization

Imaging (TDI), deformation imaging, and three-dimensional echocardiography have been proposed as alternative techniques to optimize VV delay. In this approach, the optimal VV delay is chosen according to the lowest dyssynchrony index (65).

Acute and medium-term effects of CRT optimization

Several hemodynamic and echocardiographic studies have reported acute favorable effects of AV delay optimization compared with standard settings, in terms of increase in LV filling and systolic function (20, 85, 86). Further acute hemodynamic benefits, expressed by an improvement in LV dyssynchrony and systolic performance, have been documented after VV delay optimization (87-90).

However, few studies have evaluated the clinical effects of CRT optimization during long-term follow-up. In a non-randomized study, Mortensen et al. (70) showed no significant improvement in NYHA class and 6-min walking distance at 3-month follow-up in patients who were VV optimized compared with patients who were not. In the RHYTHM II ICD study (91), a single-blind, randomized trial of 121 recipients of a CRT-D device randomly assigned to simultaneous or optimized biventricular pacing, VV delay optimization conferred no additional clinical benefit at 6-month follow-up compared with simultaneous biventricular stimulation. The Insync III study (92) showed improved exercise capacity, but no change in functional status or quality of life, in patients with optimized CRT compared with patients from the MIRACLE trial receiving simultaneous pacing. A similar increase in 6-min walking distance following AV and VV optimization was found by Vidal et al. (93) in a prospective nonrandomized study with a mid-term follow-up. However, in the DECREASE-HF trial (94), optimized CRT did not have significant advantages over simultaneous biventricular pacing in terms of LV remodeling and systolic function at 6-month follow-up.

The evidence so far supports the idea that CRT optimization can provide acute hemodynamic benefits and has potential for improving at least the short-term clinical outcomes (65). However, studies to date have shown few long-term clinical benefits, possibly because of inadequate statistical power to detect changes or because of the techniques used for optimization (66).

Open issues in CRT optimization

It is still not known whether CRT optimization can impact not only acute hemodynamic variables, but also clinical outcome measures at long-term follow-up. It is also unknown whether CRT optimization can change non-responders into responders. Studies suggest that the optimal AV and VV delays may vary considerably over time (95, 96), which raises the question of how often optimization should be performed. Further data on repeated tailoring approaches could be helpful in deciding the optimal timing of CRT optimization.

Current techniques for CRT optimization are time consuming, have limited reproducibility and lack of a standard protocol and gold standard. Whether novel device-based automated algorithms may be helpful in CRT optimization is currently being evaluated and developed further (80, 82). Finally, CRT optimization is usually performed in a supine, resting patient. Studies have shown that exercise can induce dynamic changes in LV activation pattern (97, 98). Further knowledge about optimal CRT programming in different body positions or during exercise is needed to improve the response to CRT.
The main purpose of this thesis was to evaluate further the electromechanical effects of CRT, at rest and during stress, and to investigate novel techniques for CRT optimization. The specific aims were:

- To study the electromechanical effects of CRT at rest and during pharmacological stress, during both active and withheld CRT.

- To investigate changes in regional coronary blood flow (CBF) under different CRT pacing modes by means of transthoracic Doppler echocardiography.

- To investigate prospectively the long-term variations in optimal CRT programming, as assessed by echocardiography.

- To assess rest-exercise variations in optimal CRT programming, assessed by both echocardiography and a device-based algorithm, and to evaluate the impact on acute hemodynamic variables of CRT optimization performed during exercise.

- To evaluate whether intracardiac impedance (ICZ) can be used to monitor hemodynamic variations in CRT patients, and to investigate acute changes in multiple vector ICZ signals during different CRT pacing modes.
Methods

Patient selection
The study population comprised heart failure patients who had been implanted with a CRT device between 2000 and 2007 at the Karolinska University Hospital (studies I, II, IV, V). CRT patients from study III had been implanted at the Institute of Cardiology of the University of Bologna. The initial indication for CRT was drug-refractory NYHA class III or IV heart failure, wide QRS complexes (≥120 ms) and low LVEF (≤35%).

More specifically, the study population for each study comprised the following groups. Study I included 21 consecutive heart failure patients implanted with a CRT device between 2000 and 2003. The inclusion criterion was successful response to CRT, defined as any improvement in functional class, walking distance, and quality of life after 6 months of CRT.

Study II included 22 consecutive heart failure patients implanted with a CRT device between 2003 and 2006. Inclusion criteria were idiopathic dilated cardiomyopathy (without any evidence of significant coronary artery disease at a previous angiography) and a successful response to CRT after at least 3 months. As in study I, a positive response to CRT was defined as an improvement in functional class, by at least one class, and any improvement in exercise tolerance.

Study III included 37 consecutive heart failure patients implanted with a CRT device between 2002 and 2006 at the Institute of Cardiology of the University of Bologna. Study IV included 24 consecutive heart failure patients implanted specifically with a St. Jude Medical CRT defibrillator (St. Paul, MN, USA) between 2003 and 2007. Exclusion criteria from the study were: complete AV block, atrial fibrillation, suboptimal echocardiographic images, and inability to perform supine exercise echocardiography.

Study V included 12 heart failure patients implanted with a CRT device between 2006 and 2007.

An overview of the distribution of patients is shown in Figure 7. There was a slight overlap of populations between studies II and IV (n = 6).

Figure 7. Distribution of patients among the studies.
Study design

In study I patients were evaluated twice: during active biventricular pacing (CRT ON) and (2) after biventricular pacing had been switched off for 2 weeks (CRT OFF). On both occasions, patients were assessed by dobutamine stress echocardiography, clinical evaluation, and measurement of brain natriuretic peptide concentration. The clinical, neurohormonal, and echocardiographic response to CRT (at rest and during dobutamine stress) was compared between the “on” and “off” conditions (see Figure 8).

In study II patients underwent an echocardiographic assessment of the left anterior descending coronary artery (LAD) flow and intraventricular dyssynchrony (by TVI) during four pacing conditions: intrinsic conduction (IC), RV pacing, simultaneous biventricular pacing, and biventricular pacing with LV preactivation. Changes in LAD flow variables were correlated with simultaneous variations in intraventricular dyssynchrony.

In study III, the study protocol was based on echocardiographic optimization of AV and VV delays within 48 hours of implantation, which was then repeated during the follow-up. At each time, a standard echocardiographic assessment of LV volumes and LVEF was performed.

In study IV, all patients first underwent AV and VV delay optimization using echocardiography and a novel automated intracardiac electrogram (IEGM) method (80) under resting conditions (see Figure 9). The patients then performed two consecutive supine exercise tests (exercises A and B) on a bicycle ergometer with the capacity for left lateral tilt (Ergoline GmbH & Co KG, Bitz, Germany). The workload was kept constant at 30 W during the test. Each exercise was performed during spontaneous rhythm until a steady 20-beat increase in heart rate was achieved. Thereafter, AV and VV delay optimization was performed using the IEGM (exercise A) or the echocardiogram method (exercise B) in a random order.

In study V, ICZ signals were recorded between the RV and LV leads in 12 patients during implantation of a biventricular device. At the same time, intracavitatory ventricular electrograms were recorded, and hemodynamic parameters (stroke volume, cardiac output, pulse pressure) were recorded non-

Figure 8. Design of study I: for explanations, see the text. DSE: Dobutamine stress echocardiography; BNP: brain natriuretic peptide; QoL: quality of life; MWT: 6 min walk test.
invasively with a plethysmographic blood pressure monitor (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands) (99). Within 1 week from implantation, all patients underwent a postoperative echocardiographic evaluation of ventricular dimensions and function. All variables were assessed during four programming modes: (1) IC, (2) RV synchronous LV pacing, (3) LV stimulation, (4) RV stimulation. Variations in ICZ variables were correlated with the noninvasive hemodynamic and echocardiographic variables.

**CRT implantation**

CRT implantation was performed according to the standard technique for biventricular stimulation (15) as follows: one transvenous pacing lead was positioned in the right atrium and another in the RV apex or in a mid-septal position. A coronary sinus lead was also inserted in a lateral or postero-lateral coronary sinus tributary. Patients were implanted with either a CRT-P or a CRT-D device. During the study period, the value of primary preventive defibrillation therapy was established and influenced the clinical practice (63). Hence, the percentage of implanted CRT-D systems increased in the latest years of the study period. The pacing lead configuration was similar in both CRT-P and CRT-D, except for the RV lead, which was positioned preferably in the RV apex in the CRT-D system, and in a septal position in the CRT-P system. Lower and maximal heart rates of CRT devices were programmed based on clinical considerations. After discharge, patients underwent a regular clinical follow-up and periodic controls of the device system.

**Echocardiography**

In study I, standard transthoracic Doppler echocardiography was performed using a 2.5 MHz transducer (System V, Vingmed A/S, Horten, Norway). In studies II, IV, and V, a Vivid 7 system (Vingmed-General Electric, Horten, Norway), equipped with a phased array 3.5 MHz transducer (Doppler frequency, 5.0–3.5 MHz), was used. Acquisitions were stored digitally on a dedicated server and analyzed off-line using EchoPAC software (GE EchoPAC, version 5.1.0, Horten Norway). In study III, echocardiography was performed with a Sonos 5500 (Philips, Andover, MA, USA), using a second harmonic mode (1.8-3.6 MHz), and images were analyzed online.
**Dobutamine stress echocardiography: study protocol**

In study I, after resting images had been acquired, dobutamine infusion was given at 5 µg/kg/min for 3 min and then increased to 10 µg/kg/min for an additional 5 min before the acquisition of stress images was started. Echocardiography sequences were carried out in the same order, both at rest and after dobutamine infusion, and included parasternal long- and short-axis and apical four- and two-chamber views.

LV diameters were determined from two-dimensional images of the parasternal long axis view. From the apical four-chamber view, LVEDV and LVESV were calculated according to Simpson's equation, and LVEF was derived (100). The degree of mitral regurgitation was expressed according to a 0-4 score with steps of 0.5, based on the percentage jet area relative to the left atrial size in the apical four-chamber view (101). The rate of systolic LV pressure rise (LV dp/dt) was determined from the continuous wave Doppler mitral regurgitation velocity curve (102). Pulsed Doppler echocardiography was used to assess the transmitral and transaortic flow velocities.

Interventricular dyssynchrony was expressed by the interventricular mechanical delay (IVMD), calculated as the difference between the aortic and pulmonary pre ejection times (41, 103), measured from the QRS onset to the start of Doppler flow in the aortic and pulmonary outflow tracts, respectively. Intraventricular dyssynchrony was evaluated by pulsed TDI, by placing the Doppler sample volume at the basal level of the LV lateral, septal, anterior, and inferior walls. Peak tissue velocities during systolic contraction (Sm), early diastolic (Em), and late diastolic filling (Am) were measured as the average value from these four locations. For each wall, regional electromechanical delays were expressed as the time to peak Sm (Ts), measured from the QRS onset to Sm peak (41, 103). Intraventricular dyssynchrony was expressed as the septal-to-lateral delay, calculated as the difference between Ts of the septum and lateral wall (41), and as the maximal intra-LV electromechanical delay, defined as the time difference between the shortest and longest electromechanical delays among the four LV walls (104).

The intraobserver variability, expressed by the coefficient of variation between two series of separate measurements, was 2.1% for the LV filling time, 5.0% for the IVMD, and 6.2% for the LVEF.

**Coronary flow imaging**

In study II, CBF was measured in the mid portion of the LAD, which was identified using color Doppler in a modified apical short- axis view (see Figure10), by moving the transducer cranially and towards the sternum (105, 106). The Nyquist limit was set to 18 cm/s. From the short axis view, the image plane was rotated 90 degrees to a long-axis view of the LAD in the coronary colour Doppler application. The angle between the mid-LAD and the Doppler beam was kept to a minimum during the recording and typically did not exceed 30 degrees during flow measurement. No angle correction was made during recording. The flow profile in the mid-LAD was recorded using standard pulsed Doppler technique, which confirmed the typical predominantly diastolic velocity profile in the mid-LAD. The sample volume was set to 3 mm for the recordings and was kept in the same position throughout the recordings, when changing pacing modalities. Peak coronary flow velocity (CFV) and gradient (CFG), mean CFV and CFG, coronary VTI, and diastolic flow slope were measured in the post-processing analysis. For each cardiac beat, the time of coronary flow was measured and the ratio between time of coronary flow and RR interval was calculated. The mean value of three cardiac cycles was taken for each variable at different pacing modalities. The intraobserver variability,
All patients from studies I-III underwent AV and VV delay optimization at rest immediately after implantation. In study III, optimization was repeated at 6 and 12 months. In study IV, CRT optimization was performed during exercise after 10 ± 2 months from implantation. In all patients, AV and VV delays were optimized by echocardiography. Additionally, in study IV optimization was performed with an automated electrogram-based algorithm, and the results were compared with those suggested by the echocardiographic method.

**Echocardiographic optimization**

AV delay optimization was performed according to the Doppler mitral inflow method in studies I and III, and according to the Ritter formula in study II. In study IV, AV delay was optimized by pulsed Doppler analysis of LVOT VTI. In both the mitral inflow and in the LVOT VTI method, AV delay optimization was performed during atrial-triggered simultaneous biventricular pacing. AV delays were analyzed between 60 and 200 ms (study III), or between 80 and 180 ms (study IV), using a stepwise protocol. In the mitral inflow method, based on pulsed Doppler analysis of the transmitial flow, the AV delay that provided the longest LV filling time and best
separation between the E and A waves, without interruption of the A wave, was chosen as optimal (84). In the LVOT VTI method, based on pulsed Doppler analysis of the aortic flow velocities in the LVOT, optimal AV delay was chosen according to the maximum aortic flow (65). The offset between atrial-sensed and paced AV delays was set at 30 ms (studies I-III) or 50 ms (study IV).

VV delay optimization was performed in studies II-IV. In all patients, VV delay was optimized after AV delay programming. We analyzed VV intervals ranging from −80 ms (LV pacing first) to +80 ms (RV pacing first) (study III), or from −40 ms to +40 ms (studies II-IV), using a stepwise protocol. VV timing was optimized by measuring the aortic VTI by continuous (study III) or pulsed (studies II-IV) Doppler analysis of the transaortic flow, and optimal VV delay was determined by the highest value of aortic VTI.

During both AV and VV optimization, three consecutive cardiac cycles were analyzed for each parameter, and the average value was taken. Intraobserver and interobserver variability, expressed as the coefficient of

Figure 11: Peak systolic velocities of the septum and lateral wall by Tissue Velocity Imaging. The septal-to-lateral delay was calculated as the difference between time to peak velocity of the septum and lateral wall. A before and B after CRT optimization.
variation (%) between two assessments, were 2.9 % and 4.0% for AV delay and 5.7 % and 6.6% for VV delay, respectively.

**Intracardiac electrogram optimization**

IEGM optimization was performed using an automated programmer algorithm that calculates the optimal AV and then the VV delays from measurements performed during specific sensing and pacing tests (QuickOpt™, St. Jude Medical) (80, 108). In synthesis, mitral valve closure is estimated by measuring the interatrial conduction time (P wave duration). The IEGM P wave duration represents the sum of right and left atrial activation. The algorithm uses this measurement to calculate the optimal sensed and paced AV delays, with the goal of maximizing preload and allowing for proper timing of mitral valve closure. For VV delay optimization, paced and sensed tests are performed to characterize the conduction properties of the ventricles. The onset of isovolumic contraction is measured using the peak of the R wave. Interventricular conduction delays are calculated by evaluating simultaneous RV and LV IEGMs and measuring the time between the peaks of the R waves. The goal is to time the right and left ventricular activation so that the paced wave fronts can resynchronize ventricular contraction.

In more detail, to achieve AV delay optimization, the algorithm measures the width of the atrial intrinsic depolarization and adds an offset factor of 30 ms if the intrinsic depolarization is ≥ 100 ms, or 60 ms if the intrinsic depolarization is < 100 ms. The offset factor makes it possible to deliver ventricular pacing after the completion of atrial electrical activation and mechanical contraction. Paced AV delay is calculated as the sum of the sensed AV delay and the pacing latency (50 ms). The VV delay algorithm includes two components: the conduction delay (Δ) and the correction term (ε). Δ is the difference between the time of peak intrinsic activation on the LV lead (R_{LV}) and the RV lead (R_{RV}) [Δ = R_{LV} – R_{RV}]. The correction term ε is the difference in the interventricular conduction delay (IVCD) between two ventricular paced propagation waveform time delays. IVCD’RL is the interventricular conduction delay when the RV lead is paced and the delay is sensed at the LV lead. IVCD’LR is the interventricular conduction delay when the LV lead is paced and the delay is sensed at the RV lead. During the test, each chamber is paced with a short AV delay to ensure the absence of fusion. The correction term equation is ε = IVCD’LR – IVCD’RL. The IEGM optimal VV delay is calculated as (VV) = 0.5(Δ + ε). If VV >0, the LV is activated first; if VV <0, the RV is activated first.

The reproducibility of the IEGM method, calculated in 10 patients and expressed as the coefficient of variation (%) between two separate measurements, was good for all parameters (3.3% for AV delay; 6.5% for VV delay).

**Intracardiac impedance measurement**

ICZ signals between ventricular lead electrodes were collected by an external research device (St. Jude Medical). Two ICZ vectors were studied (see Figure 12): (1) a bipolar impedance vector between the RV ring and RV tip (Z1), and (2) a quadripolar impedance vector between the LV and RV lead electrodes (Z2). The Z1 impedance signal was measured as the voltage between the tip and ring electrodes on the bipolar RV lead, with excitation current applied between the same electrodes. The Z2 impedance signal was measured as the voltage between the RV ring and LV tip electrodes, with excitation current applied between the RV tip electrode and pacemaker case. The impedance equipment was implemented in analogue technique, using a 4 kHz square wave current injection with the amplitude of 10 µA. To calculate peak-to-peak (p2p) amplitude and slope, the voltage response signal was filtered and amplified to create an impedance signal.
with bandwidth 0.25-50 Hz. To calculate the average amplitude, the signal was low-pass filtered with bandwidth DC-180 Hz. From the impedance signals delivered over each vector configuration, the following variables were calculated (see Figure 13): (1) average amplitude, which is the median impedance; (2) p2p amplitude calculated as the difference between the maximum and minimum values of ICZ during systole; and (3) systolic slope, which is the maximum rate of change of the impedance signal during systole. ICZ signals were recorded, and variables averaged, over at least 60 heart cycles for each pacing mode.

Statistics

Normally distributed continuous variables are presented as mean±1 standard deviation. Differences between means were tested for significance using the $t$ test. One-way repeated-measures analysis of variance (ANOVA) was used to compare more than two groups. If the $F$-ratio was significant,
post-hoc contrasts between mean values were then performed. In paper II, the Cochran Q test was used to test whether there was a systematic difference between the pacing modes for the variable “synchrony” (yes/no). When the distribution of some variables was positively skewed, log-transformation was performed before the analyses (studies II and IV). In paper V, to compare the effect of different pacing modalities in the study population, ICZ signals were normalized in each patient and presented as both absolute values and percent changes. Relations between continuous variables were assessed using the Pearson correlation coefficient. Spearman rank correlation coefficient was calculated for continuous variables that were not normally distributed (study IV); p<0.05 was considered significant.

In study III, analysis of variance for nonparametric data (Friedman test) and the Student-Newman-Keuls test for multiple comparisons were performed to compare pacemaker parameters (AV and VV delay) at baseline, and at 6 and 12 months. Weighted-Kappa with quadratic weights was used to assess the agreement of non-continuous pacemaker parameters between subsequent follow-up evaluations (study III), between rest and exercise (study IV), and between echocardiographic and IEGM assessments (study IV).

Statistical analyses were performed using Mixed Model Analyses in SAS® (studies I, II, IV, and V), or the SPSS statistical package (version 12.0, Chicago, IL, USA) and Primer of Biostatistics (study III).

**Ethical considerations**

The investigations conformed to the principles outlined in the Declaration of Helsinki. The study protocols were approved by the Ethics Committee of the Karolinska University Hospital. Study III was approved by the Ethics Committee of the Policlinico S. Orsola-Malpighi, University of Bologna. All patients provided written informed consent to participate.
Results

Study I
In this study the electromechanical effects of CRT at rest and during low-dose dobutamine stress were evaluated both during active CRT (“on”) and 2 weeks after treatment cessation (“off”). Twenty-one patients (62±12 yr), who had been treated successfully with CRT for at least 6 months, were enrolled. Heart failure etiology was ischemic in 13 (62%) patients. At the time of enrollment, mean LVEF was 33±7%. There was a slight clinical deterioration from “on” to “off”, reflected in a significant decrease in walking distance (p=0.004), a trend towards impaired quality of life, and an increase in brain natriuretic peptide (p=0.06). Dobutamine stress echocardiography was well tolerated by all the patients. The main results are presented in Table 2.

Echocardiographic changes at rest during CRT “on” and “off”
The withdrawal of biventricular pacing was associated with an increase both in

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<th>Table 2. LV function and synchrony variables during rest and dobutamine stress with CRT “on” and “off”.</th>
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<td>CRT on</td>
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<tr>
<td>Rest</td>
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<td>LVEDD (mm)</td>
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<td>LVESD (mm)</td>
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<td>LVEF (%)</td>
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<td>Aortic VTI (cm)</td>
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<td>MR degree (cm²)</td>
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<td>LV dp/dt (mmHg/s)</td>
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<td>LV filling time (ms)</td>
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<td>IVMD (ms)</td>
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<td>Septal-to-lateral delay (ms)</td>
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<td>Maximal intra-LV electromechanical delay (ms)</td>
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<td>Blood pressure (mmHg)</td>
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<td>Heart rate (bpm)</td>
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* = p < 0.05 vs. rest “on”; † = p < 0.05 vs. rest “off”; # = p < 0.05 vs. stress “on”. LVEDD: left ventricular end-diastolic diameter. LVESD: left ventricular end-systolic diameter. LVEF: left ventricular ejection fraction. VTI: velocity time integral. MR: mitral regurgitation. LV: left ventricle. LV dp/dt: rate of systolic LV pressure rise. IVMD: interventricular mechanical delay.
interventricular dyssynchrony, expressed as IVMD (p<0.001), and in intraventricular dyssynchrony, expressed as septal-to-lateral delay (p=0.01) and maximal intra-LV electromechanical delay (p=0.007). The loss of intraventricular synchrony during “off” was associated with a reduced LV systolic performance, reflected in decreases in LVEF, aortic VTI, and LV dp/dt, and an increase in LV dimensions (p<0.05). With regards to diastolic function, a decrease in LV filling time was observed after 2 weeks of inactive CRT (p=0.03).

Echocardiographic changes during dobutamine stress with CRT “on” and “off”

Low-dose dobutamine infusion induced a small but significant increase in heart rate and systolic blood pressure, resulting in an increase in the rate-pressure product by 34% and 31% during “on” and “off”, respectively. In the “on” stage, IVMD, septal-to-lateral delay, and the maximal intra-LV electromechanical delay were low at rest and remained unchanged after dobutamine infusion, suggesting the persistence of inter- and intraventricular synchrony during stress. In contrast, during “off”, inter- and intraventricular dyssynchrony variables remained prolonged during stress. Dobutamine infusion was associated with an increase in LV systolic function during both “on” and “off”. Although the functional parameters changed to a similar extent from rest to stress during both conditions, peak values of LV dp/dt and aortic VTI were lower during stress at “off” compared with “on”. Accordingly, trends toward lower LVEF (p=0.09) and LV filling time (p<0.05) were observed during stress at “off”.

Conclusions

Temporary cessation of CRT was associated with deterioration in LV performance and a slight clinical impairment. The beneficial effects of CRT on LV systolic and diastolic function, observed at rest, were sustained during low-dose dobutamine stress, mainly because of maintained improvement in inter- and intraventricular synchrony.

Study II

In this study we investigated regional changes in LAD coronary flow under different CRT pacing modes using transthoracic Doppler echocardiography. Twenty-two consecutive patients (67±11 yr) with idiopathic dilated cardiomyopathy, who had been treated successfully with CRT for at least 3 months, were recruited for the study. Significant coronary artery disease had been ruled out by angiography in all patients. At the enrollment, mean LVEF was 36±9%. All patients were in sinus rhythm, except for three who had absent intrinsic conduction due to advanced AV block.

Coronary flow variables

As shown in Figure 14, mean CFV increased vs. IC during simultaneous biventricular pacing (p=0.0063) and biventricular pacing with LV pre-activation (p<0.0001), and was higher in the latter programming mode (p=0.027). The same trend was observed for mean CFG. Peak CFV and CFG were higher during biventricular pacing with LV pre-activation than during the other programming modes. An increase in LAD flow VTI was observed during simultaneous biventricular pacing and biventricular pacing with LV pre-activation, but reached statistical significance vs. IC only in the latter programming modality (p=0.0005). No significant changes in coronary flow slope or time of coronary flow were observed. The intra observer variability for CBF variables was <10%. Figure 15 shows an example of the improvement in LAD flow, assessed by pulsed Doppler ultrasound, during simultaneous biventricular pacing and biventricular pacing with LV pre-activation, compared with IC and RV pacing.
Figure 14. Variations in mean and peak values of coronary flow velocity (CFV) and gradient (CFG) during different pacing programming modalities. IC: intrinsic conduction. BIV 0 ms: simultaneous biventricular pacing. BIV LV 40 ms: biventricular pacing with 40 ms left ventricular pre-activation. RV: right ventricular pacing.

Figure 15. Pulsed Doppler ultrasound of the left anterior descending (LAD) coronary artery during different pacing modes in a patient with idiopathic dilated cardiomyopathy, implanted with a CRT device. An improvement in LAD flow can be observed during simultaneous biventricular pacing and biventricular pacing with LV pre-activation (lower panels). For abbreviations see Figure 14.
**Tissue Velocity Imaging variables**

As reported in Figure 16, intraventricular dyssynchrony, expressed as septal-to-lateral delay, decreased significantly during simultaneous biventricular pacing and biventricular pacing with LV pre-activation. Using a septal-to-lateral delay ≥65 ms as an indicator of intraventricular dyssynchrony (41), 16 patients (94%) were dyssynchronous during IC, 15 (88%) during RV pacing, and 3 (18%) during both simultaneous biventricular pacing and biventricular pacing with LV pre-activation ($p<0.05$, Cochran Q Test). There was a significant inverse correlation between the percentage increase in coronary VTI and the percentage decrease in septal-to-lateral delay during biventricular pacing with LV pre-activation ($r=-0.48$; $p=0.04$). A similar trend, although not significant, was found during simultaneous biventricular pacing ($r=-0.38$; $p=0.12$). Peak systolic velocity in the basal septum was significantly higher during simultaneous biventricular pacing and biventricular pacing with LV pre-activation than during IC ($p=0.026$ and $p=0.001$, respectively). Post systolic velocity in the basal septum was observed in 9 patients (53%) during IC, and decreased significantly after switching to simultaneous biventricular pacing and biventricular pacing with LV pre-activation ($p=0.0018$).

**Conclusions**

In patients with idiopathic dilated cardiomyopathy, simultaneous biventricular pacing and biventricular pacing with LV pre-activation increased regional LAD blood flow, and this increase was associated with a reduction in intraventricular dyssynchrony.

**Study III**

In this study we prospectively investigated long-term variations in AV and VV delays in patients receiving echo-guided optimization of CRT programming. Thirty-seven consecutive heart failure patients (median age, 66 yr, range, 15 yr) were included in the study. Heart failure was caused by idiopathic dilated cardiomyopathy in 22 (59%) patients and ischemic cardiomyopathy in the other 15 (41%). All patients underwent an echocardiographic optimization within 48 hours from CRT implantation and after 6 months. Additionally, optimization at 12 months was performed in the first enrolled 14 patients.

**AV delay variations**

In all enrolled patients no difference in optimal AV delay was observed between baseline and 6 months: median (range) values were 100 ms (45 ms) vs. 100 ms (40 ms) ($p=0.08$).
Among the 14 consecutive patients with available 12-month follow-up data, an overall reduction in median AV delay became evident at 12 months: 85 ms (23 ms) vs. 115 ms (38 ms) at baseline (p<0.05).

**VV delay variations**

At implant, the optimal VV interval was achieved by simultaneous biventricular pacing in 4 (11%) patients, LV followed by RV pacing in 17 (46%) patients, and RV followed by LV pacing in 16 (43%) patients. At 6 months, echocardiographic optimization led to a change (compared with baseline) of at least one step (10 ms) in VV delay programming in 29 (78%) patients; variations ≥ 40 ms were observed in 15 (41%) patients. At 12 months, all 14 patients exhibited changes (compared with baseline) in VV delay programming; variations ≥ 40 ms were observed in 8 (57%) patients vs. 6 months, and in 11 (79%) patients vs. baseline. A non concordance of optimized VV delays was found between each subsequent assessment (Kappa test = 0.23 between baseline and 6 months, 0.04 between 6 and 12 months, and −0.22 between baseline and 12 months). VV delay optimization was associated with increases in aortic VTI at all three time points (+9%, +13%, and +12% vs. simultaneous biventricular pacing at baseline, 6 months, and 12 months, respectively).

**LV reverse remodeling**

In all enrolled patients, a trend towards a decrease in LVESV (p=0.06) and an improvement in LVEF (from 25%, range 13%, to 28%, range 11%; p=0.002) were observed at 6 months. In the patients with available long-term follow-up data, a reduction in both LVEDV and LVESV was evident at 12 months. Median LVEF values at 12 months were 35% (22%) compared with 26% (8%) at baseline (p=0.14).

**Conclusions**

Echocardiographic optimization of AV and VV delays was associated with broad intra-individual variability during follow-up. A new assessment of optimized VV delays during long-term follow up revealed a non concordance with previous values and increased the forward stroke volume.

**Study IV**

In this study we investigated the effects of exercise on optimal AV and VV delays, assessed by both echocardiography and an automated IEGM method. We also sought to evaluate the acute impact of exercise CRT optimization on hemodynamic variables. A total of 63 patients were screened for the study. Thirty-nine patients were not enrolled because of atrial fibrillation (n = 11), complete AV block (n = 5), inability to perform an exercise test (n = 10), suboptimal echocardiographic images (n = 5), and refusal to participate in the study (n = 8). The remaining 24 patients were included in the study. Heart failure etiology was ischemic in 58% of patients. At the enrollment, the mean time of CRT treatment was 10±2 months.

**Echocardiogram and intracardiac electrogram optimization of AV and VV delay at rest and during exercise**

Optimized AV and VV delays, according to the echocardiogram and IEGM methods, and agreement between the two methods, expressed as Kappa values, are presented in Table 3. The optimal AV delay at rest, as assessed by echocardiography, was 140 ms (range, 120 to 155 ms). No significant difference in AV delay was observed between rest and exercise (p=0.26). Median VV delay at rest was 0 ms: the optimal pacing configuration was achieved by simultaneous biventricular pacing in 17 patients (71%), by LV pre-activation in 5 patients (21%), and by RV pre-activation in 2 patients (8%). Exercise induced a change in VV delay programming in 14 patients (58%). Rest-exercise variations in optimal VV delay ranged from 20 to 60 ms, with a median of 20 ms. We found no concordance between rest
CRT effects and optimization

and exercise optimal VV delays (Weighted Kappa = -0.05). Results from the IEGM optimization were consistent with those from the echo optimization. In particular, no significant changes in AV delay were observed between rest and exercise (p=0.43), whereas VV delay programming changed during exercise in 13 patients (54%). A substantial agreement in deriving optimized AV delays was observed between the echocardiogram and the IEGM method, both at rest and during exercise. The agreement in optimizing VV delay between the two methods was fair at rest and became stronger during exercise.

Effects of exercise CRT optimization on left ventricular dyssynchrony and aortic flow

During exercise, median (range) septal-to-lateral delay during spontaneous rhythm was 30 ms (13-60 ms). The delay was further decreased to 18 ms (10-22 ms) by exercise IEGM optimization (p=0.036), and was reduced to a similar extent by the echocardiographic optimization (p=0.007 vs. spontaneous rhythm; p=0.56 vs. IEGM). A significant correlation was found between septal-to-lateral delay measured after the IEGM and the echocardiographic optimization (r = 0.61; p = 0.001). Exercise was associated with an increase in LVOT VTI during spontaneous rhythm (from a median of 13.7 cm, range 11.5-17.9 cm, to 16.0 cm, range 13.2-20.0 cm, p<0.0001). Biventricular pacing with the IEGM optimal setting improved LVOT VTI to 17.1 cm, range 13.7-21.8 cm (p<0.0001). A similar increase was induced by the echocardiographic optimization (p<0.0001 vs. spontaneous rhythm; p=0.06 vs. IEGM). A strong linear relationship was found between LVOT VTI measured after the IEGM and the echocardiographic optimization (r = 0.99; p<0.001). Reassessment of the optimal AV/VV configuration during exercise by echocardiography was more effective on LVOT VTI than maintaining the same pacing configuration as at rest (median 17.1 cm, range 13.6-21.6 cm, vs. 16.5 cm, range 13.5-20.8 cm, p<0.001). Similar results were found with the IEGM method.

Conclusions

Significant rest-exercise changes in optimal VV delay, but not in AV delay, were observed in heart failure patients undergoing CRT optimization according to both the echocardo-

Table 3. Echocardiogram and intracardiac electrogram (IEGM) optimized delay values

<table>
<thead>
<tr>
<th></th>
<th>Echo Median (P25 - P75) (ms)</th>
<th>IEGM Median (P25 - P75) (ms)</th>
<th>Weighted Kappa (95% CI)</th>
<th>Echo vs. IEGM</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV delay (ms)</td>
<td>rest 140 (120 – 155)</td>
<td>130 (100 – 140)</td>
<td>0.55</td>
<td>(0.31, 0.79)</td>
</tr>
<tr>
<td></td>
<td>135 ± 28</td>
<td>124 ± 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>exercise 125 (100 – 140)</td>
<td>130 (100 – 140)</td>
<td>0.64</td>
<td>(0.36, 0.92)</td>
</tr>
<tr>
<td></td>
<td>128 ± 23</td>
<td>126 ± 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VV delay (ms)</td>
<td>rest 0 (0 – 0)</td>
<td>0 (-20 to 10)</td>
<td>0.38</td>
<td>(-0.22, 1.0)</td>
</tr>
<tr>
<td></td>
<td>-6 ± 18</td>
<td>-6 ± 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>exercise 0 (-10 to 0)</td>
<td>0 (-18 to 10)</td>
<td>0.71</td>
<td>(0.53, 0.89)</td>
</tr>
<tr>
<td></td>
<td>-3 ± 15</td>
<td>-1 ± 15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AV = atrioventricular; echo = echocardiogram; IEGM = intracardiac electrogram; VV = interventricular.

and exercise optimal VV delays (Weighted Kappa = -0.05). Results from the IEGM optimization were consistent with those from the echo optimization. In particular, no significant changes in AV delay were observed between rest and exercise (p=0.43), whereas VV delay programming changed during exercise in 13 patients (54%). A substantial agreement in deriving optimized AV delays was observed between the echocardiogram and the IEGM method, both at rest and during exercise. The agreement in optimizing VV delay between the two methods was fair at rest and became stronger during exercise.

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Conclusions

Significant rest-exercise changes in optimal VV delay, but not in AV delay, were observed in heart failure patients undergoing CRT optimization according to both the echocardo-
graphic and the IEGM method. Reassessment of optimal device programming during exercise resulted in an improvement in LV dyssynchrony and hemodynamic parameters, giving an additional benefit to that provided by a resting optimization. The IEGM method seems to be a promising alternative to the standard echocardiographic approach both at rest and during exercise.

**Study V**

In this pilot study, conducted in heart failure patients during implantation of a biventricular device, we evaluated the acute changes in multiple vector ICZ signals during different pacing modes, and we investigated whether ICZ may be used to monitor hemodynamic variations. Twelve patients (70±11 yr) were enrolled in the study. Heart failure etiology was ischemic in 3 (25%) patients. At the time of implantation, mean LVEF was 22±8%. Bipolar (Z1) and quadripolar (Z2) impedance signals, recorded in RV, and between LV and RV, respectively, were analyzed with respect to average and p2p amplitude and systolic slope, and correlated with noninvasive hemodynamic and echocardiographic variables.

**Variations in intracardiac impedance signals**

There was a broad inter individual variability in the absolute values of ICZ. However, within each patient Z1 and Z2 signals were stable and reproducible, with a coefficient of variation <10% during IC. As shown in Figure 17, in all patients the only ICZ variable showing significant variations during different pacing conditions was p2p amplitude, which decreased during LV pacing in both Z1 (p=0.021 vs. IC; p=0.014 vs. RV synchronous LV pacing) and in Z2 configuration (p=0.022 vs. IC; p=0.041 vs. RV pacing).

**Variations in hemodynamic, echocardiographic, and electrogram variables**

There was a trend towards an increase in stroke volume during RV synchronous LV pacing (p=0.08). Regarding the echocardiographic variables, LVEDV decreased slightly during RV synchronous LV pacing compared with RV stimulation (193±73 ml vs. 200±68 ml, p=0.05). LVEF improved vs. IC during both RV synchronous LV pacing (from 25±7% to 30±10%, p=0.02) and LV stimulation (from 25±7% to 33±9%, p<0.001). The improvement in LV function was associated with a decrease in LV dyssynchrony. No significant changes in RV end-diastolic volume were observed during different pacing modes. RV ejection fraction (RVEF) decreased vs. IC during LV stimulation (from 63±20% to 55±21%, p=0.007), and showed a trend toward a reduction also during RV stimulation (p=0.06). Regarding the electrogram variables, the interventricular conduction delay improved vs. IC during RV synchronous LV pacing (from 97±57 ms to 35±8 ms, p=0.02), whereas it was worsened by RV stimulation (p=0.002).

**Correlations between intracardiac impedance and functional variables**

Both Z1 and Z2 variables correlated positively with all noninvasive hemodynamic variables, LVEF, and RVEF. An inverse correlation was also found between ICZ variables and LV and RV volumes. Z2 systolic slope correlated with the interventricular conduction delay (r = 0.33, p<0.05).

**Conclusions**

Multiple vector ICZ measurements are feasible in heart failure patients with a biventricular pacing device. Variations in ICZ may be observed during different pacing modes and seem to correlate with hemodynamic and echocardiographic variables. Multiple vector ICZ measurement may be a feasible tool for hemodynamic assessment in patients treated with biventricular pacing.
Figure 17. Variations in Z1 and Z2 variables during different programming modes. IC: intrinsic conduction; LV: left ventricular stimulation; RV: right ventricular stimulation; Sync: RV synchronous LV pacing; Z1: impedance vector covering the right ventricle; Z2: quadripolar impedance vector between the right and left ventricle.
Discussion

CRT is a valuable additive treatment for patients with drug-refractory heart failure and electromechanical dysynchrony (7, 10, 11, 109-111). In these patients, CRT has been shown to improve myocardial function, heart failure symptoms, exercise capacity and survival (22, 23, 38, 112-114). These beneficial effects are attributable to an improvement in interventricular and intraventricular synchrony, leading to an increase in LV systolic function (29, 32). Based on the available evidence, current guidelines support the use of CRT in patients with advanced chronic heart failure (NYHA class III or IV), severe LV dysfunction (LVEF ≤35%), and wide QRS complex (≥120 ms) (1, 9). Despite the encouraging results from large clinical trials (22, 26, 34-38), around 30% of patients fail to benefit from CRT, the so-called “non responders” (8). The mechanisms underlying the lack of response to CRT are not entirely clear, but suboptimal lead position (115, 11), scar tissue in the area of the LV pacing lead (51), absence of mechanical dyssynchrony despite wide QRS complexes (117, 118), or inappropriate device programming may play a role (119).

This thesis focuses on the evaluation of partially explored effects of CRT (namely the electromechanical effects of CRT during pharmacological stress and the impact of CRT on CBF). Furthermore, open issues concerning optimal CRT programming (such as long-term and rest-exercise variations, and novel techniques for CRT optimization) have been addressed.

Electromechanical effects of CRT

In heart failure patients with severe LV systolic dysfunction and wide QRS duration, delayed intraventricular depolarization (i.e. electrical dyssynchrony) leads to differences in the timing of contraction between the myocardial segments (i.e. mechanical dyssynchrony), thus causing an inefficient pattern of LV activation (6, 64, 120). Ventricular resynchronization by biventricular pacing improves the sequence of electrical activation and restores a more coordinated and efficient LV contraction (32, 64). The duration of the QRS complex tends to decrease with biventricular pacing (121), although the effect is variable and does not correlate well with the improvement in LV systolic function (4, 18). Mechanical, rather than electrical, synchrony seems therefore to be the crucial factor in achieving a benefit with biventricular pacing (4, 122). Furthermore, up to 30% of heart failure patients with mechanical dyssynchrony have narrow QRS on the surface electrocardiogram (56).

Electromechanical resynchronization by biventricular pacing induces acute hemodynamic benefits, expressed as an increase in pulse pressure, stroke volume, cardiac index, and a decrease in pulmonary-capillary wedge pressure (14, 18, 19). A reduction in LV dimensions and an improvement in LV systolic function and mitral regurgitation, because of a decrease in intraventricular dyssynchrony, have been demonstrated after CRT by several echocardiographic studies (30, 32, 123). Furthermore, the effects of CRT on LV geometry and function seem to be maintained, or even improved, over time (3, 124), and the extent of LV reverse remodeling at mid-term follow up has been shown to predict long-term outcome (125, 126). Of note, nonischemic patients show significantly greater LV reverse remodeling than ischemic patients (127). The impact of CRT on diastolic function is not fully understood (119). An improvement in diastolic filling and a reduction in LV filling pressures have been documented during biventricular...
pacing (128); however, E/A ratio seems to be unchanged (128).

Although typical clinical and pathophysiological manifestations of heart failure are particularly apparent during exercise, most of the studies on CRT have been performed in the resting patient, and the response to CRT during stress has not been evaluated in detail. In study I, we investigated whether the effects of CRT on ventricular dyssynchrony and function are sustained during pharmacological stress. Dobutamine infusion has a primary impact on contractility with increased oxygen demand, mimicking the effects of exercise (129). Furthermore, dobutamine stress echocardiography allows for comprehensive image recording under stress conditions, and permits the investigation of elderly patients with poor exercise capacity or severe heart failure. The results of our study suggest that in long-term responders, even if dobutamine infusion improves LV contractility both during active CRT (“on”) and after two weeks of pacing withdrawal (“off”), LV systolic function during stress is still significantly greater during “on” than during “off”. These observations suggest that the benefit of CRT during stress is independent from and additive to a purely inotropic effect, and is mainly related to the improvement in LV synchrony, which is maintained during stress. The results may therefore provide an important link between experimental data and clinical evidence of improvement in exercise capacity with CRT.

Effects of CRT on myocardial perfusion

To date, relatively limited and conflicting data are available concerning the effects of CRT on CBF (130). CRT was found not to alter global CBF at rest despite an increase in LV function (131-135). However, the heterogeneous regional distribution of resting CBF in the failing LV seems to be normalized by CRT (132, 136, 137). Nevertheless, general conclusions from these previous studies on CRT and CBF are limited by the use of heterogeneous methods and study designs, as CBF was evaluated after different follow-up periods and with different techniques, like positron emission tomography (PET) (131-136, 138, 139), single-photon emission computed tomography (SPECT) (137), cardiac catheterization (21), and transesophageal echocardiography (140). Furthermore, limited data are available regarding non-invasive measurements of CBF in heart failure patients treated with CRT (141).

In study II we investigated acute changes in LAD flow under different CRT pacing modes by means of transthoracic Doppler echocardiography. Noninvasive imaging of CBF was developed in the late 1990s as a new application for two-dimensional Doppler echocardiography (106). Since then, several studies have shown that transthoracic measurement of CFV and reserve gives a reproducible evaluation of CBF (105, 106, 142) and microvascular function (143), with a good correlation with invasive techniques (105, 142, 143). The results of our study suggest that in CRT patients with idiopathic dilated cardiomyopathy significant changes in regional LAD flow occur in response to different pacing modalities. CBF variables seem to be mostly improved by simultaneous biventricular pacing and biventricular pacing with LV preactivation, and this is associated both with an increase in regional longitudinal myocardial contraction and with a decrease in intraventricular dyssynchrony.

Several mechanisms, depending on the driving pressure and the resistance offered by the vascular bed, are involved in CBF regulation. In heart failure patients with dilated cardiomyopathy and LBBB, late activated myocardial regions start to contract at higher wall stress and also stretch early activated regions as they enter relaxation (28). This asynchronous electro-mechanical activation most likely decreases metabolic demands in the septum and may explain the reduced septal perfusion observed by PET investigations in patients with severe dilated
cardiomyopathy and LBBB (132, 137, 144). CRT seems to restore balance to regional perfusion heterogeneities without altering global CBF, by reducing the unfavourable LBBB associated ventricular activation and contraction pattern. This has been documented by PET as an increase of CBF and myocardial oxygen consumption in the interventricular septum, with a simultaneous decrease in the lateral wall (132, 136). The results of our study not only confirm an increase of LAD flow during CRT, but also suggest that these changes are associated with a more synchronous activation pattern, expressed as a shortening of septal-to-lateral delay and a decrease in post-systolic motion in the basal septum (107). No significant differences either in blood pressure or in diastolic filling time were observed between different CRT pacing modes. However, an acute invasive evaluation of LV filling pressures was not performed.

Up to now, the results of available studies on the effects of CRT on regional myocardial blood flow have been controversial (130). Our findings are in line with previous PET studies (132, 136) suggesting an increase in CBF in the septum and a normalization of regional perfusion during CRT. In an experimental animal study, Lafitte et al. (145) showed that myocardial perfusion of the septum under ischemic conditions tends to improve during LV pacing, while it is acutely impaired by RV pacing and almost unaffected by biventricular pacing. Nelson et al. (21) found no significant modifications in proximal LAD flow, measured by intracoronary Doppler catheter, before and during CRT. The lack of increased LAD flow during CRT, differently from our findings, could perhaps be explained by the characteristics of the study protocol, based on an invasive hemodynamic evaluation performed under sedation, and by different LV pacing sites, compared with the chronic CRT systems evaluated in our study.

**CRT optimization**

Current CRT devices permit programming of both the AV delay, which influences the atrioventricular activation sequence, and the VV delay, affecting the coordination of ventricular contraction (64, 67, 119, 146). Programming the AV delay is important because it has the potential to influence LV systolic performance by modulating the preload (119). However, although in acute studies optimal AV delay programming was shown to improve LV dP/dt max and stroke volume (89), the long-term consequences of AV delay optimization are still not completely known. VV delay optimization was shown to decrease LV dyssynchrony (90) and improve LV function (89, 119). Although the impact of optimization on clinical outcome measures is still unknown, VV optimization may partially compensate for suboptimal LV lead positioning by tailoring ventricular timing, and may also correct for individual heterogeneous ventricular activation patterns (119).

Echocardiography plays a central role in CRT optimization (40, 64-67, 119). However, in clinical practice, routine performance of echocardiographic optimization is limited by several factors, including time requirement and lack of a standard protocol. Therefore, assessing whether optimal AV and VV delay may change during follow-up, thus suggesting an opportunity for periodical echocardiographic reassessments, is an important practical issue. In study III we prospectively investigated variations in AV and VV delays among patients undergoing echo-guided optimization of a CRT device over a 12-month follow-up. In line with previous studies (70, 79, 88-90, 95), at implantation wide variations in AV and VV delays were recorded. Such variations may be related to different patterns of mechanical activation (caused by conduction system abnormalities or myocardial scars) and to different positioning of LV leads (90). Moreover, variations in optimal AV and VV
delays were observed in each patient during long-term follow up, and this was associated with the time-related remodeling effects of CRT. Even if the reprogramming of a CRT device is only one of the multiple factors interacting in the combined therapy of heart failure patients, it is possible that changes in optimal AV and VV programming during follow-up may further improve the beneficial effect of CRT on LV geometry and function. In fact, studies (30, 103, 125, 126) suggest that the more synchronous LV contraction pattern provided by CRT is a major determinant of LV function improvements. It remains unclear how to program AV and VV delays during exercise. It is known that exercise may induce dynamic changes in LV activation pattern in heart failure patients (97, 98), and this suggests that a fixed activation sequence during biventricular pacing may not be physiological. Exercise-induced changes in LV activation pattern may vary considerably from patient to patient, and cause variations in hemodynamic parameters (98). In study IV we investigated the effects of exercise on optimal AV and VV delays, assessed by both echocardiography and an automated IEGM method, in heart failure patients implanted with a CRT defibrillator. Optimal VV delay was found to differ significantly from rest to exercise in a high proportion of cases, while optimized AV delay did not change. Bordachar et al. (147) reported similar changes in optimal VV delay in 57% of patients undergoing an echo-guided CRT optimization during bicycle exercise. With regard to AV delay, available data from the literature are still conflicting. In previous multicenter CRT trials (22, 37), a relatively short AV delay was selected at rest to ensure ventricular capture, and it was programmed either fixed or with dynamic shortening. More recently, Scharf et al. (148) suggested that in CRT patients the AV delay should be prolonged at increased heart rates to improve the hemodynamic response to exercise. Studies suggest that in heart failure patients the dilatation and myocardial stretch of the atria, related to LV dysfunction and loading conditions, may alter the intra-atrial conduction pattern (149). This can be responsible for the need for fixed or even dynamically lengthening AV delays in CRT programming. Furthermore, the results of our study suggest that a reassessment of the optimal pacing configuration during exercise leads to an additional increase in stroke volume compared with the resting setting. Since significant changes in optimal programming were observed for VV, and not for AV delay, it is conceivable that VV delay reassessment during exercise provided the highest additional hemodynamic contribution.

CRT optimization by echocardiography is time-consuming, expertise- and cost-demanding. Several techniques have been proposed as possible alternatives (40, 68, 119). Of them, automated programmer-based algorithms seem to be a feasible option for CRT optimization (80-82). In study IV, AV and VV delays were optimized according to a novel IEGM method, which recommends the optimal programming based on the analysis of endocavitary electrograms (80, 108). In line with previous studies (80, 108), a good concordance in defining optimal AV and VV delays was found between the IEGM and the echo-based methods, with similar acute hemodynamic effects (80, 108). These data further suggest that IEGM algorithms may be a valuable alternative to the standard echocardiographic optimization, with the advantage of being easily performed in daily practice.

A novel approach to the use of ICZ to determine the effectiveness of biventricular pacing has been evaluated in study V. Significant variations in intracardiac impedance variables were found during different pacing modes, and correlated with hemodynamic and echocardiographic indices of ventricular function. This suggests that ICZ measurement may be a promising means of monitoring hemodynamic variations and automatically optimising pacemaker
parameters (150). Previous studies have shown that intrathoracic impedance, measured between electrodes placed on the chest, allows cardiac output calculation on a beat-to-beat basis, and can be used to optimize pacemaker settings (75, 76, 151). In our study ICZ correlated not only with hemodynamic and echocardiographic indices of ventricular function, but also with the interventricular activation delay, the reduction of which is the target of the optimization process. Novel automated algorithms, based on integrated multiple vector impedance measurements, may need to be developed to monitor heart function and automatically optimize pacemaker settings in patients implanted with a biventricular device. Device-based hemodynamic monitoring may be an additive tool to facilitate early therapeutic interventions and prevent overt clinical decompensation (152). However, the clinical experience in this field is still at an early stage (153-157), and further data on the impact of this strategy on outcome measures are expected to arise from ongoing trials (158, 159).

Clinical implications and future perspectives
Beneficial electromechanical and clinical effects have been reported in a high percentage of heart failure patients treated with CRT. However, one troubling issue is still the lack of response in about one-third of patients. Improving the response rate to CRT, through appropriate patient selection, optimal LV lead positioning and possibly tailored device programming, is the major current challenge.

Since LV dyssynchrony was shown to be a strong predictor of response (8), the addition of mechanical dyssynchrony criteria to standard indications for CRT could improve patient selection. However, current echocardiographic dyssynchrony parameters have shown low feasibility and high inter-laboratory variability (44). Clinically reliable, simple and accurate dyssynchrony parameters are therefore needed. It is possible that response or non-response to CRT may involve not only LV dyssynchrony, but also multiple interrelated mechanisms (43). A better understanding of the pathophysiological basics of the lack of response to CRT is therefore required.

The analysis of CBF and CBF velocity reserve during biventricular pacing may provide useful pathophysiological insights. In patients with nonischemic dilated cardiomyopathy, the assessment of an abnormal CBF reserve was shown to be an independent marker of poor prognosis (160). Conflicting results have been reported regarding the effects of CRT on hyperemic dipyridamole or adenosine-stimulated myocardial flow (131, 132, 135). Whether CBF reserve may be a predictor of response to CRT is currently unknown, and may deserve further investigation.

The response rate to CRT could be improved by optimal LV lead positioning. Recent studies have shown that pacing at the site of latest mechanical activation results in better prognosis during long-term follow-up (116, 125). Whether LV pacing alone or multiple sites LV pacing may be clinically favorable in selected subgroups of patients is under evaluation (52, 55).

After CRT implantation, optimization of device settings may acutely improve ventricular dyssynchrony and function by tailoring the ventricular activation sequence (119). However, many uncertainties exist concerning the real clinical benefits of CRT optimization. The changes in optimal device programming during follow-up and the acute hemodynamic benefit provided by AV and VV optimization at each follow-up visit suggest that periodical echocardiographic reevaluations and optimal reprogramming of the device parameters may be useful. Furthermore, assessment of the optimal pacing configuration during exercise seems to yield an additional acute hemodynamic benefit to that provided by resting optimization. Whether the optimal CRT programming
during exercise may vary over time has not yet been investigated. Furthermore, even if a repeated tailoring approach seems to provide acute hemodynamic benefits, the impact of CRT optimization on clinical outcome measures at long-term follow-up has yet to be demonstrated.

Since echo-guided CRT optimization may have an unfavorable cost-effectiveness profile, the implementation in CRT devices of algorithms allowing automatic AV and VV delay optimization could be a useful feature. Despite encouraging results from animal studies (111, 112), whether device-based ICZ measurements may be used in humans for hemodynamic monitoring and biventricular optimization requires further investigation. How ICZ signals vary over time and correlate with hemodynamic parameters during long-term follow-up is currently unknown. Furthermore, it would be interesting to investigate the effects of different anatomical substrates and pacing lead locations on ICZ variables. Device-based continuous hemodynamic monitoring and automatic optimization of pacemaker parameters may be an additional promising means of increasing the response rate to CRT.
Conclusion

CRT improves LV performance both at rest and during pharmacological stress in long-term responders. This is because of an improvement in LV synchrony, which is maintained during stress. Temporary cessation of biventricular pacing is associated with deterioration of LV synchrony and function, leading to clinical impairment.

In patients with idiopathic dilated cardiomyopathy, simultaneous biventricular pacing and biventricular pacing with LV preactivation are associated with an increase in regional LAD flow, which is coupled with a more synchronous ventricular contraction pattern.

Intraindividual changes in optimal AV and VV delay can be observed during the first year of follow-up. At each six-monthly visit, a new assessment of optimal CRT programming reveals no concordance with previous values and provides acute hemodynamic benefits.

Rest-exercise variations in optimal VV delay, but not in AV delay, can be observed in heart failure patients undergoing CRT optimization according to both the echocardiogram and the IEGM method. Reassessment of optimal device programming during exercise results in an acute hemodynamic benefit additional to that provided by resting optimization.

At the time of implantation of a CRT device, variations in ICZ may be observed during different pacing modes, and correlate with hemodynamic parameters. Multiple vector ICZ measurements may be a feasible tool for hemodynamic monitoring in CRT patients.
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