Cardiac resynchronization therapy : determinants of patient outcome and emerging indications

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Chapter 1

General introduction and outline of the thesis

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Heart failure is a clinical syndrome resulting from a functional or structural cardiac disorder that impairs the ability of the heart to fill or eject blood matching the needs of the body. Based on left ventricular (LV) ejection fraction (LVEF), heart failure patients can be divided into 2 groups; 1) patients with primarily systolic dysfunction and 2) patients with diastolic dysfunction.[1] Patients with a low LVEF (≤45%) are considered to have systolic dysfunction. These patients typically have an enlarged LV and low cardiac output. Conversely, patients with heart failure but a preserved LVEF (>45%) are considered to have diastolic dysfunction (impaired LV filling).

Heart failure is the most frequent cardiovascular diagnosis in developed countries with an estimated 550 000 new diagnoses each year in United States.[2-4] Furthermore, approximately 300 000 patients die of heart failure each year.[5] In the Netherlands, around 24.000 patients are admitted for heart failure, and over 6000 people die of heart failure every year. Apart from the physical and social consequences associated with the disease, heart failure is also a considerable economic burden, with an estimated annual costs of $40 billion in the United States alone.[6] It has been suggested that the costs associated with heart failure represent approximately 1-2% of the total healthcare budget in several countries.[7] The prevalence and burden of heart failure will likely increase in developed countries due to the improved survival of other cardiovascular conditions, such as myocardial infarction, and heart failure itself.[4] Despite advances in diagnosis and medical therapy in the last few decades, the morbidity and mortality of heart failure patients remain high.

Patients with heart failure and depressed LVEF may show impaired electromechanical coupling, which may further impair LV performance.[8] The most common conduction abnormalities include prolonged atrio-ventricular conduction (first-degree atrio-ventricular block) and prolonged ventricular conduction.

This prolonged ventricular conduction (as evidenced by a QRS width ≥120 ms) is found in approximately 30% of all heart failure patients with an impaired LVEF.[9-15] Left bundle branch block (LBBB) is the most frequently observed type of QRS prolongation.[9, 16] Prolonged ventricular conduction may cause regional mechanical delay within the LV, which in turn reduces ventricular systolic function, causes mitral regurgitation (MR) and LV dilatation with further impairment of LV performance. A study of Stellbrink et al indicated that the incidence of QRS prolongation (≥120 ms) increased from 10% to 32% and 53% when patients moved from New York Heart Association (NYHA) functional class I to II and III respectively.[17]

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) devices were designed to improve LV performance by restoring the synchronicity at 3 levels (atrio-ventricular, interventricular and intraventricular) which subsequently increases LV filling time, reduces MR, and corrects septal dyskinesis.[18] CRT has shown to be an effective therapy in improving clinical prognosis and systolic LV function of patients with end-stage, drug-refractory heart failure. To date, 14 landmark randomized and multicenter trials, including a total of 8475 patients were conducted (Table 1).[19-34] Although these trials all used slightly different inclusion criteria, they have generally shown that CRT improves functional status (reducing NYHA functional class, improving quality-of-life scores and increasing 6-minute walking distance) and reduces all-cause mortality and heart failure hospitalizations (Table 2). In addition, available echocardiographic data of these trials demonstrated that CRT induces LV reverse remodeling with significant reduction in LV volumes, improvement in LV systolic function and reduction in MR (Table 2). These results have been confirmed in recent meta-analyses with pooled data from these randomized, controlled trials.[4, 35] For example, pooled data from 5 trials randomizing 2371 patients to CRT (n = 1343) vs. medical therapy (n = 1028) have shown the superiority of CRT over medical treatment in reducing all-cause mortality with 29% of relative risk reduction.[35] In addition, another meta-analysis, including 5 randomized controlled trials provided information on the number of hospitalizations for heart failure. Pooled data from these studies, including 713 patients treated with CRT and 698 patients treated with medical therapy, demonstrated that CRT decreased the number of hospitalizations for heart failure by 38%.[4] These results led in 2008 to the American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines to consider CRT a class I indication in patients with end-stage heart failure (NYHA class III-IV) with an LVEF ≤35% and a QRS complex duration ≥120 ms.[8] Similar recommendations were provided by the European Society of Cardiology in 2007.[36]

Despite the widely proven beneficial effects of CRT, 20% to 30% of the patients treated with CRT do not show any clinical improvement, and are considered "non-responder" patients.[18] Furthermore, when echocardiographic criteria of response are applied (reduction in LV end-systolic volume [LVESV] ≥10-15%, increase in LVEF ≥5%), the percentage of non-responder patients increases up to 40%.[18] Several factors may determine the response to CRT: LV dyssynchrony, extent and location of scarred tissue and position of the LV pacing lead.[37-43] In order to optimize CRT response rate, numerous studies have focused on identifying possible responders before implantation by means of echocardiographic evidence of LV dyssynchrony.[44-48] PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) was the first large-scale, multicenter clinical trial that evaluated the performance of several echocardiographic measures of mechanical ventricular dyssynchrony to predict response to CRT.[49] Various markers of dyssynchrony contributed significantly to prediction of clinical outcome and reverse remodeling at 6 months follow-up. Furthermore, the extent

and location of myocardial scar and the LV lead position have also shown to be determinants of CRT response.[39, 40, 43, 50, 51] Therefore, non-invasive multimodality cardiac imaging may play a central role in patient selection for CRT. Whether LV dyssynchrony, LV scar or LV lead position have the same value in predicting response to CRT remains currently unknown. In addition to these efforts to enhance patient outcome in the currently indicated population, many researchers focused on expanding CRT to other patient groups. A recent meta-analysis studied 5 clinical trials including 4,317 patients with NYHA functional class I/II heart faliure.[52] Among mildly symptomatic (NYHA functional class II) patients, CRT was associated with significantly lower mortality and heart failure hospitalization (Hazard Ratio [HR] 0.73, p<0.001). In asymptomatic (NYHA functional class I) patients, heart failure hospitalization risk was lower (HR 0.57, p = 0.04) with CRT. There was however no difference in mortality. The abovementioned outcomes resulted in a recent addition to the European Society of Cardiology guidelines for cardiac pacing and CRT.[53] CRT is now also considered a class I indication in patients with mild symptoms of heart failure (NYHA class II) with an LVEF ≤35% and a QRS complex duration ≥150 ms.[53] There are currently many other clinical trials in CRT ongoing, including CRT in

Table 1. Inclusion criteria in randomized clinical trials evaluating cardiac resynchronization therapy in heart failure

Trial (Ref. #)	Patients	NYHA class	LVEF (%)	LVEDD (mm)	SR/AF	QRS (ms)	ICD
MUSTIC-SR[19]	58	III	≤35	≥60	SR	≥150	No
MIRACLE[20]	453	III, IV	≤35	≥55	SR	≥130	No
MUSTIC-AF[21]	59	III	≤35	≥60	AF	≥200	No
PATH-CHF[22]	41	III, IV	≤35	NA	SR	≥120	No
MIRACLE-ICD[23]	369	III, IV	≤35	≥55	SR	≥130	Yes
CONTAK-CD[24]	490	II-IV	≤35	NA	SR	≥120	Yes
MIRACLE-ICD II[25]	186	II	≤35	≥55	SR	≥130	Yes
PATH-CHF II[26]	86	III, IV	≤35	NA	SR	≥120	Yes/No
COMPANION[27]	1520	III, IV	≤35	NA	SR	≥120	Yes/No
CARE-HF[28, 29]	813	III, IV	≤35	≥30	SR	≥120	No
RETHINQ[30]	172	III	≤35	NA	SR	<130	Yes
REVERSE[31, 32]	610	I, II	≤40	≥55	SR	≥120	Yes/No
MADIT-CRT[33]	1820	I, II	≤30	NA	SR	≥130	Yes
RAFT[34]	1798	II, III	≤30	>60	SR/AF	≥130 ≥200[a]	Yes

[a]Patients in AF

AF = atrial fibrillation; CARE-HF = Cardiac Resynchronization-Heart Failure; CONTAK-CD = CONTAK-Cardiac Defibrillator; COMPANION = Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter defibrillator; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MIRACLE = Multicenter InSync Randomized Clinical Evaluation; MUSTIC = Multisite Simulation in Cardiomyopathies; NA = not applicable; NYHA = New York Heart Association; PATH-CHF = Pacing Therapies in Congestive Heart Failure; RAFT: Resynchronization/defibrillation for ambulatory heart failure trial; RETHINQ: Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS; REVERSE: Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction; SR = sinus rhythm

Table 2. End-points and main findings in randomized clinical trials evaluating cardiac resynchronization therapy in heart failure

Trial (Ref. #)	Primary end-points	Secondary end-points	Main findings
MUSTIC-SR[19]	- 6 MWT	- NYHA class, QoL, peak VO_2 - LV volumes, MR - Hospitalization, mortality	- Improvement in 6 MWT, NYHA class, QoL, peak VO_2 - Reduction in LV volumes and MR - Reduction in hospitalization
MIRACLE[20]	- NYHA class, 6 MWT, QoL	- Peak VO_2 - LVEDD, LVEF, MR - Clinical composite response	- Improvement in NYHA class, QoL and 6 MWT - Reduction in LVEDD, MR, increase in LVEF
MUSTIC-AF[21]	- 6 MWT	- NYHA class, QoL, peak VO_2 - Hospitalization, mortality	- Improvement in 6 MWT, NYHA class, QoL, peak VO_2 - Reduction in hospitalization
PATH-CHF[22]	- Peak VO_2 - 6 MWT	- NYHA class, QoL - Hospitalization	- Improvement in NYHA class, QoL and 6 MWT - Reduction in hospitalization
MIRACLE-ICD[23]	- NYHA class, 6 MWT, QoL	- Peak VO_2 - LVEDD, LVEF, MR - Clinical composite response	- Improvement in NYHA class, QoL, peak VO_2
CONTAK-CD[24]	- NYHA class, 6 MWT, QoL	- LV volume, LVEF - Composite of mortality, VT/VF, hospitalization	- Improvement in 6 MWT, NYHA class, QoL - Reduction in LV volume, increase in LVEF
MIRACLE-ICD II[25]	- Peak VO_2	- NYHA class, QoL, 6 MWT - LV volumes and LVEF - Clinical composite response	- Improvement in NYHA class - Reduction in LV volumes, increase in LVEF
PATH-CHF II[26]	- Peak VO_2 - 6 MWT	- NYHA class, QoL	- Improvement in 6 MWT, QoL, peak VO_2
COMPANION[27]	- All-cause mortality or hospitalization	- All-cause mortality - Cardiac mortality	- Reduction in all-cause mortality or hospitalization
CARE-HF[28, 29]	- All-cause mortality or hospitalization	- All-cause mortality - NYHA class, QoL	- Reduction in all-cause mortality or hospitalization - Improvement in NYHA class, QoL
RETHINQ[30]	- Peak VO_2	- NYHA class, QoL - LVESV	- Improvement in NYHA class
REVERSE[31, 32]	- Clinical composite score	- All-cause mortality, hospitalization - LVESV	- Reduction in hospitalization - Reduction in LVESV
MADIT-CRT[33]	- All-cause mortality or heart failure event	- All-cause mortality - LVESV	- Reduction in all-cause mortality or heart failure event - Reduction in LVESV
RAFT[34]	- All-cause mortality or heart failure hospitalization	- All-cause mortality - Cardiac mortality - Heart failure hospitalization	- Reduction in all-cause mortality or heart failure hospitalization

6 MWT = 6 minute walk test; AF = atrial fibrillation; CARE-HF = Cardiac Resynchronization-Heart Failure; CONTAK-CD = CONTAK-Cardiac Defibrillator; COMPANION = Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter defibrillator; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MIRACLE = Multicenter InSync Randomized Clinical Evaluation; MR = mitral regurgitation; MUSTIC = Multisite Simulation in Cardiomyopathies; NYHA

heart failure patients with a narrow QRS complex, triple site pacing and CRT with a targeted LV pacing lead.[54] This makes CRT one of the most active research areas in cardiology today.

Objectives and outline of the thesis

The objectives of this thesis were to investigate determinants of mid-term response and long-term prognosis after CRT, as well as to explore possible future indications. In **Part I**, determinants of patient outcome are discussed, both at 6 months follow-up (**Part IA**), and during long-term follow-up (**Part IB**). Chapters 2 and 3 focus on the predictive value of echocardiographic parameters of LV dyssynchrony in predicting response to CRT, while in Chapter 4, a comprehensive analyses of electrical parameters is performed by means of the 12-lead surface ECG. In Chapters 5 and 6, a more multiparametric approach is used for identifying possible predictors of response to CRT, including a sub-analysis of the multicenter PROSPECT trial. Chapter 7 describes the value of widely used echocardiographic measures of dyssynchrony for the prediction of long-term cardiovascular events after CRT. In Chapter 8, prognosis during long-term follow-up is related to the extent of LV reverse remodeling at 6 months follow-up. Chapter 9 investigates the effect of impaired renal function before device implantation on remodeling at 6 months follow-up and survival during long-term follow-up. Finally, in Chapter 10, prognosis after CRT is assessed in a very large cohort of heart failure patients and related to a wide array of baseline characteristics.

In **Part II**, a detailed description is provided on issues related to the LV pacing lead. In Chapter 11, a comprehensive analysis of LV dyssynchrony and the site of latest mechanical activation in patients with ischemic and non-ischemic heart failure is performed with novel echocardiographic methods. Chapter 12 describes the extent of LV reverse remodeling as well as prognosis after CRT in relation to the location of the LV pacing lead. In Chapter 13, specific attention is given to the position of the LV lead with regard to LV dyssynchrony and myocardial scar in patients with ischemic heart failure. The interplay between these parameters and its impact on survival is also investigated. Chapter 14 assesses the optimal LV lead position with another technique; phase analysis on gated myocardial perfusion SPECT. In Chapter 15, the effect of optimizing the interventricular pacing interval on LV systolic function in ischemic and non-ischemic patients is analyzed. Finally, Chapter 16 describes the requirement for LV pacing lead interventions as well as the effectiveness of endovascular replacement during long-term follow-up after CRT.

In **Part III**, several special considerations in CRT are discussed in detail. In Chapter 17, various patterns of LV dyssynchrony (including dyssynchrony in the longitudinal and radial direction) are described in patients with ischemic and non-ischemic heart failure and in patients with a wide and a narrow QRS complex. Chapter 18 discusses the value of the surface ECG in detecting right ventricular dilatation in the presence of LBBB, as this may have important

prognostic implications in heart failure patients undergoing CRT. Chapter 19 focuses on the effects of CRT in patients in NYHA class IV heart failure. Although these patients have a class I indication for CRT, benefit of CRT (and consequentially prognosis) may be limited in this group. In Chapter 20 it was investigated whether the improved LV systolic function associated with CRT results in an increase in cerebral blood flow, as this is frequently decreased in patients with heart failure. Chapter 21 describes the phenomenon of biventricular pacing-induced acute response in baroreflex sensitivity and its predictive value for mid-term response (reverse remodeling) to CRT. In Chapter 22, the consequences of discontinuation of CRT at 6 months follow-up on LV systolic function and dyssynchrony are discussed.

Finally, the possible future applications and emerging indications of CRT are described in **Part IV** of the thesis. Chapter 23 provides an overview of the use of CRT outside the (current) guidelines and the general future perspective of this therapy. In Chapters 24 and 25, the use of CRT in heart failure patients with a narrow QRS complex is extensively discussed. More specifically, Chapter 25 discusses a sub-group from the earlier mentioned PROSPECT trial, which only included patients with a QRS complex <130 ms. The possible use of CRT as a therapeutic option in heart failure patients with moderate-severe functional MR and a high operative risk is evaluated in Chapter 26.

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