Hemodynamic Aspects of Biventricular Pacing in Heart Failure

by

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Stockholm 2010
To Cecilia, Elin and Ester
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ABSTRACT

Background and aims
Biventricular pacing or cardiac resynchronization therapy (CRT) is an established treatment option for selected heart failure (HF) patients. We aimed at evaluating acute and longer-term hemodynamic effects of different pacemaker programmings in CRT patients. For the latter purpose, 10 CRT patients also received an implantable hemodynamic monitor (IHM), allowing for long-term hemodynamic monitoring during ambulatory periods.

Study I
The hemodynamic effects of varying the atrioventricular delay (AVD) within a clinical relevant range (± 40 ms) were investigated in 27 CRT patients in different body positions and during exercise. Nine patients with 3rd degree AV block, and left ventricular ejection fraction ≥ 45% served as controls. A small but significant reduction in cardiac output (CO) was found when AVD was shortened, while prolongation had no effect. The magnitude of individual CO response to AVD modifications was larger in CRT patients compared with controls, differed substantially between individuals and was associated with left atrial size.

Study II
We evaluated the accuracy of an algorithm based on pressure waveform characteristics from the IHM to track CO changes. The proposed method (CO IHM) was compared to a non-invasive reference method (inert gas rebreathing, RB) in 12 HF patients. The median inter-patient correlation coefficient (r = 0.83) as well as bias (-0.39 L/min, 11%) and limits of agreements (± 1.57 L/min) were found to be acceptable and appeared favorable compared with 2 clinically accepted methods: Doppler echocardiography and impedance cardiography. CO IHM was subsequently applied in study III and IV for the determination of CO.

Study III
We investigated the acute hemodynamic effects of different biventricularly paced heart rates (HRs) in 10 CRT patients who had also received an IHM. Increasing the paced HR in the range 60 – 100 bpm reduced cardiac filling pressures and increased CO. Moreover, a positive force frequency relationship, usually blunted in HF patients, was observed in the right ventricle.

Study IV
The hemodynamic effects of programming different basic HRs (60 or 80 bpm) were investigated during 2-week periods in a single-blind cross-over study. Hemodynamic data was continuously recorded with the IHM and at the end of each study period patients were assessed by quality of life (QoL), a 6-minute walk test (6MWT) and Brain Natriuretic Peptide (BNP). During pacing at 80 bpm compared with 60 bpm, filling pressures were reduced and CO was increased. However, during the period of pacing at 80 bpm there was a trend of increased filling pressures and stroke volume over time suggestive of a potential gradual deterioration with increased HR. QoL-score, the 6MWT and BNP-levels were unchanged comparing the 2 study periods.

Conclusions
Varying the AVD within a clinical relevant range in CRT patients has little effect on CO. However, the CO response varies largely between individual patients, suggesting that AVD optimization should be performed routinely not to miss those who may gain a potentially important hemodynamic benefit. A simple IHM algorithm can track CO changes in HF patients with reasonable accuracy. This method was subsequently used to demonstrate beneficial short-term effects of pacing with an elevated HR both at rest and during periods of ambulatory living. Considering the potentially large hemodynamic and clinical effects of differential HR programming in CRT patients, this issue demands further evaluation.

Keywords: Heart failure, biventricular pacing, hemodynamic monitoring, heart rate, cardiac output
## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AVD</td>
<td>Atrioventricular delay</td>
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<td>CO</td>
<td>Cardiac output</td>
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<td>CRT</td>
<td>Cardiac resynchronization therapy</td>
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<tr>
<td>DTI</td>
<td>Diastolic time interval</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<td>EF</td>
<td>Ejection fraction</td>
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<tr>
<td>ePAD</td>
<td>Estimated pulmonary artery diastolic pressure</td>
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<tr>
<td>ETI</td>
<td>Ejection time interval</td>
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<tr>
<td>FFR</td>
<td>Force-frequency relationship</td>
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<td>HF</td>
<td>Heart failure</td>
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<tr>
<td>IHM</td>
<td>Implantable hemodynamic monitor</td>
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<tr>
<td>LV</td>
<td>Left ventricle</td>
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<td>LVOT</td>
<td>Left ventricular outflow tract</td>
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<td>MR</td>
<td>Mitral regurgitation</td>
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<td>NYHA I-IV</td>
<td>New York Heart Association functional class I-IV</td>
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<tr>
<td>PAD</td>
<td>Pulmonary artery diastolic pressure</td>
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<tr>
<td>PEI</td>
<td>Pre-ejection interval</td>
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<tr>
<td>PP</td>
<td>Pulse pressure</td>
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<tr>
<td>RV</td>
<td>Right ventricle</td>
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<tr>
<td>RV + dP/dt</td>
<td>Maximum rate of pressure increase in the right ventricle</td>
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<tr>
<td>RVDP</td>
<td>Right ventricular diastolic pressure</td>
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<tr>
<td>RVSP</td>
<td>Right ventricular systolic pressure</td>
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<tr>
<td>STI</td>
<td>Systolic time interval</td>
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<tr>
<td>SV</td>
<td>Stroke volume</td>
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<tr>
<td>VTI</td>
<td>Velocity time integral</td>
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<td>VVD</td>
<td>Interventricular delay</td>
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LIST OF ORIGINAL PAPERS

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

I
Cardiac output response to changes of the atrioventricular delay in different body positions and during exercise in patients receiving cardiac resynchronization therapy.
*Europace* 2009; 11: 1160-1167

II
Estimating changes in cardiac output using an implanted hemodynamic monitor in heart failure patients

III
Ståhlberg M, Kessels R, Linde C, Braunschweig F.
Acute hemodynamic effects of increase in paced heart rate in heart failure patients recorded with an implantable hemodynamic monitor.
*(Submitted)*

IV
Ståhlberg M, Hilpisch K, Linde C, Braunschweig F.
Hemodynamic effects of different basic heart rates in ambulatory heart failure patients treated with cardiac resynchronization therapy.
*(Submitted)*
INTRODUCTION

Since the 1990s, implantable devices have advanced the treatment and management of patients with heart failure (HF). Biventricular pacing, commonly referred to as cardiac resynchronization therapy (CRT), was first introduced in the 1990s as a novel technique to treat the deleterious effects of electromechanical dyssynchrony on cardiac function, which are often observed in failing hearts. Since then, a series of pivotal clinical trials have demonstrated that the addition of CRT, alone (CRT-P) or in combination with a defibrillator (CRT-D), to pharmacological therapy reduces morbidity and mortality in selected HF patients. As a result, patients who are treated with CRT-P/D constitute a growing population; In Europe, the implantation rate with CRT-P/D reached 100 per 1 million inhabitants in 2008 (1). Implantable devices for HF not only are used to deliver effective treatment but also offer a unique opportunity to record information on physiological variables which can improve patient management. Recent advances in the field suggest that device-based diagnostic methods may alert patients and treating physicians to early clinical deterioration providing a window of opportunity for action before more severe deterioration occurs, and are unique tools with which treatments can be evaluated. From a research perspective, this technology has the advantage of continuous data collection during everyday activities which may contribute to novel pathophysiological insights.

This thesis is based in part on a sample of patients in whom an implantable hemodynamic monitor was combined with a CRT device to study acute and long-term hemodynamic effects of various pacemaker programmings. We also aimed to improve the capacity of the monitor by testing an algorithm to acquire additional, potentially important information. Pacing strategies to resynchronize a failing heart can be referred to as biventricular, multisite, or triple site, in addition to the most commonly used term, CRT. To emphasise that the patients in this thesis were paced biventricularly (as opposed to, for example, by left ventricular stimulation only) the term “biventricular pacing” appears in the title. In the text the terms “CRT” and “biventricular pacing” are used as appropriate.

Heart failure

Definition and epidemiology

According to the guidelines of the European Society of Cardiology, HF is defined as a clinical syndrome where patients have a combination of three features (2): 1) symptoms that are typical of HF, including breathlessness at rest or during exertion, and fatigue; 2) typical clinical signs, such as peripheral edema and pulmonary rales, tachypnea and tachycardia; and 3) objective evidence of structural or functional abnormalities at rest, as evidenced by appropriate cardiac imaging techniques. The clinical syndrome of HF typically evolves from a variety of underlying cardiovascular conditions, such as coronary artery disease, various cardiomyopathies, hypertension and valvular disease (2). HF is a common disease that affects 1-2 % of the adult population in the Western world (3) with a marked increase in prevalence in the age group above 60 (4). Although mortality rates in patients with HF have improved during recent decades (5,6), the 5-year mortality rate remains approximately 50% (2). Moreover, HF imposes a vast economic burden on society, accounting for approximately 2% of national expenditures on health (7).
Pathophysiology

The human cardiovascular system has developed adaptive mechanisms to swiftly counteract major insults, such as hemorrhage and severe dehydration. Although they are beneficial in maintaining adequate blood pressure and tissue perfusion in the short term, these mechanisms can be detrimental when the insult becomes chronic or if the adaptation persists. According to the neurohormonal hypothesis of HF, an initial insult to the cardiovascular system (“index event”) is followed by neurohormonal activation contributing to cardiac remodeling and subsequently to the clinical syndrome of HF (8). The “index event” can be acute myocardial infarction, hypertension, myocarditis or valvular disease. In patients with idiopathic dilated cardiomyopathy, the index event is unknown.

Neurohormonal activation in response to decreased cardiac pump function consists primarily of increased sympathetic activity and upregulation of the renin-angiotensin-aldosterone system (RAAS) (Figure 1) (9). Plasma norepinephrine (NE), an indirect measure of total sympathetic activity, is elevated (10) and is associated with an increased risk of mortality (11,12). Moreover, cardiac, renal (13) and muscle sympathetic activity (14) is elevated in HF patients compared with age-matched controls. Increased sympathetic activity is associated with a number of deleterious effects on cardiovascular function, which can be reversed by pharmacological blockade of sympathetic receptors. For example, sympathetic overactivity exerts direct cellular toxicity in the myocardium, which is mitigated by administration of beta blockers (15). Beta adrenergic receptors are down-regulated in failing human myocardium, resulting in a less pronounced response to beta agonist stimulation (16). Conversely, beta blockers increase beta receptor density and improve the response to dobutamine stress (17). Lastly, NE also induce myocyte hypertrophy (18). Increased sympathetic activity is accompanied by upregulated activity of the RAAS, causing salt and water retention and vasoconstriction (19).

Several hemodynamic, cellular and interstitial alterations contribute to typical changes in shape, size and function of the heart in patients with HF. This cardiac remodeling is characterized by myocyte apoptosis (20) and hypertrophy (21), tissue fibrosis (22), activation of metalloproteinases (23), and increased cardiac expression of cytokines (24). Furthermore, energy starvation is believed to contribute to the pathophysiology of HF (25). In hypertrophied and dilated ventricles, subendocardial perfusion can be compromised (26) and capillary/unit mass values decrease (27), impairing the capacity of oxidative phosphorylation. The intrinsic ability of cardiac myocytes to increase the force of contraction in response to higher stimulation frequencies—the force frequency relationship (FFR)—was first described as early as 19th century (28). Attenuation of the FFR in HF has been demonstrated in isolated muscle strips (29) and during atrial- and right ventricular pacing (30,31) and contributes to reduced exercise tolerance (29,32). Therefore it is considered to be an important pathophysiological mechanism in HF.

Heart rate

Epidemiological data from long-term follow-ups of healthy individuals demonstrate a clear association between resting heart rate (HR) and cardiovascular morbidity and mortality (33-35), irrespective of gender or age (36). In patients with coronary artery disease, the association between elevated HR and cardiovascular mortality (37,38), major ischemic coronary events (38,39), sudden cardiac death (39), and all-cause mortality (37,38) has been well established from large cohort studies. The prognostic impact of elevated HR has also been documented in HF patients—in several large trials, elevated resting HR was a predictor of hospitalization.
Figure 1. The Pathophysiology of Heart Failure. Unloading of high-pressure baroreceptors (blue circles) in the left ventricle, carotid sinus, and aortic arch generates afferent signals (black) that stimulate cardioregulatory centers in the brain, resulting in the activation of efferent pathways in the sympathetic nervous system (green). The sympathetic nervous system appears to be the primary integrator of the neurohumoral vasoconstrictor response to arterial underfilling. Activation of renal sympathetic nerves stimulates the release of renin and angiotensin II, thus activating the renin–angiotensin–aldosterone system. Concomitantly, sympathetic stimulation of the supraoptic and paraventricular nuclei in the hypothalamus results in the nonosmotic release of arginine vasopressin (AVP). Sympathetic activation also causes peripheral and renal vasoconstriction, as does angiotensin II. Angiotensin II constricts blood vessels and stimulates the release of aldosterone from the adrenal gland, and it also increases tubular sodium reabsorption and causes remodeling of cardiac myocytes. Aldosterone may also have direct cardiac effects, in addition to increasing the reabsorption of sodium and the secretion of potassium and hydrogen ions in the collecting duct. The blue lines designate circulating hormones. Adapted with permission from Shrier & Abraham, N Engl J Med 1999;341:577-85.
for HF, cardiovascular mortality, and all-cause mortality (40-43). Moreover, Kjekshus and Gullestad analyzed data from several drug trials in HF patients and noted a positive relationship between HR reduction and declines in mortality (Figure 2) (44). Results from the CIBIS-II study are consistent with this finding demonstrating that bisoprolol-induced change in HR is an independent predictor of mortality (42). These findings suggest that HR reduction should be a therapeutic aim in HF.

Yet, in the MERIT-HF study, the benefit of metoprolol was achieved independently of HR reduction (40). In a recent study, HR reduction with ivabradine failed to reduce mortality or hospitalization in patients with depressed cardiac function (45). These findings imply that mechanisms other than HR reduction per se influence the apparent association between HR reduction and outcome in clinical trials. Notably, although also dependent on vagal drive, resting HR correlates with sympathetic activity measured as plasma NE levels and muscle sympathetic nerve activity, in healthy controls as well as in patients with HF (46). In addition, increased sympathetic activity is associated with several adverse effects, presumably independent of increased HR (15,18). Therefore, despite the clear association between HR and survival it remains to be proven that increased HR per se is a predictor of mortality independent of other factors—in particular, sympathetic activity.

In the context of CRT, artificial elevation of HR by device programming may differ from those that are observed in the general HF population in the absence of pacing. Despite the significant potential hemodynamic and clinical impact of HR programming in CRT patients, the acute and chronic effects of various HR settings within a clinically relevant range remain largely unclear, rendering the choice of an appropriate basic HR in clinical practice empirical.

Cardiac dyssynchrony
Electromechanical dyssynchrony is a common feature in patients with HF and can exist on the atrial level (intra-atrial conduction delay), between the atria and ventricles (atrioventricular dyssynchrony), and between and within the ventricles (inter- and intra ventricular dyssynchrony).
Atrioventricular electrical dyssynchrony typically presents as PQ-prolongation on the Electrocardiogram (ECG) and is associated with disease progression in HF patients (47). When the intrinsic PQ-time is severely prolonged, atrial contraction occurs early relative to the beginning of ventricular systole resulting in decreased atrial contribution to ventricular filling (48), shortened left ventricular filling time (49), and increased pre systolic mitral regurgitation (MR) (50). Suboptimal atrial contribution to ventricular filling can reduce ventricular contractility and stroke volume (SV) through the Frank-Starling mechanism. A prolongation of the QRS-duration (>120ms) on the ECG, which is present in up to 30% of patients with symptomatic HF (51,52), reflects prolonged electrical activation of the cardiac ventricles, which is associated with intra- and inter ventricular mechanical dyssynchrony. QRS prolongation is an independent risk factor for mortality in patients with and without HF (53,54). The abnormal electrical activation pattern results in an abnormal sequence of contraction. Typically, in Left Bundle Branch Block (LBBB), septal regions are activated early relative to regions in the lateral wall (55,56) causing early septal contraction, followed by systolic stretch, due to contractions in late-activated LV lateral wall regions. Conversely, systolic shortening is increased and relaxation is delayed in late-activated LV lateral wall regions. The dyssynchronous pattern of activation-contraction results in regional differences in cardiac work (55), oxygen consumption (56), and subsequently, reduced pump function (57). Hemodynamically, LBBB is associated with increased isovolumetric contraction intervals, increased LV ejection time, and reduced diastolic filling time (Figure 3) (57). In addition to impairing pump function, chronic dyssynchronous activation may result in ventricular dilatation and asymmetrical hypertrophy, thereby contributing to the development of HF (58,59). Electrical activation of the LV is similar during LBBB and RV apical pacing (60,61). As shown by Auricchio et al., patients with HF and LBBB morphology display a U-shaped pattern of the LV activation sequence (62). The site of functional electrical block, however, varied between patients and upon pacing from different sites, implicating diffuse disease of the electrical conduction system within the failing LV rather than an isolated block within the left bundle branch.

Figure 3. Interrelation between right and left ventricular events in normal subjects (a) and left bundle branch block (LBBB) groups (b). In the normal group, left ventricular events either preceeded or occurred simultaneously with the right ventricle. In LBBB, the sequence was reversed with right ventricular events preceding that of the left ventricle. po, to, ao, mo, time of pulmonic, tricuspid, aortic, and mitral valve opening, respectively; pc, tc, ac, mc, time of respective valve closure. Adapted with permission from Grines et al. Circulation 1989;79;845-53.
Cardiac resynchronization therapy

Mechanism of action
With CRT the detrimental effects of cardiac dyssynchrony can be partly restored. Firstly, an appropriate timing of the interval between atrial and ventricular stimulation can enhance atrioventricular synchrony (63). The coupling of atrial contribution to ventricular filling improves cardiac contractility and SV by the Frank-Starling mechanism. Secondly, representing the chief effect of CRT, intra- or inter ventricular dyssynchrony is attenuated by stimulating the right and left ventricle simultaneously or near simultaneously (biventricular pacing). Alternatively, only the left ventricular lateral wall is activated which allows for concurrent intrinsic activation through the right bundle branch (LV-only pacing). With biventricular pacing, 2 activation fronts are generated at the sites of stimulation, resulting in reduced intra- and inter ventricular activation times (64). During LV-only pacing, the electrical wavefront that is generated by the pacemaker merges with the intrinsic activation through the right bundle branch. Similar to biventricular pacing, these dual wavefronts reduce intra- and inter ventricular activation times compared with LBBB (64). The addition of a second LV pacing lead, in order to further improve intra-ventricular resynchronization has demonstrated promising, initial efficacy compared with conventional biventricular stimulation (65).

Hemodynamic effects
Biventricular pacing and single site LV-pacing acutely modify cardiac pump function, leading to an immediate increases in LV +dP/dt, PP, EF, SV, stroke work and systemic arterial blood pressure (64,66-69). Moreover, CRT acutely reduces the functional MR, commonly present in dilated ventricles, in part by increasing LV +dP/dt (70) and is associated with reduced LV filling pressures (66,68). These acute hemodynamic improvements are maintained throughout long follow-ups (71-73) and translate into reduced circulating levels of NT-proBNP (74). Notably, these benefits are obtained with improved energy efficiency (75-77). CRT also decreases neurohormonal activation and improves the disturbed autonomic balance and autonomic control that are associated with HF, as assessed by muscle sympathetic nerve activity (78,79), cardiac NE reuptake and retention (80,81), baroreflex sensitivity (82,83), and heart rate variability. The beneficial effects on hemodynamics and neurohormonal activation result in reverse remodeling, as evidenced by decreases in left ventricular volume and mass in patients who receive CRT (84,85).

Clinical effects
Major clinical trials that have demonstrated the clinical efficacy of CRT with or without an implantable cardioverter defibrillator (ICD) are summarized in Table 1. A series of randomized controlled studies, including patients with drug-refractory HF in NYHA class III-IV, prolonged QRS-duration, LV EF ≤ 35%, and sinus rhythm, consistently noted improved functional status with CRT treatment (86-90). In these studies, CRT improved the distance covered in the 6-minute walk test (6-25%), QoL (13-59%), peak VO₂ (6-8%), and NYHA class. Subsequent larger trials, that had longer follow-up periods, demonstrated reduced mortality and hospitalization rates with CRT compared with medical treatment alone (72,73). Accordingly, the European Society of Cardiology has conferred a class I recommendation (level of evidence A) to CRT as a treatment for NYHA class III-IV patients with QRS duration ≥ 120 ms and LV EF ≤ 35% to improve symptoms and reduce hospitalization and mortality (2). Furthermore, recent trials have observed the efficacy of CRT in NHYA class I-II patients (91,92).
Although the general benefit of adding CRT to medical therapy has been firmly established for the indications above, trials have reported consistently that approximately 30% of patients fail to respond (89,90). Whether improved patient selection or optimization of CRT delivery can increase the number of responders has been the focus of many studies for the past several years. Various baseline factors have been suggested to predict poorer response to CRT, including narrow QRS width (86,92), ischemic HF etiology (93), large myocardial scar burden or unfavorable scar location (94), right bundle branch block pattern on ECG (95), NYHA-class IV status (72) and right ventricular pathology (96).

Further, a wide variety of echocardiographic measures of mechanical dyssynchrony have been proposed to improve patient selection, compared with QRS duration alone (97-103). However, a recent multicenter trial that investigated the prospective ability of several echocardiographic parameters to predict response to CRT reported large variability in the analysis of dyssynchrony and modest sensitivity and specificity in identifying responders from baseline measurements (104).

Table 1. Major clinical trials documenting the efficacy of CRT-P/D.

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Year</th>
<th>n=</th>
<th>design</th>
<th>endpoints</th>
<th>results</th>
</tr>
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<tr>
<td>MUSTIC</td>
<td>2001</td>
<td>67</td>
<td>CO</td>
<td>6MWT, QoL, peak VO₂, NYHA</td>
<td>6MWT ↑ 23%, QoL ↑ 32%, peak VO₂ ↑ 8%, ↓ NYHA</td>
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<tr>
<td>PATH-CHF</td>
<td>2002</td>
<td>41</td>
<td>CO</td>
<td>6MWT, QoL, peak VO₂, NYHA</td>
<td>6MWT ↑ 25%, QoL ↑ 59%, ↓ NYHA</td>
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<tr>
<td>PATH-CHF II</td>
<td>2003</td>
<td>89</td>
<td>CO</td>
<td>6MWT, QoL, peak VO₂, NYHA</td>
<td>6MWT ↑ 6%, QoL ↑ 24%, peak VO₂ ↑ 10%</td>
</tr>
<tr>
<td>MIRACLE</td>
<td>2002</td>
<td>453</td>
<td>PA</td>
<td>6MWT, QoL, NYHA</td>
<td>6MWT ↑ 13%, QoL ↑ 13%</td>
</tr>
<tr>
<td>MIRACLE-ICD</td>
<td>2003</td>
<td>369</td>
<td>PA</td>
<td>6MWT, QoL, peak VO₂, NYHA</td>
<td>QoL ↑ 44%, peak VO₂ ↑ 8%, NYHA ↓</td>
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<tr>
<td>CONTAK-CD</td>
<td>2003</td>
<td>490</td>
<td>PA, CO</td>
<td>6MWT, QoL, peak VO₂, NYHA</td>
<td>6MWT ↑ 15m, peak VO₂ ↑ 0.8ml/kg/min</td>
</tr>
<tr>
<td>COMPANION</td>
<td>2004</td>
<td>1520</td>
<td>PA</td>
<td>CE 1</td>
<td>CE1, HR=0.81 with CRT</td>
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<tr>
<td>CARE-HF</td>
<td>2005</td>
<td>813</td>
<td>PA</td>
<td>CE 2</td>
<td>CE1, HR: 0.63; D, HR: 0.64 with CRT</td>
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<tr>
<td>REVERSE</td>
<td>2008</td>
<td>610</td>
<td>PA</td>
<td>CCS, LVESVI, TTH</td>
<td>TTH, HR: 0.48; LVESVI ↓ with CRT</td>
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<tr>
<td>MADIT-CRT</td>
<td>2009</td>
<td>1820</td>
<td>PA</td>
<td>CE 3</td>
<td>CE3, HR: 0.66 with CRT</td>
</tr>
</tbody>
</table>

MUSTIC=Multisite Stimulation in Cardiomyopathies (87), PATH-CHF=Pacing Therapies in Congestive Heart Failure (88), MIRACLE=Multicenter InSync Randomized Clinical Evaluation (89), MIRACLE-ICD=Multicenter InSync ICD Randomized Clinical Evaluation, (90) CONTAK-CD=Biventricular pacing study, COMPANION=Comparison of Medicial Therapy Pacing and Defibrillation in Heart Failure (72), CARE-HF: Cardiac Resynchronization in Heart Failure (73), REVERSE=Resynchronization Reverses Remodelling in Systolic Left Ventricular Dysfunction (91), MADIT-CRT=Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy (92). Year=Publication year, CO=Cross over design, PA=Parallel arm design, 6MWT=6-minute walk test, QoL=Quality of life, peak VO₂=peak oxygen consumption during symptom limiting exercise, NYHA=New York Heart Association functional class, CE 1= Combined endpoint of time to death or hospitalization, CE 2=Combined endpoint of time to death or hospitalization for major cardiovascular event, CCS= Clinical composite score, LVESVI=Left ventricular end systolic volume index, TTH=Time to heart failure hospitalization, HR=Hazard ratio, CE 3= Combined endpoint of death or non-fatal heart failure event, D=Death.

Although the general benefit of adding CRT to medical therapy has been firmly established for the indications above, trials have reported consistently that approximately 30% of patients fail to respond (89,90). Whether improved patient selection or optimization of CRT delivery can increase the number of responders has been the focus of many studies for the past several years. Various baseline factors have been suggested to predict poorer response to CRT, including narrow QRS width (86,92), ischemic HF etiology (93), large myocardial scar burden or unfavorable scar location (94), right bundle branch block pattern on ECG (95), NYHA-class IV status (72) and right ventricular pathology (96). Further, a wide variety of echocardiographic measures of mechanical dyssynchrony have been proposed to improve patient selection, compared with QRS duration alone (97-103). However, a recent multicenter trial that investigated the prospective ability of several echocardiographic parameters to predict response to CRT reported large variability in the analysis of dyssynchrony and modest sensitivity and specificity in identifying responders from baseline measurements (104).
Device optimization

Modern CRT devices allow for individual tuning of the intervals between sensed or paced atrial activity and subsequent pacing in the ventricles (atrioventricular delay, AVD) or between stimulation of the 2 ventricles (ventricular-ventricular delay, VVD). Therefore, identifying the optimal AVD might be important to maximize the atrial contribution to ventricular filling. Assessed by mitral inflow methods, a suboptimal long AVD will result in superimposition of the atrial contribution (A-wave) on the passive ventricular filling phase (E-wave), resulting in shortened diastolic filling time (DFT), and increased susceptibility to pre-systolic MR (Figure 4). Further, an extremely long AVD, can result in spontaneous ventricular activation and the subsequent loss of biventricular stimulation (106). On the other hand, with an inappropriately short AVD, DFT will be prolonged, but the A-wave may be truncated as ventricular contraction begins. Therefore, an optimal AVD would couple the end of the A-wave to the ventricular contraction in order to maximize DFT while maintaining complete atrial contribution to ventricular filling.

Varying the AVD in resting supine patients improves LV +dP/dt, PP, and arterial systolic blood pressure acutely by 13-34% (66,67,107,108). In most of these studies, the majority of patients display inverse U-shaped hemodynamic responses to different AVDs (Figure 5). Furthermore, there is wide inter-patient variability with regard to optimal AV-timing in CRT patients (63,66).

Although invasively measured LV dP/dt has been used frequently to determine optimal AVD in research studies, this method is limited in the clinical setting due to its complexity and associated risks. Therefore several non-invasive techniques have been proposed to optimize timing intervals, including echocardiography (109-111), impedance cardiography (112,113), finger plethysmography (108,114), and automated algorithms based on cardiac activation derived from intra cardiac electrograms (115). There is no consensus as to which method should be considered “gold standard”.

Figure 4. Schematic illustration of the effects of a suboptimal long- (A) and short (B) AVD on the mitral valve inflow profile. See text for details.
Hemodynamic Aspects of Biventricular Pacing

In clinical CRT trials, AVD has been optimized using invasive LV +dP/dt or several echocardiographic methods, preferably those that optimize mitral inflow. Subsequently, this approach is recommended in the European guidelines for CRT treatment (116). Yet, only 2 randomized controlled studies have reported on the clinical effects of individual optimization compared to an AVD “out of the box” which typically is 120 ms (sensed) (117,118). Although these small single-center evaluations demonstrated greater improvements in NYHA-class and LV EF with individually optimized AVD compared with the empirical setting of 120 ms, the evidence that individual AVD optimization improves clinical outcomes in CRT patients is weak.

VVD optimization (or sequential biventricular pacing) may attenuate residual dyssynchrony remaining after CRT implantation with simultaneous biventricular stimulation. Indeed, acute hemodynamic improvements have been demonstrated by individualizing the ventricular-to-ventricular stimulation interval (107,119,120) although to a lesser extent than AVD optimization (119). Prospective randomized controlled trials have noted similar outcomes in NYHA-class, the 6MWT and echocardiographic measurements of reverse remodeling between individually tailored sequential ventricular stimulation and simultaneous biventricular pacing (121,122).

**Hemodynamic monitoring in heart failure**

**Background**

In clinical routine, HF therapy is typically guided by the evaluation of patients’ self-reported symptoms and clinical signs. The symptoms (123), signs (124), and disease severity, however, can be inconsistent. In particular, pulmonary rales and jugular venous extension can be absent in cases of volume overload, as evidenced by increase in pulmonary capillary wedge pressure (PCWP) (124). Moreover, the current recommendation to request that patients contact physicians or nurses when their gains in body weight exceed 2 kg in 3 days has poor sensitivity in detecting clinical deterioration (125). Therefore, improved diagnostic tools for hemodynamic assessment in the outpatient setting seem desirable.

Elevated cardiac filling pressures play a key role in the development of congestive symptoms...
in HF patients (126), and hemodynamically guided therapy that is aimed at reducing PCWP has been suggested to improve outcomes in patients with severe HF (127). In this respect, therapy guidance with repeated conventional hemodynamic assessments is limited by several factors. First, the gold standard evaluation - right heart catheterization - is cumbersome and is associated with risks. Second, catheterization or echocardiographic appraisal only provides a snap-shot of the hemodynamic status of a patient who is in a resting supine position. Third, applying these methods to make serial measurements requires frequent hospital visits for the patient. To circumvent some of these limitations, an implantable hemodynamic monitor (IHM) was developed in a collaboration between Medtronic Inc. and the Department of Cardiology at Karolinska University Hospital (128,129). Based on the permanent implantation of an RV pressure sensor, this technology allows for continuous hemodynamic recordings during ambulatory periods, which may provide a more representative profile of a patients’ hemodynamic condition without requiring frequent hospital visits. A detailed technical description of the IHM is presented in the Methods section of this thesis.

Although a reasonable correlation between right and left ventricular filling pressures has been demonstrated in a large cohort of patients with severe HF (130), pulmonary artery diastolic pressure (PAD) and PCWP, reflect the diastolic pressure in the left side of the heart more accurately (131-133). To measure PAD from the RV, a concept of estimated PAD (ePAD) was developed and incorporated into the IHM.

Early experimental studies documented that RV +dP/dt occurs close to the opening of the pulmonic valve (134). Therefore, measuring the RV pressure at the time of RV +dP/dt yields an estimate of PAD pressure. This concept was validated in 3 acute studies that used Millar catheters in the RV and pulmonary artery demonstrating acceptable agreement between actual PAD and ePAD values (135-137) (Table 2). The acute and long-term accuracy of the IHM in measuring RV pressure and ePAD was subsequently evaluated in HF patients for a wide range of physiological provocations (Table 2) and shown to be accurate and stable over time (129,138).

Although it measures RV pressures and indices of LV filling pressures, the IHM lacks the capacity to measure variables directly reflecting LV hemodynamics. Therefore, the ability to measure major determinants of global cardiac systolic performance that are equal on the left- and right side of the heart, such as SV or CO, is desirable.

In earlier models of the IHM, attempts were made to estimate CO from an oxygen sensor that measures mixed venous oxygen saturation (SvO₂) continuously. Although the accuracy of the sensor was adequate in the acute setting compared with the catheter-based standard (139), the SvO₂ sensor failed frequently during long-term follow-up (129) resulting in its removal from newer versions of the IHM.

A different approach would be to use established relationships between pressure and flow to estimate SV and CO from RV pressure waveforms. In Study II, we determined the accuracy and precision of a simple algorithm that was based on RV pressure data in tracking changes in CO compared with established noninvasive methods, which we found to be acceptable. Subsequently, we implemented the algorithm in Studies III and IV to make acute and long-term estimations of CO during various pacemaker programminngs.

Clinical application
It has been shown that RV pressures and ePAD increases 4-39 days before acute hospitalization or urgent office visits for HF decompensation (140-142). Thus, increased pressures can be
an early warning sign of imminent volume overload. Furthermore, if treating physicians become aware of pending hemodynamic deterioration, early intervention may prevent acute in-hospital treatment.

This hypothesis was tested in the COMPASS-HF study (143). In this randomized, controlled, multicenter trial, 274 NYHA III-IV patients received an IHM that regularly transmitted pressure data to a central server by home monitoring. In the active monitoring group, physicians had full access to patients’ pressure trends and could act accordingly while this information was blocked in the control group.

The trial results were ambiguous. The primary endpoint of cumulative HF events was not met, but the secondary endpoint of time to first HF-related hospitalization showed a significant risk reduction of 36% in the active monitoring group. Therefore, additional trials are needed to establish the clinical usefulness of IHM-guided patient management.

Recent research also suggests that the hemodynamic trends derived from the IHM can aid in tailoring dialysis (144) and diuretic treatment (145) and optimizing CRT devices (146) in individual HF patients. Moreover, continuous hemodynamic monitoring with an IHM can lead to pathophysiological insights into mechanisms such as the transition from compensated to decompensated HF (140).

Table 2. Summary of studies validating ePAD and RV pressures compared with catheterization.

<table>
<thead>
<tr>
<th>Ref #</th>
<th>n=</th>
<th>Patients</th>
<th>Methods</th>
<th>Protocol</th>
<th>Provocations</th>
<th>Variable</th>
<th>R²</th>
<th>e.q.</th>
<th>Bias (mmHg)</th>
</tr>
</thead>
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<tr>
<td>136</td>
<td>10</td>
<td>Cath</td>
<td>Millar</td>
<td>A</td>
<td>IVS, Va</td>
<td>ePAD</td>
<td>0.81</td>
<td>ePAD=0.88 X PAD + 2.53</td>
<td>-2.5</td>
</tr>
<tr>
<td>135</td>
<td>8</td>
<td>CHF</td>
<td>Millar</td>
<td>A</td>
<td>Va, Exe, Dob, Nit, LR</td>
<td>ePAD</td>
<td>0.77*</td>
<td>N.R.</td>
<td>5.6 *</td>
</tr>
<tr>
<td>137</td>
<td>10</td>
<td>CHF</td>
<td>Millar</td>
<td>A</td>
<td>Va, Exe, Dob, Nit</td>
<td>ePAD</td>
<td>0.88</td>
<td>ePAD=0.92 X PAD+3.2</td>
<td>1.0</td>
</tr>
<tr>
<td>139</td>
<td>21</td>
<td>CHF</td>
<td>IHM</td>
<td>A+L</td>
<td>Va, Exe, Dob, Nit</td>
<td>ePAD</td>
<td>0.75*</td>
<td>N.R.</td>
<td>0.1 *</td>
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<tr>
<td>138</td>
<td>32</td>
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<td>IHM</td>
<td>A+L</td>
<td>Va, Exe</td>
<td>ePAD</td>
<td>0.84</td>
<td>N.R.</td>
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<tr>
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<td></td>
<td></td>
<td>RVSP</td>
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<td>SP=int=0.99 X SP+4.5</td>
<td>-5.0</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>RVDP</td>
<td>0.79</td>
<td>DP=int=0.95 X DP+5.0</td>
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</tr>
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</table>

Ref# = Reference number, n=number of patients included in study, Millar=validating concept of estimating pulmonary artery diastolic pressure (ePAD) from RV pressure at dP/dt max using Millar catheters in RV and PA respectively, IHM=validating measurements of RV pressures and ePAD comparing Implantable Hemodynamic Monitoring (IHM) and Swan-Ganz catheters, A=Acute setting, A+L=Acute + Long term follow up (repeated catheterizations up to 12 months after implant), IVS=Isovolumetric Stress, Va=Valsalva maneuver, Exe=Bike exercise, Dob=Dobutamine infusion, Nit=Nitroglycerine, e.q.=equation for the linear relationship, Bias=Mean bias between estimated/IHM derived and gold standard, N.R.= Not reported Results are presented as multiple correlation coefficient and mean bias of pooled data from all interventions and patients. * Result not in original publication but derived from reference 128. Table is adopted with modifications from Bennett et al. PACE 2005;28:573-84.
AIMS

The general aim of the study was to

• Investigate hemodynamic effects of device programming in heart failure patients treated with biventricular pacing

The specific aims of the study were:

• To study the hemodynamic effect of modulating the AV-delay within a narrow, clinically relevant range in CRT patients.

• To investigate if an algorithm based on RV pressure waveforms, derived from an implanted hemodynamic monitor, can track changes in cardiac output in heart failure patients.

• To assess acute effects of different biventricularly paced heart rates on hemodynamics recorded with an implantable hemodynamic monitor in heart failure patients.

• To investigate the longer-term hemodynamic effects of different programmed basic heart rates in ambulatory heart failure patients treated with CRT.
Patient selection

An overview of the distribution of patients in the different studies is given in Figure 6.

We included 28 CRT patients in Study I. Eight of these also had an IHM implanted. Patients were asked to participate if they had met standard criteria for CRT at the time of implantation (drug refractory HF, NYHA III-IV, QRS ≥ 120 ms, LVEF ≤ 35%, sinus rhythm). Moreover, 11 patients without systolic LV dysfunction (EF ≥ 45%) or clinical HF who were implanted with a dual chamber pacemaker for third degree atrioventricular block were included to serve as control. Subjects with concomitant obstructive lung disease, a condition which may limit the accuracy of the inert gas rebreathing method, and those who were unable to perform bicycle exercise were excluded.

12 HF patients with an IHM were recruited to Study II. IHM implantation had been performed in the context of previous study protocols requiring either that patients met the standard criteria for CRT (n=10) or had clinical HF in NYHA-class II-III at the time of device implant.

In Study III and IV, 10 CRT-patients received an IHM (Figure 7). They had been implanted with a biventricular pacemaker at least 3 month prior to the study and were considered treatment responders based on improved NYHA class and/or 6-min walking distance (10%). In addition to standard CRT criteria, inclusion required LBBB pattern on the ECG. Patients with uncorrected congenital heart disease, tricuspid or pulmonic stenosis, a mechanical right heart valve prosthesis, a terminal illness unrelated to their HF with life expectancy less than 1 year or subjects who were expected to undergo heart transplantation within 12 months were excluded.

All patients provided signed informed consent prior to participating in any of the studies.

Figure 6. Overview of the distribution of patients in the different studies. See text for details.
Study design

A baseline echocardiographic evaluation was performed in all studies prior to the start of the experimental protocol to characterize patients’ cardiac function and optimize the pacemaker devices.

The experimental protocol in Study I and II was designed in order to investigate different aspects of pacemaker programming and hemodynamic monitoring in conditions reflecting daily living. Patients were positioned in the left lateral- (LAT), horizontal supine- (SUP), sitting- (SIT) and standing- (STA) body position (BP) in consecutive order. Thereafter, they performed two standardized, steady-state bicycle exercises at 20 W with a resting period of 10-15 min in between.

In Study I, an analysis of 56 consecutive echocardiographic CRT optimization procedures, performed at our institution, revealed that all optimal AVDs fell within ± 40 ms of the preprogrammed “out of the box” AVD of 120 ms (sensed). The range of ± 40 ms was therefore considered clinically relevant and used for modifications of the AVD in this study. Three AVDs were programmed in each BP (randomized order): optimal AVD according to baseline echocardiography, optimal - 40 ms, and optimal + 40 ms. CO and SV were measured twice in each AVD by inert gas rebreathing. In the 8 patients with an IHM, RV pressure data were continuously recorded throughout the protocol and subsequently analyzed off-line.

Study II investigated the performance of a simple algorithm, based on characteristics of RV pressure waveforms recorded by the IHM, to track changes in CO. The IHM derived CO was compared with CO measured by inert gas rebreathing, the a priori designated non-invasive “gold standard” method. In addition, to set the accuracy of the IHM algorithm into the context of other established methods for CO measurements, impedance cardiography and Doppler echocardiography (VTI-LVOT) were also performed. During the experimental protocol outlined above, CO and RV pressures were recorded in a beat-to-beat fashion by impedance cardiography and the IHM, respectively, while inert gas rebreathing was measured twice and Doppler echocardiography once in each BP.

In Study III, patients were evaluated while resting comfortably in supine position. After a resting period of at least 10 minutes, 7 different biventricularly paced HRs ranging from 60-120 bpm (steps of 10 bpm) were programmed in random order and maintained for 60 seconds. Each step was preceded by a 60 second period of pacing at 70 bpm to allow for hemodynamic recovery. The protocol was repeated in the same way after 1 week. RV pressures and non-invasive arterial blood pressure were measured on a beat-to-beat basis by the IHM and a Portapres® device, respectively.
Study IV was designed as a single-blind, randomized, cross-over study to investigate the hemodynamic effects of different programmed basic HRs in CRT patients. An outline of the study protocol is shown in Figure 8. Patients were paced for 2 weeks at a basic HR of either 60 or 80 bpm and were thereafter crossed over to 2 weeks in the other basic HR programming. Central hemodynamic variables were continuously recorded by the IHM. At the end of each 2 week period blood samples were drawn for analysis of creatinine and Brain Natriuretic peptide (BNP), a 6-minute walk test (6MWT) was performed and quality of life (QoL) was assessed by the Minnesota Living with Heart Failure Questionnaire (MLHF). At the follow-up visits pacemaker interrogation was performed and body weight and blood pressure were measured.

**Implantable hemodynamic monitoring**

The IHM consists of a monitor with data storage capacity (Chronicle®, model 9520, Medtronic Inc., MN, USA) and a RV lead carrying a pressure sensor (Figure 9). Similar to a pacemaker implantation, the monitor is implanted subcutaneously in the subclavicular region and the lead is inserted transvenously and passively fixated in the RV outflow tract. The IHM records the following hemodynamic parameters from each cardiac cycle with a sampling frequency of 256 Hz (Figure 10): RR interval, Right Ventricular Systolic Pressure (RVSP), Right Ventricular Diastolic Pressure (RVDP), maximum positive- (RV +dP/dt) and negative
(RV \(-dP/dt\)) pressure change over time and ePAD. In addition, Pre Ejection Interval (PEI) is determined as the time between R-wave on the EGM and RV + dP/dt and Systolic Time Interval (STI) as the time between R-wave and RV – dP/dt. Furthermore, estimated mean pulmonary artery pressure (eMPAP) can be calculated using a formula based on the systolic and diastolic pressure difference and time intervals (147). The pressure sensor measures absolute cardiac pressures and to correct for surrounding air pressure, a time synchronized External Pressure Reference (EPR) records barometric pressures every minute. Data from the IHM and EPR are synchronized upon interrogation with a programmer. Using a 128 kb random access memory, the beat-to-beat measured data can be stored in different time resolutions ranging from a median value for every 2 seconds (for 4 hours of data) to every hour (for 3 months of data).

In Study I, II and III beat-to-beat RV pressure waveforms were digitally stored using a specialized programmer with proprietary software and analyzed off-line. In Study I and II hemodynamic data was calculated as the median value of the 60 seconds immediately preceding each inert gas rebreathing maneuver. In study III, we allowed for 20 seconds of hemodynamic adaptation after each change of HR programming and subsequently calculated median values.

Figure 10. Schematic illustration of RV pressure waveforms as recorded by the Implantable Hemodynamic Monitor (Chronicle®). The figure displays the temporal relationships between the intracardiac electrogram signal (EGM) and pressure waveforms from the Pulmonary Artery (PA) and Right Ventricle (RV). At the bottom is the first derivative of the RV pressure signal (RV dP/dt). See text for further details. Courtesy of Barbro Kjellström.
during the last 40 seconds at each HR level. In Study IV, the IHM was programmed to store 1 median value for each 24 minute period. Hemodynamic effects of different basic HRs were reviewed in a longitudinal- and a circadian analysis. In the longitudinal evaluation daily mean values were calculated for each hemodynamic parameter. In the circadian analysis mean values for every hour were calculated and a comparison between nighttime (midnight–4 a.m.) and daytime (8 a.m. – 8 p.m.) was performed.

A detailed description of the algorithm tested in Study II is presented in the Methods section in paper II. In short, the systolic- and diastolic pressure difference during the ejection phase is converted to a velocity difference by reversing the simplified Bernoulli equation. This velocity difference is then multiplied by the ejection time to approximate a velocity time integral (VTI) of the RV outflow tract (RVOT). In order to measure absolute CO this VTI estimation needs to be multiplied by the RVOT cross sectional area and HR and divided by patient specific indices of RV afterload. We treated the RVOT and RV afterload indices as a patient specific constant and calibrated the IHM derived CO to actual inert gas rebreathing CO in the first BP (LAT).

**Inert gas rebreathing**

An inert gas rebreathing method (Innocor®, Innovision A/S, Denmark) was used to measure CO in Study I and II. Patients were accustomed to the method by practicing the rebreathing maneuver 3 to 5 times before the start of the protocol. After a 10 minute period of hemodynamic adaptation to any new BP, subjects were instructed to breathe a gas mixture of 0.5% N₂O and 0.1% SF₆ in mainly nitrogen and oxygen, in a closed system with a constant ventilation rate. Innocor® then measured pulmonary capillary blood flow (PBF) from the rate of uptake of N₂O in the blood. In the absence of pulmonary shunts, PBF equals CO. In order to reach steady state during exercise, patients cycled for at least 3 minutes before CO was measured. CO was measured twice in each AVD (Study I) or BP (Study II) and the 2 values were averaged.

**Impedance cardiography**

In Study II, CO was also measured with impedance cardiography (Task Force ® Monitor 3040i, CNSSystems Medizintechnik GmbH, Austria). This device continuously records alterations in transthoracic electrical impedance to measure CO and SV. For this purpose 1 shortband electrode was placed at the nap of the neck and 2 on the thorax wall. A software function designed to filter out pacemaker potentials from the impedance signal was applied. The electrodes were left unchanged throughout the experimental protocol and hemodynamic data was collected beat-to-beat. SV and CO were calculated as the median of the 60 second period immediately preceding each rebreathing maneuver. Since rebreathing was duplicated in each body position, 2 sets of 60 second median values where averaged to represent each BP.

**Echocardiography**

All baseline echocardiographic investigations (Vivid 7 system, Vingmed®, General Electrics, Horten, Norway) were performed by an experienced echocardiographer after patients had rested comfortably in the left lateral BP for at least 10 minutes. Cardiac dimensions and systolic- and diastolic function were analyzed as follows: Left ventricular end diastolic-
systolic- and left atrial diameter were measured by 2D echocardiography in the parasternal long-axis view. Left ventricular ejection fraction (EF) was measured by Simpsons’ biplane method (148). Pulsed-wave Doppler was used to measure transmitral early (E) and late (A) phases of LV filling from the apical four chamber view. During the baseline echocardiographic evaluation, all pacemaker carrying patients were also subject to AVD optimization according to the mitral inflow method (109) with the exception of one CRT patient in study III and IV who had developed atrial fibrillation. Following AVD optimization, the VVD was individually tuned in the CRT patients. VVDs ranging from – 80 (RV – first) to + 80 ms (LV – first) were programmed in steps of 20 ms and the interventricular delay setting yielding the largest VTI-LVOT was selected. In all studies, SV and CO was measured by the VTI-LVOT approach. At least 3 consecutive VTIs were collected using pulsed wave Doppler. The LVOT diameter was measured in the parasternal long axis. Care was taken to keep the interrogating ultrasound beam in close alignment to the blood flow through the aortic root in order to minimize the impact of angle. SV was calculated by multiplying the averaged VT1 with the LVOT cross sectional area and CO was calculated as SV X HR.

6-minute walk test

In Study IV patients’ functional status was assessed by the 6-minute walk test (6MWT). This test was developed as a simple tool to evaluate functional capacity in HF patients (149). It has been shown that the distance covered in the 6MWT correlates with peak VO$_2$ (150) and is an independent predictor of morbidity and mortality in HF patients (151). Patients were instructed to walk as far as possible during 6 minutes in a 24 m long, flat hallway (back-to-back). They were encouraged in a standardized fashion by one of the research nurses who timed and measured the walk. After completion of the test subjects were asked to rank the perceived exertion using the Borg scale (6-20).

Quality of life assessment

In Study IV, Qol was assessed using the MLHF-questionnaire (152). This self assessment questionnaire is constructed to cover main elements of patients QoL that can be affected by HF (physical, emotional and social dimension) and is constructed as a 6-point Likert scale, range: 0-5, covering 21 items. Hence, the minimum score is 0 and maximum score is 126. The questions asked are formulated so that a higher score indicates a worse QoL. The test is reliable, in terms of good correlation between repeated baseline assessments (153). The validity of the test was acceptable when compared to other QoL measurements (154). The MLHF-questionnaire has been used in both drug- (155) and device- (87) trials to demonstrate significant improvements in QoL. The questionnaire was administered by a research nurse and completed by the patients in private.

Brain natriuretic peptide

BNP is a biologically active 32 amino polypeptide secreted from the cardiac ventricles in response to volume overload and wall stretch (156,157). This biomarker was measured at the end of each intervention period in Study IV. Blood samples were drawn from an antecubital vein and collected in EDTA containing tubes, immediately put on ice and centrifuged within 20 minutes. Serum BNP levels were analyzed at the biochemical laboratory of the Karolinska University Hospital with a specific immunoradiometric assay (Shinogi, Osaka, Japan).
Statistical methods

Continuous variables are presented as mean ± SD or median (inter quartile range) as appropriate. In Study I, differences in baseline characteristics between the CRT- and control group were analyzed with a two tailed unpaired student’s t-test or Mann Whitney U-test (chi-square/Fischer exact for nominal data). One-way repeated measures ANOVA was used for significance testing of the hemodynamic impact of different BPs in Study I and II and AVDs in Study I, as well as for different HRs in Study III. Fischer-LSD or planned comparisons were used for post hoc testing and appropriate levels of Bonferroni corrections were applied. In study II, a two-way repeated measures ANOVA using Procedure Mixed in SAS was performed for significance testing of CO changes between the body positions within and between the CRT- and control group. A two-way repeated measures ANOVA was also used in study IV to test the effects of HR and day after reprogramming. In study I and II measurement error was calculated as the coefficient of variation (%): SD/mean x 100. In study II the agreement between the different CO methods was analyzed with Bland-Altman and regression statistics. Moreover, a mixed model with slope and intercept as random effects was constructed to allow for correlation of pooled data. Due to its robustness in small samples and independence of the assumption of normal distribution, Wilcoxon matched pairs test was used to compare the clinical outcome variables in study IV.
RESULT

A summary of the baseline characteristics of the patients in study I-IV is given in Table 3.

Study I

Study I investigated the effect of shortening or prolonging the AVD with 40ms from optimal in different BP at rest and during exercise. Three patients, who had performed the baseline echocardiographic evaluation, were excluded on the day of the study protocol due to paroxysmal atrial fibrillation, extensive ventricular extrasystoles or symptoms of unstable angina (1 CRT, 2 controls) reducing the final study population to 27 CRT- and 9 control patients. As expected, the CRT group had lower EF (33 ± 14 vs. 54 ± 7 %, p < 0.001) and larger left ventricular end diastolic diameters (61 ± 11 vs. 47 ± 6 mm, p<0.001) compared with the control group. The optimal paced AVD was similar in the CRT- and control group (145 ± 16ms vs. 137 ± 14 ms, p=ns). BP change and exercise was associated with significant CO changes in both groups. CO decreased in STA body position and increased during exercise (CRT-group: 3.8 ± 1.0 L/min at SUP, 2.9 ± 0.8 L/min at STA, 4.9 ± 0.9 L/min during EXE, p<0.05 for all). AVD shortening slightly decreased CO (-0.07 ± 0.17 L/min) and increased ePAD (+1.1 ± 0.8 mmHg, p<0.05 for both) while AVD prolongation had no significant effect (Figure 11). The magnitude of CO response to AVD changes was larger in the CRT- compared with control group (median: 0.25 vs. 0.20 L/min, p < 0.05) and varied substantially between individuals ranging from 0.12 L/min to 0.56L/min in the CRT group (Figure 12). The magnitude of individual response correlated with left atrial diameter (r = 0.61, p < 0.001) in the whole patient population and with ePAD in the 8 patients with an IHM (r = 0.69, p < 0.05). The relative change in CO was significantly higher in the STA (13.1 ± 14.3 %, p < 0.05, vs. all other) compared with the other BPs (e.g. 7.6 ± 5.1 % at SUP, 6.0 ± 4.3% during EXE).

Study II

Twelve HF patients with an IHM were included in study II aiming at evaluating the accuracy of an algorithm that estimates changes in CO from IHM derived RV pressure data. IHM derived CO (CO\textsubscript{IHM}) was compared with inert gas rebreathing (CO\textsubscript{RB}) and 2 other clinically accepted methods, impedance cardiography (CO\textsubscript{ICG}) and Doppler echocardiography (CO\textsubscript{ECO}).

Table 3. Baseline characteristics of patients in study I-IV

<table>
<thead>
<tr>
<th>Study</th>
<th>n=</th>
<th>Age (yrs) mean±SD</th>
<th>Male/ Female n=</th>
<th>Ethiology (ICM/DCM) n=</th>
<th>Rhythm (SR/AF) n=</th>
<th>EF (%) mean±SD</th>
<th>LVEDD (mm) mean±SD</th>
<th>NYHA (II/III) n=</th>
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<tbody>
<tr>
<td>I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>4/5</td>
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<td>7/3</td>
<td>9/1</td>
<td>30±8</td>
<td>61±12</td>
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</table>

ICM: ischemic cardiomyopathy; DCM: dilated cardiomyopathy; SR: sinus rhythm; AF: atrial fibrillation; EF: left ventricular ejection fraction; LVEDD: left ventricular end diastolic diameter; NYHA: New York Heart Association functional calss; na: not applicable.
One patient had artifacts on the RV pressure waveforms and was excluded from the analysis. The measurement error, expressed as coefficient of variation, was low for \( \text{CO}_{\text{IHM}} \) (4±1%) and \( \text{CO}_{\text{RB}} \) (7±3%), indicating good precision for both methods. Comparing \( \text{CO}_{\text{RB}} \) and \( \text{CO}_{\text{IHM}} \), the median intra-patient correlation coefficient \( (r) \) was 0.83 (Figure 13). The association was even stronger in the mixed model (coefficient of determination, \( R^2 = 0.91, p < 0.001 \)) where intra-patient variations in slope and intercept were treated as random effects. However, it must be noted that the intra-patient correlation coefficient \( (r) \) ranged from 0.63 to 0.98 indicating that the IHM algorithm did not perform equally well in all patients. The Bland-Altman analysis of the agreement between \( \text{CO}_{\text{IHM}} \) and \( \text{CO}_{\text{RB}} \) (Figure 14) resulted in a mean

**Figure 11.** Cardiac output and ePAD as a mean of all body positions at optimal (AVD\(_{\text{opt}}\)), shortened (AVD\(_{-40\text{ms}}\)), and prolonged AVD (AVD\(_{+40\text{ms}}\)). *P < 0.05 compared with AVD\(_{\text{opt}}\) and AVD\(_{+40\text{ms}}\).

**Figure 12.** Individual changes in CO with AVD prolongation or shortening in CRT patients and controls averaged over all body positions. Black, horizontal bars denote the median change in each group. The between-group effect (ANOVA) was significant at \( P = 0.03 \).
bias of –0.39 L/min (11%), limits of agreement of ± 1.57 L/min and a 21% relative error. The tested algorithm appeared favourable compared with $\text{CO}_{\text{ICG}}$ (median intra-patient $r = 0.63$, bias = -1.15 L/min (31%), limits of agreement = ± 3.5 L/min and, relative error = 51%) and $\text{CO}_{\text{ECHO}}$ (median intra-patient $r = 0.73$, bias = -0.45 L/min (13%), limits of agreement = ± 1.7 L/min and, relative error = 23%).

Figure 13. Comparison of calibrated cardiac output (CO) derived from the Implantable Hemodynamic Monitor (IHM) and CO measured with foreign gas rebreathing (RB). The figure displays the individual data points and regression lines comparing calibrated $\text{CO}_{\text{IHM}}$ and $\text{CO}_{\text{RB}}$.

Bias = $-0.39 \text{ L/min}$

Figure 14. Bland-Altman plot showing the agreement between calibrated cardiac output (CO) derived from the Implantable Hemodynamic Monitor (IHM) and CO measured with inert gas rebreathing (RB). The figure displays the difference between the two methods plotted against the mean value. The bold black line marks mean bias (-0.39 L/min) and the dotted black lines mark the upper and lower limits of agreement (±1.57 L/min).
Study III

In Study III, the acute effects of different biventricularly paced HRs (60-120 bpm) were measured in 10 CRT patients, who were also implanted with an IHM. The algorithm validated in Study II was used to measure CO and estimates of vascular resistance. Filling pressures (ePAD and RVSP) decreased significantly in the range of 60 – 100 bpm (p < 0.03 and p < 0.003, respectively) but tended to level out or even increase at HRs > 100 bpm (Figure 15). CO increased over the whole range of tested HRs and was significantly higher at 120 bpm (5.6 ± 1.3 L/min) compared with 60 bpm (3.9 ± 0.9 L/min, p < 0.001). A positive force frequency relationship was observed in the RV, as evidenced by a significant increase in RV + dP/dt with increase in paced HR (main effect, p < 0.001). There was a positive correlation betweenRV + dP/dt and paced HR ($R^2=0.95$) best described by a 2:nd degree polynomial equation: RV + dP/dt = 0.02 x HR^2 - 2.2 x HR + 361. Arterial diastolic blood pressure increased significantly with increased paced HR (72 ± 18 mm Hg at 60 bpm vs. 82 ± 23 mmHg at 120 bpm, p < 0.01) while arterial mean- and systolic blood pressure was unchanged. Mainly due to the increase in CO estimated pulmonary arterial- and total peripheral resistance decreased with increase in paced HR (p < 0.01 for both).

*:	p<0.01	vs.	60	bpm.

**Figure 15.** Effect of increase in biventricularly paced heart rate on cardiac output, estimated pulmonary artery diastolic pressure (ePAD) and right ventricular systolic- and diastolic pressure. Data is presented as mean ± SEM. *: p<0.01 vs. 60 bpm.
Study IV

Study IV aimed at investigating the hemodynamic response to different programmed basic HRs (60 or 80 bpm for 2 weeks each) in ambulatory CRT patients. Complete hemodynamic data was available for 12 consecutive days in each HR programming. As expected, HR (mean of the 12 daily averages) was significantly higher with 80 bpm compared with 60 bpm (+13.4 ± 5.5 bpm, p < 0.05). Mean ePAD decreased during pacing at 80 bpm (23.4 ± 6.2 mmHg) compared with 60 bpm (25.1 ± 6.5 mmHg, p = 0.02) (Figure 16). Similarly, RVSP and RVDP were lower with a basic HR of 80 bpm. (p < 0.05). Mean CO, on the other hand was significantly higher with 80 bpm (4.5 ± 1.3 L/min) compared to 60 bpm (4.2 ± 1.4 L/min, p < 0.05). The hemodynamic effects observed were not due to different activity levels since activity counts were similar during the study periods. Although mean RV pressures and ePAD were lower during the period with 80 bpm compared to 60 bpm, there was a significant trend of increasing RVSP, RVDP, SV and ePAD over time during pacing at 80 bpm (main effect, p < 0.05 for all). The hemodynamic effects did not translate into changes in 6MWT, QoL or BNP, which were all similar comparing the 2 periods with different basic HRs in this small sample.

![Graph showing longitudinal effects of pacing with a basic heart rate of 60 bpm or 80 bpm in ambulatory CRT patients.](image)

**Figure 16.** Longitudinal effects of pacing with a basic heart rate of 60 bpm or 80 bpm in ambulatory CRT patients. The analysis of daily means ± SEM of heart rate, patient activity, cardiac output and filling pressures (ePAD) are displayed. Heart rate and cardiac output were significantly higher, while ePAD was significantly lower during the period of 80 bpm (HR: p<0.05). ePAD increased with time during the period of 80 bpm (DAY: p<0.05) and there was a trend toward increase in cardiac output during 80 bpm (DAY: p=0.066). Activity was largely unaffected by basic heart rate programming.
GENERAL DISCUSSION

This thesis examined the hemodynamic aspects of various pacemaker programmings in HF patients receiving CRT. We observed a small, but significant decrease in CO when an optimized AVD was reduced within a narrow range, similar to changes that are applied in clinical practice. The extent of the CO response to changes in the AVD was larger in CRT compared with control patients and varied substantially between individuals. Further, a simple algorithm that uses pressure data from an implantable hemodynamic monitor (IHM) was found to be useful in tracking CO changes in HF patients. The algorithm was then applied in studies to examine the effects of different biventricularly paced HRs in the acute setting and during ambulatory periods in CRT patients. A basic HR of 80 bpm, compared with 60 bpm, improved hemodynamics acutely and during a 2-week period. However, trends indicated deterioration over time with 80 bpm.

AVD optimization

Varying the AVD widely in resting supine CRT patients results in acute hemodynamic changes in the order of 13-34% (66,107,119). Typically, the responses with regard to systolic hemodynamic parameters generate an inverse U-shape that is fairly wide in the middle, where smaller AVD changes elicit limited hemodynamic effects. In contrast, more pronounced effects are generally seen with excessively long and short AVDs, which are unlikely to be applied in clinical practice. In fact, our analysis of 56 consecutive clinical AVD optimizations using the “Ritter” procedure demonstrated that all optimal AVDs were ± 40 ms of the preprogrammed, empirical AVD setting of 120 ms (sensed). Applying this range to the optimal AVD in CRT patients, we noted a significant decrease in CO with a shortened AVD, but prolongation had no effect. Although it was significant, the magnitude of change was only 2 % and, thus, had unclear clinical relevance.

This small change is contrasted by studies that have shown CO effects of 10% to 32% with AVD modulation in a similar range as in our study using echo- or impedance cardiography (111,112,158,159). This discrepancy might be attributed to several factors, such as differences concerning the patients included or methodological aspects. Although the patients in these studies had similar baseline characteristics as in Study I, AVD optimization was performed within 1 week of implantation; in our study, patients had been treated with CRT for 21 ± 11 months. We may speculate that the reverse remodeling (84) and improved autonomic control (82) that result from CRT improve cardiac adaptation to preload changes and hence diminish the effect of different AVDs after some months of treatment.

Although the mean effect of changing the AVD was small in the entire patient population, the large impact on CO that we observed in certain individuals suggests that AVD optimization should be performed routinely in all patients, in order not to miss those in whom CO can be greatly affected. But, AVD and VVD optimization procedures are time-consuming, expensive and, in the case of invasive methods, add potential risk for the patients.

In addition, the clinical efficacy of optimization is unclear (117,122). Therefore, many centers routinely maintain the intervals that have been preset by the manufacturer at implantation and perform device optimization only in patients who do not improve by CRT or deteriorate for unclear reasons during the course of treatment.
Given the notable hemodynamic contribution by AVD modification in certain individuals, an even better strategy appears to be identifying patients who benefit most from device-tuning already at baseline.

In Study I, individual hemodynamic responses to AVD modifications varied widely. The magnitude of change correlated with left atrial diameter and ePAD. Because left atrial size is a marker of elevated filling pressure and diastolic dysfunction (160-162) this finding is consistent with other studies that have suggested that greater hemodynamic improvements are seen with AVD optimization in patients with more severe diastolic dysfunction and increased filling pressures (163,164). These data suggest that information on atrial size, diastolic function, and filling pressures, often known at implantation, can aid resource allocation and selection of patients which should be offered device optimization. However, more studies are needed to determine the impact of filling pressures and diastolic function on AVD programming and the efficacy of strategies for patient selection.

An alternative approach to circumvent the obstacles that are associated with current optimization procedures is to develop automated algorithms that are incorporated into the device and optimize its settings in a closed loop manner. Several methods are readily available or under evaluation (165-167) that are based on electrical delays measured by EGM (165), endocardial acceleration that is measured in the RV by a sensor electrode (166), or changes in intracardiac impedance (167). Although these methods have been validated against established hemodynamic measurements, they are limited by their inability to measure actual LV performance and still warrant evaluation of clinical utility.

In Study II, we demonstrated that a simple algorithm, applied in an IHM, can track changes in CO, a measurement of global systolic performance. It may be speculated that an IHM or hemodynamic sensor that measures CO/SV and is incorporated into or linked with a CRT device can scan for optimal pacemaker settings in a closed loop manner. This feature would offer the advantage of automated AVD optimization based on regularly measured central hemodynamic information.

Yet, the findings in Study II do not support the direct application of the algorithm in clinical practice in its current form due to its weak performance in certain patients. Moreover, additional validation studies that compare the IHM method with invasive measurements of CO are needed to document its bias and precision further. Therefore, supplementary studies are warranted to develop and validate this method. An initial evaluation of the usefulness of IHM-guided device optimization that is based on ePAD responses has been reported by our institution (146).

The need for quick and simple optimization procedures has been underscored by studies that have suggested that optimal AVDs and VVDs may change over time, implying the necessity of repeated optimization procedures during follow-up (168-170).

**Cardiac output in heart failure**

CO and left-sided filling pressures are important physiological variables that describe hemodynamic status in HF patients. Typical HF symptoms commonly reflect elevated left-sided filling pressures and subsequent pulmonary congestion (126), while symptoms in the context of decreased resting CO, such as lack of energy and fatigue, are less specific (171). Nohria et al. assessed the hemodynamic profile of 452 patients who were referred to a specialist clinic. In patients presenting with signs of decompensated HF, two-thirds had evidence of only elevated filling pressures, and one-third had signs of a combination of elevated filling pressures and reduced CO (172).
This study also documented that the 1-year risk of death or heart transplantation was twice as high in the latter group, suggesting that the supervening of reduced CO is an important factor in the course of clinical deterioration into decompensated HF and that patients with both pulmonary congestion and reduced CO are at greater risk compared with those who have only pulmonary congestion.

Furthermore, the CO response to exercise is an important variable that describes HF severity. Exercise intolerance, most frequently measured as peak oxygen uptake (peak VO₂) during symptom-limited exercise, contributes to morbidity and is a strong predictor of mortality in HF patients (173). Peak VO₂ and peak CO are linked (174), and more direct indices of cardiac pump function, such as CO reserve (CO peak exercise – CO rest), have been proposed to add prognostic power compared with peak VO₂ in patients with mild to moderate HF (175).

Another pathophysiological concept that describes the role of CO in circulatory pathophysiology, the “arterial filling hypothesis,” developed by Shrier et al., states that CO and vascular resistance are the most important determinants of the regulation of body fluid volume (9). According to this hypothesis, a reduction in CO translates to “arterial underfilling,” which is sensed by receptors in the high-pressure circulation, causing increased sympathetic activity and RAAS activation to maintain the integrity of arterial circulation by vasoconstriction and water and sodium retention.

The direct Fick method, introduced in the 19th century by the German physiologist Adolf Eugen Fick (1829 – 1901), is still considered the gold standard for measuring CO (176). Requiring samples of arterial and mixed venous blood and oxygen consumption, it was largely replaced as the method of choice in clinical cardiology when Swan and Ganz introduced their balloon-tipped catheter in 1970, allowing for simpler CO measurement by thermodilution (177). Both techniques require cardiac catheterization and are, thus, associated with risk, high cost, and the need for advanced equipment and trained personnel.

To overcome some of these difficulties, several non-invasive techniques for determining CO have been proposed, such as Doppler echocardiography (178), inert gas rebreathing (179), impedance cardiography (180), and finger arterial blood pressure methods (181). These methods share the advantage of safety and are generally easy to perform. Moreover, they have been validated in comparison with invasive CO measurements in HF patients (178-180). But they are limited by their inability to measure actual CO and other methodological concerns.

Doppler echocardiography depends on the close alignment of the ultrasound beam and bloodstream and an accurately measured aortic diameter. Furthermore, representative cardiac cycles must be selected carefully for analysis. Reliability measures of Doppler echocardiography derived CO during exercise have been reported to reach 15% (182). Inert gas rebreathing techniques to measure CO are also associated with some limitations that are related to the actual measurement of pulmonary capillary blood flow (PBF) and the assumption that PBF equals CO. Measurements of PBF can be inaccurate due to uneven distribution between ventilation, lung tissue volume, alveolar volume, and pulmonary blood flow, which might exist in more severe forms of pulmonary disease (183). Also, the actual PBF measurement is not equal to CO if blood is shunted through poorly ventilated parts of the lungs (179). Nevertheless, from a practical perspective, these limitations are relatively easy to control for (179). According to some experts, inert gas rebreathing is the ideal method of measuring peak CO during exercise—even superior to the invasive gold standard—because it does not require steady state conditions (184) which may be difficult to maintain with strenuous exercise.

Impedance cardiography can over- and underestimate SV in the presence of heart valve insufficiency and stenosis, respectively (180). Other potential sources of error include cardiac
shunts, reduced compliance of the aorta and high fluid accumulation in the thorax. Clearly, these limitations can compromise its use in HF patients. Although impedance cardiography has been validated during exercise (184), problems with impedance cardiograms due to movement and respiration have been reported during exercise (184). In our experience, the stimulation impulses from a pacemaker, particular in CRT patients with 2 separate ventricular spikes due to sequential VVD programming, can interfere with the transthoracic impedance signal.

Notably, all non-invasive CO methods merely deliver “snap-shots” of information. Although continuous CO monitoring with temporary catheterization and other methods have been proposed to guide treatment in critically ill patients (185-187), no method exists for long-term, continuous monitoring of CO in ambulatory patients.

For this purpose we developed an algorithm in collaboration with Medtronic Inc. to track CO changes with an IHM. Study II evaluated the accuracy of the algorithm compared with inert gas rebreathing. The mean bias was −0.39 L/min, or 11% (bias / mean), with limits of agreement of ± 1.57 L/min. IHM-derived CO appeared favorable compared to both echo- and impedance cardiography. In a meta-analysis, Critchley & Critchley, identified 25 studies that compared Doppler echocardiography or impedance cardiography with invasive techniques, including the direct Fick method and thermodilution (188). Mean bias and limits of agreement for the 23 impedance cardiography studies were 0.6 ± 1.7 L/min, and for Doppler echocardiography (n=11 studies) 0.8 ± 3.4 L/min. This reference data suggest that the accuracy and precision of the IHM algorithm is similar to those observed with Impedance cardiography and Doppler echocardiography in previous studies.

However, the proposed CO method did not perform equally well in all patients, as evidenced by the wide range in individual correlation coefficients. Therefore, further testing is needed before it is applied routinely in a clinical setting. The method can potentially be improved by excluding the segment of the systolic pressure curve that represents reflective pulses from the pulmonary artery. This step could estimate peak systolic pressure during the ejection phase more accurately. Such an algorithm has been proposed by Karamanoglu et al. (147,189) and warrants validation in HF patients. However, the algorithm proposed by Karamanoglu et al. requires advanced analysis of individual RV pressure waveforms by custom software that is unavailable in current IHM models, while the simplicity of our formula allows for its application in existing IHM datasets.

**CRT and heart rate**

Although it is a potentially impactful factor, the clinical role of differential programming of the basic HR in pacemaker patients, and in particular those with a CRT device, is unclear. We used an IHM and the algorithm that was evaluated in Study II to determine the acute hemodynamic effects of increasing the biventricularly paced HR in resting CRT patients. Hemodynamic improvements were observed when the biventricularly paced HR was increased within the range 60–100 bpm. Moreover, a positive FFR was noted in the RV. Several groups have investigated various hemodynamic aspects of increasing biventricularly paced HRs in resting supine patients in the range 70-140 bpm (71,190-193). These studies demonstrated that biventricular pacing improves the blunted FFR, which is typically associated with HF. Notably, this phenomenon was observed only with biventricular stimulation—not with RV-pacing (190) or atrial pacing (71,192).

The acute improvement in contractile response to increased stimulation frequencies with biventricular pacing can be attributed to prolonged diastolic filling times with CRT compared...
with RV-only pacing, which renders the contractile state of the heart less susceptible to preload reduction at higher stimulation frequencies (190). Another mechanism of the CRT-associated improvement in FFR was proposed by Mullens et al., who demonstrated that several months of CRT resulted in the upregulation of genes that regulates myocardial contractile functions (192). The improved contractile responses to higher stimulation frequencies might in part explain the increased exercise capacity that is associated with CRT.

In Study III we documented a significant positive FFR also in the RV. The implications of this result remain unclear, because we lack data on LV +dp/dt. However, despite its “shadow existence” in the literature, the contribution of RV function in HF is highly important, and thus, we believe our finding is of significant value.

Steendjik et al. observed that CO is maintained at higher HRs during CRT, in contrast to atrial pacing (71). Vollmann et al. showed that biventricular stimulation— but not RV pacing— improves the FFR in HF patients. Moreover, RV pacing with an HR > 120 bpm resulted in increased filling pressures (LVEDP), while CRT was associated with unchanged filling pressures at higher HRs (190).

These results clearly demonstrate that biventricular stimulation improves the hemodynamic response to increased HRs, manifested by increased contractility, reduced filling pressures, and maintained CO, compared with rapid RV or atrial pacing. Less is known, however, about the hemodynamic effects of increased biventricularly paced HRs in the clinically relevant range (50–100 bpm).

In Study III, biventricular pacing within 60-100 bpm reduced cardiac filling pressures and estimates of vascular resistance, and CO and arterial diastolic pressure increased. This observation might be important, because reduced filling pressures (194) and increased diastolic pressure (195) have been associated with reduce sympathetic activity, presumably through reflex sympathoinhibition that is mediated by cardiopulmonary and arterial baroreceptors. Therefore, it may be speculated that increase in paced HR reduce sympathetic activity. This hypothesis has not been tested in CRT patients, but studies in patients with atriosynchronous RV pacing have demonstrated that muscle sympathetic nerve activity declines with increased HR between 60-100 (196) and 100-120 bpm (197). Because sympathetic reduction is considered a primary target of HF treatment, studies that investigate the relationship between paced HR, in a clinically relevant range, and sympathetic activity in CRT patients are warranted and have been initiated by our group.

Although the observed increase in CO with increased paced HR is reasonable (CO is a function of HR and SV), other studies have noted a different relationship between the manipulation of HR and CO. Studies from the 1960s that examined the effect of increased HRs in VVI pacemakers typically demonstrated flat CO responses to elevated ventricular stimulation frequencies between 60-110 bpm (198).

Similarly, increased paced HRs with AV-synchronous RV pacing (199) and decreased HRs with ivabradine (200) result in unaltered CO levels in HF patients, indicating an inverse relationship between HR and SV and suggesting that in certain settings, direct manipulation of HR, per se does not affect CO automatically. The disparate CO response to increased HR in Study III might have several causes, such as differences in pacing configuration and the degree of cardiac dysfunction. Furthermore, our finding is supported by Voss et al., who demonstrated an increase in CO with increased biventricularly paced HRs between 40-70 bpm (201).

Although Paper III determined the acute effects of various HR settings in resting patients, different results can occur after permanent programming during longer-term follow-up in...
ambulatory patients. Therefore, Study IV assessed 2 different basic HR programmings (60 and 80 bpm) during 2-week periods of daily living activities. The indices of cardiac filling pressures were lower and CO was higher during pacing at 80 bpm, indicating hemodynamic benefits with increased basic HR. During the 80-bpm period, however, filling pressures and SV increased over time, which might reflect increased volume load and suggests that hemodynamic deterioration occurs if an elevated basic HR is maintained for a longer time-period.

The observed RV FFR from the acute setting in Study III did not impact RV contractility during ambulatory living with increased basic HR, as shown in Study IV. In contrast, RV +dP/dt was unchanged despite a mean HR difference of 14 bpm. This finding might be due to the insufficiency of the difference in mean HR to produce an important FFR. Indeed, the slope of the FFR was less pronounced at HR < 100 bpm in Study III. Alternatively, differences in preload conditions during daily activities might influence RV contractility to a greater extent than FFR, thus obliterating small HR-induced changes in contractility.

The mean reduction in cardiac filling pressures that were documented during pacing at 80 compared with 60 bpm was -1.7±1.9 mm Hg (ePAD) and -3.3±3.8 mm Hg (RVSP). Two recent studies, using the same IHM device as in this thesis, described the hemodynamic changes that developed during the 49 days (140) and 30 days (141) that preceded a major HF event (acute hospitalization or the need for urgent iv treatment). RVSP increased by 5.0 and 3.2 mm Hg, and ePAD increased by 4.0 and 3.8 mm Hg, respectively. Minor HF events, including oral adjustment of the diuretic dose, were associated with increases of 2.8 mm Hg (ePAD) and 4.4 mm Hg (RVSP) (141). In Study I, acute shortening of the AVD increased the ePAD value by 1.1 mm Hg. These reference values suggest that the effects on filling pressures in this study are clinically relevant.

Three small studies have investigated the long-term (3-14 months) effects of increased paced HR in HF patients. These studies reported worsening NYHA class and decreased EF (202), lower peak VO2 and 6MWT (203), and increased ventricular volumes (204) following long-term pacing with an elevated HR. Notably, only 1 study included CRT patients, constituting 2/3 of the studied population (202). Considering the differential acute effects of RV-only compared with biventricular stimulation, these findings might not be extrapolated directly to a CRT population. In Study IV, however, we found signs of hemodynamic deterioration after some time when an elevated basic HR was maintained, suggesting detrimental long-term effects also of elevated basic HRs in CRT patients.

Nevertheless, the findings in Studies III and IV suggest that increased basic HRs in CRT patients relieve congestion and increase CO in the short term. These observations might be useful in certain clinical situations, such as HF decompensation.
CONCLUSIONS

• Varying the AV-delay within a narrow, clinically relevant range has a small overall impact on cardiac output in CRT patients.

• The magnitude of hemodynamic response to AV-delay modifications, however, varies widely between individual patients and appears to be associated with left atrial size.

• An algorithm based on right ventricular pressure waveform characteristics, recorded with an implantable hemodynamic monitor, is able to track cardiac output changes in heart failure patients with acceptable accuracy and precision.

• Acutely increasing the biventricularly paced heart rate in the range of 60 – 100 bpm reduces filling pressures and increases cardiac output in CRT patients.

• A significant force frequency relationship is present in the right ventricle during biventricular stimulation.

• Increasing the basic heart rate from 60 to 80 bpm during an ambulatory 2-week period results in decreased filling pressures and increased cardiac output in CRT patients.

• Within this time frame, however, signs of hemodynamic deterioration over time are observed when the higher basic heart rate is maintained.

• Elevating the basic heart rate in CRT patients may be considered for short-term use to lower filling pressures and increase cardiac output in certain clinical settings.
I wish to express my sincere gratitude to all those who have contributed, in different ways, to this thesis.

In particular, I wish to thank:

Associate Professor Frieder Braunschweig, main supervisor, for supporting me in every way on my journey from being a 3rd year medical student to defending this thesis. Thank you for always being available for inspiring discussions and problem-solving, despite a very busy schedule. It has been a privilege to work with you in the environment you have created where hard work have been mixed with boat trips and cross country skiing. I am forever grateful.

Professor Cecilia Linde, co-supervisor and Head of Department of Cardiology, for all the support I have received through the years.

Dr. Morten Damgaard and Professor Peter Norsk, leading experts in inert gas rebreathing, for sharing your knowledge.

Mustafa Karamanolu, Barbro Kjellström and Tom Bennett for inviting me to contribute to the fascinating research about, and development of, implantable hemodynamic monitoring.

David Ersgård and Helena Karlsson for helping me with device management during the experimental protocols. I have had a great time working together with you.

The other members of Frieder Braunschweigs’ research group: Anders Sahlén, Kristjan Gudmundsson and Philip Aagaard for interesting discussions and valuable input.

Dr. Mikael Sander, expert in applied physiology and muscle sympathetic nerve recordings, for chairing your knowledge.

Elisabeth Berg, expert statistician, for the help with mixed models, always helping although last minute assistance was often sought.

Roger Kessels and Kathryn Hilpisch, co-authors, for valuable criticism of manuscripts and interesting discussions.

Professor Frits Prinzen, world renowned expert in the physiology of cardiac pacing, for inviting me to your research group at the University of Maastricht to learn more about device optimization.

Professor John Pernow, for providing excellent research conditions at the Department of Cardiology.

Viveka Rendelius, for help with performing the echocardiographic evaluations.
The staff at the Cardiology Unit. In particular I wish to thank Anita Fredenson for assistance with patient recruitment, Raquel Binisi for making sure my paychecks always came after all, Magnus Mossfeldt for solving all my computer problems, and Eva Wallgren for sharing your great knowledge concerning everything that has to do with clinical research.

Reidar Winter, Aristomenis Manouras and Kambiz Shahgaldi at the Department of Clinical Physiology, Huddinge for expert help with echocardiographic issues.

Thomas Fux, Lars Lund, Anders Gabrielsen and Magnus Bäck for discussions and laughs.

Fredrik Gadler and Jonas Hörnsten for implanting the devices.

Peter Horwath, for being an excellent cicerone in Boston and always responding quickly when patients were waiting and we had run out of test gas to the Innocor.

Carl-Johan Sundberg for awakening my scientific interest.

Fredrik, John, Sebbe, Daniel N, Daniel A and all other friends for forcing me to put work aside from time to time.

My brother, Henrik for knowing me so well and always making me laugh when we meet. Mia for being such a lovely person.

My sister, Kristine for being who you are. Johan for barbequing the juiciest hamburgers east of New York. Gustaf for providing hope of a bright future.

My parents Mona and Carl-Gustav for endless love and support. Your contribution to science by means of babysitting cannot be underestimated.

My parents-in-law Lena and Staffan for support and encouragement.

Cecilia, Elin and Ester. Cecilia for putting up with me being absent-minded for long periods of time, and Elin and Ester for requesting my full attention and therefore making me forget about work for a while.

And above all to the patients who willingly participated in the studies.

This work has been supported by grants from the Swedish Heart-Lung Foundation.
OTHER SCIENTIFIC CONTRIBUTIONS

Not included papers to which I have contributed:


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