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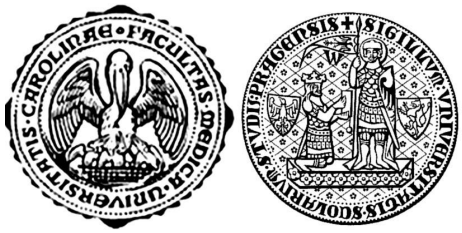

The effect of biventricular pacing as compared to single-site left-ventricular pacing and bifocal pacing of the right ventricle in patients with chronic heart failure

Ph.D. Thesis

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List of abbreviations:

ACE inhibitor – inhibitor of the angiotensin-converting enzyme

AV – atrioventricular

BFP – bifocal pacing of the right ventricle

BVP – biventricular pacing

CHF – chronic heart failure

CRT – cardiac resynchronization therapy

ICD – implantable automatic cardioverter-defibrillator

IVCD – nonspecified intraventricular conduction delay

IVS – interventricular septum

LBBB – left bundle branch block

LV – left-ventricular

LVEDD – left ventricular end-diastolic diemeter

LVEF – left ventricular ejection fraction

LVP – single-site left-ventricular pacing

NYHA class – functional class

RV – right-ventricular

RVA – right ventricular apex

CONTENT

INTRODUCTION

INTRODUCTION

Chronic heart failure (CHF) represents a very common condition that is currently one of the leading causes of the morbidity and mortality in industralized countries. A deeper understanding of the pathophysiology of CHF and the associated compensatory mechanisms has allowed the implementation of newer treatment regimens including ACE inhibitors, beta-blockers and spironolactone. These drugs are able to slow progression and improve prognosis of the disease. However, inspite of substantial improvements in pharmacological treatment that have been made over last decades, 5 to 15% of the CHF population continues to suffer from persistent severe symptoms. The rest of CHF population could be divided in two groups of similar size: one with mild and one with moderately severe symptoms[1]. Unfortunately, only some patients with advanced CHF are appropriate candidates for the heart transplant as an ultimate treatment modality in CHF.

The finding that cardiac pacing is able to improve the hemodynamic status in some patients with advanced CHF has ushered a new era in management of this condition – era of so called cardiac resynchronization therapy (CRT). The widespread use of CRT was predominantly based on the recognition that the dyssynchronous activation of the heart, especially of the ventricles, can be a factor associated with further progression of CHF and worse prognosis[2]. Furthermore, CRT was documented to slow or even stop this process, induce reverse remodeling[3-5] and reduce mortality[6,7].

However, despite growing knowledge about the mechanism of how CRT works, there are still unanswered questions, especially regarding 1) the usefulness of various pacing strategies in the treatment of the CHF and 2) the identification of different factors that can modify the magnitude of improvement during CRT or predict non-responderity to this therapy. Therefore, the aim of this dissertation was to focus on these issues.

1. DEFINITION AND EPIDEMIOLOGY OF CHRONIC HEART FAILURE

CHF is pathophysiologically defined as the affliction of the heart that is associated with reduced cardiac output despite sufficient ventricular filling. As a result, the heart is not able to meet the metabolic demands of the tissues (delivery of the oxygen, CO2 and the metabolic byproducts). Heart failure without the decrease of cardiac output may occur during excessive increase of the ventricular filling pressure[8].

In the routine clinical practice, the diagnosis and the treatment have focused on CHF as a clinical syndrome that is characterized by ventricular dysfunction and one or more signs of back- and/or forward failure (dyspnea, fatique, edemas). A precise estimate of the incidence and prevalence of CHF is difficult to obtain because it depends on the definition of CHF and early recognition of the disease. Using the above definition, CHF affects 1 to 5% of the population or 10 to 50 million people in Western countries[8,9,10]. The prevalence rapidly increases with age >65years[9-11]. Despite all advances in pharmacotherapy, the amount of people suffering from CHF is increasing every year with an annual incidence about 2-3‰ [10,12]. The reasons for the growing incidence and prevalence of CHF are mainly related to ageing of the population and to the advances made in hypertensive and coronary heart disease therapy that leads to longer life-expectancy in these patients[13].

Although new pharmacological interventions improved the survival of CHF, it still remains a condition with a high mortality rate[13]. Some studies indicate that the annual mortality of stable CHF reaches 10-20% and that only 30-45% of the CHF population is still alive 5 years after initial diagnosis of CHF[13,14]. The mortality rate is approximately six or seven times greater in a CHF population as compared to the general population of the same age[15]. The mortality of patients with a new-onset HF is even higher than in those with stable CHF and reaches 30% in the first 6months after the diagnosis[16,17].

The predominant causes of death in CHF population are progressive heart failure and sudden death. A conservative estimate is that about 50% of CHF patients die due to further progression of CHF and about 50% die suddenly[18]. Interestingly, it seems that mode of death is dependent on the severity of CHF. While patients in functional class NYHA II die predominantly on a sudden, unexpected death, further progression of CHF is the leading cause of death in patients in functional class NYHA IV[19] *(Figure 1)*. The knowledge about what causes the progression of the CHF is limited. It may be a result of recurrent and undersensed or unrecognized myocardial ischemia, arrhythmias, remodeling of the left ventricle (LV) or its combination[20]. Also sudden death does not represent a homogenous entity. As ICDs reduce the risk of sudden death by about 50%, it seems that almost 50% of sudden deaths may not be primarily arrhythmic[21].

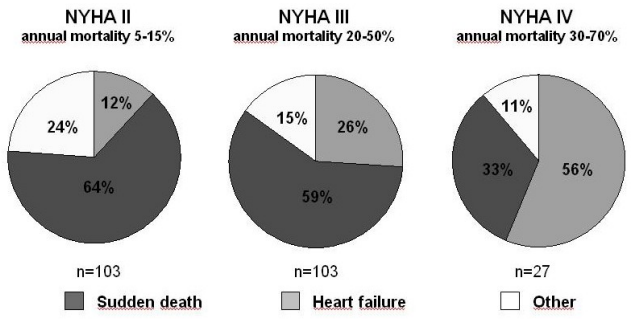

Figure 1: Modes of death in chronic heart failure
(MERIT-HF Study Group, Lancet 1999;353:2001-2007)

2. IMPORTANT ELECTROMECHANICAL FEATURES OF CHRONIC HEART FAILURE WITH REGARD TO CARDIAC RESYNCHRONIZATION THERAPY - PATHOPHYSIOLOGICAL NOTES

A complex pathophysiologic process altering both electrical and mechanical events during the cardiac cycle is often present in patients with advanced CHF. The changes result from a modified microstructure of the myocardium and from the fully expressed compensatory mechanisms[22,23]. They may affect both the working myocardium, thus leading to the deterioration of ventricular function and size, and/or specialized myocytes of the conduction system, thus harming one or more of its functions. It is: 1/ a sufficient heart rate reflecting actual metabolic demand, 2/ an optimal timing of the atrial contraction with regard to the ventricular systole, and 3/ a synchronous activation and contraction of the ventricles.

CHF is often associated with an alteration of some of these functions. It can result in sinus node dysfunction manifesting as the chronotropic incompetence. In combination with the pharmacological adrenergic blocade, it can cause worsening of the exercise tolerance in CHF patients[24].

The prolonged atrioventricular (AV) conduction shifts the atrial contraction with regard to the ventricular systole, thus producing AV dyssynchrony. In such case, the atrial contraction may fuse with the early passive filling phase and limit atrial contribution to the ventricular filling. In addition, AV conduction >250ms is associated with a shortening of the diastolic phillling phase. Moreover, optimal timing of atrial systole is important for a proper function of mitral valve. Prolonged AV conduction may cause its insufficient closing and presystolic mitral regurgitation[25,26].

However, among all above mentioned variables, the changed activation sequence of the ventricles seems to be the most crucial for the hemodynamic performance of the failing heart. Different ventricular conduction abnormalities, reflected in the widening and changed morphology of the QRS complex on the surface ECG, may occur in CHF as will be discussed later. They change electrical and mechanical interactions between the right and left ventricle (interventricular dyssynchrony) and/or between the opposite walls of the LV during the cardiac cycle (intraventricular dyssynchrony).

On an individual basis, total ventricular asynchrony may result from either interventricular or intraventricular dyssynchrony or from combination of them. In addition,

AV asynchrony may participate on the hemodynamic worsening and progression of CHF in some patients. It was estimated that ventricular dyssynchrony is present in approximately 20-30% of patients with CHF[27]. More importantly, there is a growing evidence that the presence of LV dyssynchrony (mainly on the intraventricular level) is related to the prognosis in CHF patients[28,29].

In addition, there is a close relationship and interdependence of ventricular dysfunction, dilatation of the ventricle(s) and conduction disturbances (on both the atrioventricular (AV) and ventricular level)[30-32]. Both the degree of left-ventricular (LV) dysfunction and the duration of QRS complex were identified as the independent predictors of death in CHF population[33-36]. Moreover, higher mortality was found in patients with LV systolic dysfunction, depending on the severity of conduction disturbances as reflected in QRS duration[27,37] *(Figure 2)*.

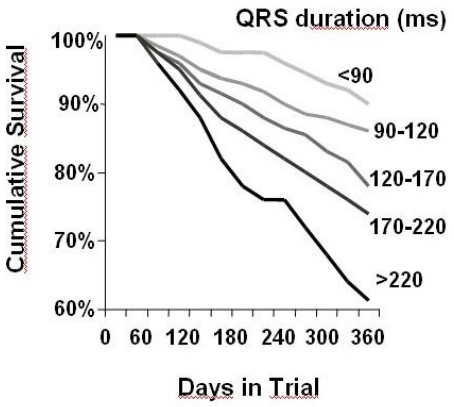

Figure 2: QRS duration and mortality
(Adapted from Gottipaty; JACC 1999;33:145A)

2.1. ELECTRICAL ACTIVATION OF THE VENTRICLES PHYSIOLOGICALLY AND DURING LBBB

In the normal hearts, electrical activation of both ventricles is preceded by depolarization of the His-Purkinje system. It results in a rapid and almost simultaneous activation of both ventricles spreading from few separate regions reflecting the bundle branching. The rest of the heart is than activated quickly with total ventricular activation time 80-100ms[38-40]. The activation wavefront of the RV started at the free wall and spreads to the interventricular septum (IVS) with the latest RV activation located usually posterobasally or anterobasally[39]. Independently to the QRS axis, the latest LV activation is located mostly in the basal posterolateral region[38,39].

Although different ventricular conduction delays can be found in patients with CHF, conduction disturbances with left bundle branch block (LBBB) morphology predominate. Prevalence of LBBB is about 30% in CHF population >65years, while it reaches only 1-3% in the general population of the same age[33,34]. In addition, the presence of LBBB, but neither right bundle-branch block nor nonspecific intraventricular conduction delay, seems to be associated with a higher morbidity and mortality in asymptomatic and apparently healthy

patients[41] and their risk increases in the presence of concomitant heart disease and/or CHF[34,35].

The presence of typical LBBB significantly modifies the ventricular activation sequence. RV usually precedes LV activation[42,43]. Although prolonged in some cases, RV activation pattern is usually similar to that observed during normal sinus beat[39]. On the contrary, LV exhibits mostly different activation sequence with right-to-left transseptal conduction[39,42-44]. The patterns of LV activation are variable, but the posterolateral basal LV region frequently represents an area with the latest activation[39,40,42,45,46]. Due to the changed activation pattern and significant reduction of the conduction velocities[39], the total LV activation time is prolonged in most patients with LBBB[39,40,42,44,45].

Prolonged and changed ventricular activation pattern (as reflected in the morphology, axis and duration of the QRS complex) may result from either prolonging between RV and LV activation onset (interventricular delay), between activation of opposing walls of the LV (intraventricular delay) or from combination of them[47,48]. In this context, QRS duration can serve as a marker of total ventricular electrical asynchrony. However, it similarly reflects LV intraventricular and interventricular dyssynchrony[29].

Despite similar QRS duration and morphology fullfilling WHO criteria of LBBB *(Table 1)*, the activation sequence may vary significantly based on both underlying heart disease and case to case. Some studies indicate differences in ventricular activation pattern between coronary artery disease (CAD) and idiopathic dilated cardiomyopathy (DCM) with more frequent intraventricular dyssynchrony in CAD and predominant interventricular dyssynchrony in DCM[40,42]. In accordance with that, CAD patients exhibit rather nonspecified conduction delay or LBBB-like pattern on the surface ECG, whereas true complete LBBB tends to be present more often in DCM[40].

A. Complete BBB (all the below): * QRS duration >0,12s in adults * Supraventricular rhythm * Absence of WPW pattern	**B. Complete right bundle-branch block (RBBB):** * R´ or r´ in V1 or V2 (r<R´) * S > R in I and V6 * S > 0,04s in I and V6 * R peak time >0,05s in V1 or V2 * 1+2 or 2+3 or 4+2/5
C. Complete left bundle-branch block (LBBB): * Broad and notched or slurred R in I, V5, V6 * Absence of Q in I, V5, V6 * R peak time >0,06s in V5, V6 * 1+2+3	**D. Nonspecific intraventricular conduction block (delay) (IVCD):** * All cases with QRS duration >0,12s that do not meet the criteria for LBBB or RBBB

Table 1: WHO criteria for bundle branch block (BBB)
(Rose G, Blackburn H. Cardiovascular survey methods. Geneva: World Health Organization; 1968. p.56.)

The interindividual variability of ventricular activation sequence is expressed especially in patients with CAD, depending on the extent and location of the postinfarction scar. Conduction velocity varies between regions and is mostly reduced close to the scar site.

In contrast to CAD, patients with DCM more often exhibit homogenous right to left activation with globally reduced conduction velocity[39,40]. These heterogeneities in the character and duration of ventricular activation may be explained by different histopathology in DCM as compared to CAD as the conduction delay strongly depends on architecture of interstitial fibrosis and on the direction of wavefront propagation with respect to the fiber direction[49].

2.2. MECHANICAL VENTRICULAR ACTIVATION UNDER PHYSIOLOGIC CONDITIONS AND DURING LBBB

Normally, mechanical activation starts with fiber shortening in the isovolumic contraction phase and onset of both systolic and diastolic events of the LV slightly preceeds or coincides with that of RV[47,50-52]**.** Mechanical activation usually starts near the interventricular septum, concordantly with the electrical one. The opposing walls of the LV and free wall of the RV are mechanically activated in a homogenous way with the base activated last. Simultaneous inward motion of IVS and LV lateral wall and similar extent and time course of contraction between various LV regions ensure effective pump function of the heart[52,53].

There is a solid evidence that LBBB itself leads to dyssynchrony and could promote LV remodelling in already dysfunctional ventricle. LBBB prolongs and/or delays mechanical activation of the ventricles, especially of the LV, on inter- and/or intraventricular level[51,53,54]. The dearrangement of the ventricular contraction sequence is associated with a deterioration of LV systolic and diastolic function as reflected by a decrease in the maximal rate of rise of LV pressure (dP/dt max) and aortic pulse pressure, by an increase of LV end-diastolic pressure, worsening of the LV relaxation etc.[47,50,51,53].

From prognostic point of view, the presence of LV intraventricular electromechanical dyssynchrony, QRS duration >140ms and LV ejection fraction <25% were identified as the independent predictors of CHF decompensation during long-term[28]. On the contrary, presence of the interventricular dyssynchrony does not seem to be associated with a worse prognosis[29].

INTERVENTRICULAR DYSSYNCHRONY

The presence of LBBB reverses physiological sequence of cardiac cycle events: the RV systole and diastole onset markedly precedes onset of systole and diastole of the LV, thus causing interventricular dyssynchrony (*Figure 3*). Premature RV electrical and mechanical activation leads to an early increase in RV pressure as compared to LV pressure, thus

reversing the transseptal pressure gradient during RV isovolumic phase and displacing IVS into the cavity of LV[47,50,51,55]. The opposite movement of the IVS is seen in the late systole.

Besides increased preejection time of the LV due to the delayed initiation of LV activation, LV systole is often also prolonged in the presence of LBBB. In addition, delayed aortic closure and mitral valve opening cause prolongation of the isovolumic relaxation time, thus causing shortening of the LV filling time relatively to RV and limiting the stroke volume[51,56].

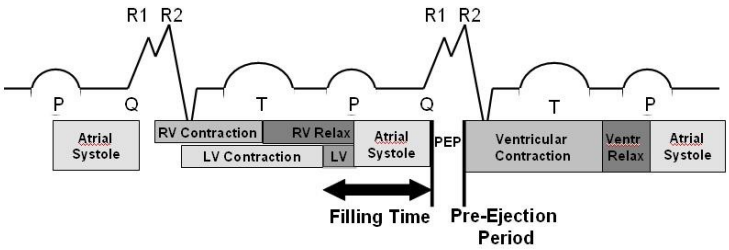

Figure 3: Events during cardiac cycle in the presence of LBBB
(Adapted from Grines; Circulation 1989;79:845-853.)

Abnormal or paradoxical septal motion present in patients with CHF and LBBB is, therefore, a result of either reversal of transseptal pressure gradient (RV contracts during end-diastolic phase of the LV) or relative increase in RV volume (RV filling time is relatively longer than the LV filling time). The abnormal septal movement reduces global LV ejection fraction in LBBB patients[51]. The greater the interventricular dyssynchrony, the greater the depression of LVEF and the greater related LV dilatation could be expected[53,57]. Interestingly, correlation between QRS duration and interventricular asynchrony was demonstrated in some studies[47,58].

INTRAVENTRICULAR DYSSYNCHRONY

In the presence of LBBB, various contraction patterns over the LV can be found as a result of delayed activation. Typically, the inward motion of the IVS induced by both its earlier activation and reversed transseptal gradient is present in the early systole. Later on, IVS moves away from the posterior wall of the LV at the time when the more delayed LV walls start to contract. The opposite is true for the LV free wall. The pre-stretch of this region, caused by the absence of activation in the early systole, is followed by the contraction that appears as the IVS begin to relax[50,59,60]. Hemodynamically, the opposite movement of the IVS and LV posterolateral wall during the systole is associated with a decrease in septal contribution to stroke volume[50,51]. In this context, the presence of significant delay between contraction of the IVS and the lateral wall of the LV >60ms was shown to be a prerequisite for the LV ejection fraction improvement during CRT[61]. All the above mentioned changes may also cause or deteriorate functional mitral regurgitation[62,63].

It seems that the regional differences in the contraction sequence are related to local variability of the myofibre length during asynchronous activation (as produced by either LBBB or RV apical pacing)[59]. In the early-activated sites, rapid and intensive shortening of the myocardium is present as an afterload of this region is still very low. This leads to a significant prestretching of the opposite walls that are not activated at that time yet. As a result of the LV pressure increase, regions with late activation present with longer myofibres at the time when all LV walls are already activated. Based on the local "Frank-Starling" relation, the later activated regions contract more vigorously and exhibit enhanced shortening during the ejection period[59,60,64]. Contraction of these segments may cause rebound stretch and a second phase of shortening in the early-activated sites during their relaxation period. Transient ventricular contraction patterns can be seen in other LV regions depending on the distance from the early and late activated site[59,65]. Interestingly, regional differences in the contraction sequence during asynchronous activation may be less pronounced during higher LV filling pressure[66].

It seems that these variations of the contraction pattern may also explain the inhomogeneous distribution of perfusion and metabolic demand in the presence of asynchronous LV contraction[67-69]. Mechanical work of the early-activated regions could be reduced up to 50% during asynchronous activation[59]. Regional work is a good predictor of regional myocardial oxygen consumption[69]. Thus, reduced glucose uptake and perfusion of the IVS in the presence of asynchronous actvation may be explained by abnormal contraction pattern with the decreased mechanical work in this region[70]. The opposite is true for the LV free wall where the enhanced regional work is accompanied by an increased blood flow and metabolic demand. In addition, the extent of wall motion abnormalities and the perfusion defects induced by asynchronous activation increase with time and are associated with gradual LV pump function deterioration[67]. Moreover, asymmetric hypertrophy of the LV with microstructural desarrangement develops over long-term period in the presence of LBBB or during RV apical pacing[71,72]. Interestingly, the most pronounced hypertrophy is present usually in the late activated regions (higher workload)[72].

The above process, called cardiac remodeling, is characterized by changed genome expression and modifications on the molecular, cellular, and interstitial level that occur after cardiac injury. It finally results in an altered shape, size and function of the heart. In addition, other factors such as hemodynamic load or neurohormonal activation may contribute to progression of cardiac remodeling[73]. The surrogate measures for ventricular remodeling

such as LV ejection fraction (LVEF), LV end-diastolic and end-systolic volumes and/or diameters are often used.

2.3. COUPLING OF ELECTRICAL AND MECHANICAL EVENTS

Insight into the physiology and pathophysiology of electrical and mechanical activation suggests that there are differences in coupling of electrical and mechanical events throughout the myocardium. In the normal heart, a gradient of electromechanical interval was demonstrated between endo- and epicardium with relatively faster coupling in the epicardium[74].

Some studies indicate that this electromechanical delay becomes even more pronounced during asynchronous activation[52,75], being dependent on both: 1) the type of conduction delay[75] and 2) the pacing site[52]. Along these lines, electromechanical delay is greater during LBBB as compared with right bundle-branch block and during single-site right ventricular (RV) pacing as compared with single-site LV pacing. In addition, it seems that the later regional activation of the LV occurs in the presence of asynchronous activation, the greater the time interval between regional electrical activation and the onset of local fibre shortening. These observations suggest that mechanical asynchrony may be larger than the electrical dyssynchrony, at least in some patients with conduction disturbances.

3. CARDIAC RESYNCHRONIZATION THERAPY (CRT)

3.1. INTRODUCTION

In medicine, the term “cardiac pacing” indicates iatrogenic manipulation of the cardiac rhythm. In contrast to conventional cardiac pacing that corrects bradyarrhythmias, CRT is not primarily indicated for rhythm correction but rather for a restoration of synchronous ventricular activation, i.e. for correction of all types of dyssynchrony.

The strategy of pacing for the treatment of CHF is not new. Dual-chamber pacing was already used in the 80´s to improve hemodynamics in selected CHF patients[76,77]. The pilot studies using short AV delay and ventricular lead placed in the RV apex (DDD-RVA) demonstrated significant clinical improvement (decreased NYHA class, reduction of pulmonary edema, heart size and the degree of mitral regurgitation). The underlying mechanism of this beneficial effect of DDD-RVA pacing seemed to be the augmentation of stroke volume due to LV diastolic filling time prolongation and reduction of mitral regurgitation. Both these effects were primarily caused by appropriate shortening

of the AV delay[78,79]. However, significant hemodynamic improvement during DDD-RVA pacing was not reproduced in the subsequent trials[80,81].

The detail analysis of different studies implies that DDD-RVA pacing with short AV delay may lead to hemodynamic and clinical improvement only in a carefully selected population of symptomatic CHF patients with rather long spontaneous AV conduction, prolonged functional mitral regurgitation (>450ms) and significant shortening of the LV filling-time (<200ms at rest)[82]. Positive impact of the AV delay optimization in others is very probably counterbalanced by deleterious effect of a single-site RVA pacing that itself causes significant ventricular asynchrony and hemodynamic deterioration similar to that during LBBB[83-85].

The important turn in the treatment of CHF by ventricular pacing occurred when the so called biventricular pacing (BVP) was introduced, i.e. pacing from more sites in both ventricles. Although the effect of simultaneous pacing from two ventricular sites in the structurally intact heart was studied in the experimental model years ago[55], the first human study describing positive acute effect of BVP after cardiac surgery was published as late as in 1995[86]. Later on, the impact of varying ventricular pacing sites started to be evaluate also among patients with advanced CHF[87-89]. It was clearly shown that stimulation of LV, either solely or in combination with simultaneous RV pacing, is superior to stimulation of RV alone in terms of the hemodynamic performance. Interestingly, some other studies indicated superiority of one pacing mode only (BVP or single-site LV pacing (LVP)) in approximately 80% of the CHF patients[90]. On the other hand, improvement during BVP or LVP does not occur in all patients with advanced CHF as these pacing modes are only effective in patients with manifest dyssynchrony[91]. In the absence of ventricular dyssynchrony, not only the LV pump function does not improve, but may even deteriorate[65,92,93].

Proposed mechanism underlying response to different pacing strategies in patients with CHF and ventricular dyssynchrony seems to be the restoration of more coordinated activation and contraction sequence of the heart. The fact that the response is present also in patients with chronic atrial fibrillation with slow or no conduction through the AV node (i.e. in the absence of atrial contribution to the ventricular filling) confirms that the hemodynamic improvement during LVP or BVP is not achieved only through restoration of AV synchrony[94-97].

All pacing strategies that are able to reduce antioventricular and ventricular dyssynchrony and thus enhance hemodynamic in CHF have been grouped under a unifying

term of CRT. In this context, it has been estimated that approximately 10% of patients with CHF might be candidates for this therapy[98].

3.2. INTRA- AND INTERVENTRICULAR MECHANICAL RESYNCHRONIZATION DURING CRT

It was shown earlier that the maximal improvement of the LV function is present when the intraventricular dyssynchrony is corrected, relatively independent of the degree of interventricular dyssynchrony. Thus, for successful CRT, pacing strategy and/or LV pacing site that provide maximum of intraventricular resynchronization should be selected[44,91,93]. Resynchronization of ventricular contraction can be achieved when two activation wavefronts from the opposing walls merge together somewhere in the middle of the LV during the late systole. It results in a ventricular contraction pattern that is similar to that observed during normal sinus beat, including equivalent orientation of the mean vector of ventricular contraction[65]. Despite that, however, the total duration of the mechanical activation during CRT was shown to be longer as compared with normal sinus rhythm[65].

During BVP, resynchronization is ensured by pacing of the LV free wall and RV. In LVP, on the contrary, it is produced by a merge of pacing-induced wavefront originating at the LV free wall with spontaneous activation via the right bundle[44,90,91,99]. An underlying mechanism responsible for intraventricular resynchronization in both BVP and LVP is less early and late stretch and rebound contractions of the opposing walls as compared with baseline asynchronous activation[59,65,99].

However, hemodynamic improvement by LVP in patients with CHF could also be demonstrated in the setting of very short AV delay or in the presence of atrial fibrillation with limited AV conduction[94]. Therefore, it is conceivable that other mechanisms may contribute to the benefit of LVP. In this context, some investigators suggest that the so-called diastolic ventricular interaction may play a role during LVP[100]. The theory presumes that in the presence of high central venous pressure, RV occupies much of the pericardial space and limits filling of the LV. In such situation, LV preexcitation enables the LV to fill before the RV and due to elevated LV preload increases the Frank-Starling effect. On the other hand, it can not be excluded that the elevated LV preload during LVP, in contrast to BVP, is responsible for lower degree of LV reverse remodeling that was observed during long-term LVP[101].

Other studies also indicate significant differences between BVP and LVP with regard to modification of ventricular dyssynchrony[102,103]:

It seems that the intraventricular resynchronization in BVP is complex. On one side, BVP prolongs the electromechanical delay (as measured by the mechanical response with respect to the QRS onset) in the regions close to IVS. LV free wall contraction remains the same or is advanced to less extent. As a result, different regions of the LV contract approximately simultaneously and synchronously during BVP[3,102]. Because of concomitant prolongation of electromechanical coupling even in RV with respect to LV, BVP reduces also interventricular dyssynchrony[3,102,104]. Timing of the increase in LV pressure then coincides with that of RV and normal transseptal pressure gradient is restored. In addition and in contrast to LVP, BVP shortens the systolic phase due to the reduction of LV preejection time, thus prolonging the diastolic filling time[3,97] (*Figure 4*).

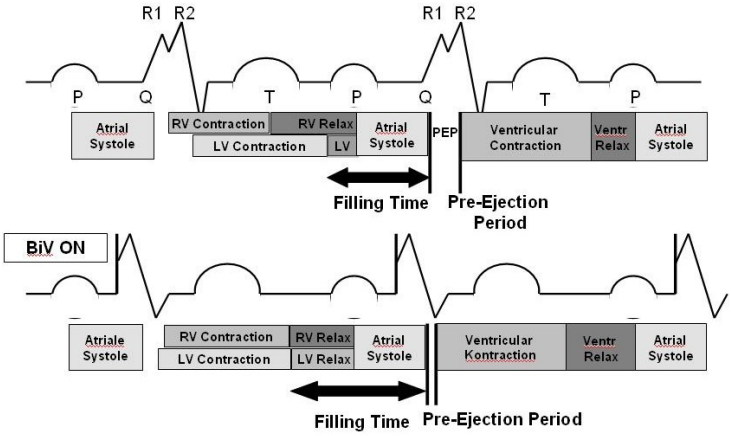

Figure 4: Events during cardiac cycle in the presence of LBBB *(A)* and during BiV *(B)* *(Adapted from Grines; Circulation 1989;79:845-853.)*

On the other hand, LVP decreases intraventricular dyssynchrony by simultaneous delaying of all segments of the LV[102]. As a result, contraction is more homogeneous, but it occurs later with regard to the electrical activation. This can lead to prolongation of the isovolumic contraction phase, shortening of the LV diastolic filling and worsening of the interventricular dyssynchrony as compared to BVP[102,103]. On the other site, ejection time is similar in both BVP and LVP[97].

3.3. IMPACT OF CRT ON THE HEMODYNAMIC PERFORMANCE

Various studies have demonstrated significant improvement of parameters reflecting LV systolic function such as LV dP/dt max, pulse pressure, cardiac output and ejection fraction during CRT[50,87,89,101,105,106]. Some other studies have shown that the greater the baseline mechanical asynchrony, the more pronounced resynchronization and LVEF increase during CRT could be expected[57,91]. Furthermore, the extent of acute systolic improvement is proportional to the decrease in biventricular asynchrony[57]. Importantly, this positive change in systolic function during CRT occurs without change of the filling pressure (in fact, the filling pressure can even decrease). Therefore, restoration of more coordinated ventricular contraction sequence during CRT reflects rather improved contractility[87]. In addition, resynchronized ventricular contraction and more coordinated function

of the papillary muscles are also often responsible for reduction of mitral regurgitation that, in turn, may further improve hemodynamic status[107]. Acute hemodynamic improvement occurs immediately after the onset of pacing and is frequently sensed by the patient as the sudden clinical improvement.

More interestingly, CRT has also impact on cardiac oxygen consumption[108]. In contrast to positive inotropic agents (such as dobutamine) that increase myocardial oxygen consumption for a given rise of contractility, BVP is able to induce comparable increase in contractility without increased energetic demand[108]. Some studies have also shown that hemodynamic improvement during CRT is associated with restoration of more homogenous glucose metabolism and perfusion in the ventricles[109]. In addition, CRT seems to modify the neurohormonal activity as it is associated with reduced sympathetic nervous activity and lowering of the plasma brain natriuretic peptid (BNP) level[110,111].

3.4. CLINICAL IMPROVEMENT

Studies of acute hemodynamic changes may not necessarily predict long-term effect of CRT. In this respect, clinical efficacy of CRT has been studied in multiple randomized and/or non-randomized clinical trials. An overview of the most important clinical trials is given in a review article “Is right ventricular outflow tract pacing an alternative to left ventricular/ biventricular pacing?” that is part of this dissertation. Briefly, besides enhancement of the LV systolic function and reverse remodeling of the LV (discussed later), BVP is able to improve quality of life, NYHA class and exercise tolerance in patients with advanced CHF.

Metaanalysis of large clinical CRT trials revealed 8-point improvement on the Minnesota Living with Heart Failure Questionnaire that represents standardized questionaire for the assessment of the quality of life among patients with CHF[112]. This improvement was shown to be greater than that defined in the placebo-controlled trials[113] and also greater than the improvement of quality of life demontrated in recent heart failure trials targeted on CHF pharmacotherapy[114].

Regaring NYHA class, around 60% of BVP recipients were shown to improve by at least 1 NYHA class as compared with 37% of controls[112]. On the other hand, higher prevalence of the improvement in NYHA class than the echocardiographically detected reverse remodeling indicates possible participation of placebo effect among NYHA responders.

CRT is also associated with an improved exercise tolerance. Metaanalysis has shown improvement in 6-minute walk test distance with a mean difference 30m in patients with NYHA class III and IV before CRT. In addition, BVP is associated with an increase in peak oxygen consumption of about 0,7ml/kg/min as assessed by cardiopulmonary stress testing[112].

Long-term effect of LVP was assessed in some studies and compared with that observed during BVP. Results of these studies imply that LVP is associated with comparable long-term improvement of NYHA class, QOL and exercise tolerance as BVP[115-118]**.** Such encouraging results led finally to approval of the concept of CRT for hemodynamic support in patients with advance CHF by the U.S.Food and Drug Administration in 2001.

3.5. CRT AND REVERSE REMODELING OF THE HEART

Reduced wall stress, enhanced LV pump function and increased efficiency at a lower preload levels during long-term BVP are associated with reverse remodeling, i.e. with a decrease in the end-diastolic and the end-systolic volumes[3,99,119,120]. The time-dependent improvement of LV function and size during CRT were demonstrated in both, non-controlled studies[3,101] as well as in multicentric clinical trials[7,120-122]. From the clinical point of view, reverse remodeling appears to be one of the most important achievments as it can be considered an ultimate goal of any treatment for CHF.

Importantly, the interruption of BVP is associated with a new deterioration of the cardiac function during the off-pacing period[3]. As the hemodynamic worsening does not occur immediately after CRT termination, non-decreasing LV ejection fraction and cardiac output found during transient stop of CRT is likely to reflect real persistent effect or functional reverse remodeling. However, long-term BiV is associated also with reduction of LV end-diastolic and end-systolic volumes and diameters that reflect rather structural reverse remodeling[3].

Observations of some studies imply that the degree of LV end-diastolic volume reduction and LVEF increase during CRT depends on the size and function before pacing onset as CRT nonresponders tend to have more elevated baseline LV end-diastolic volume and lower LVEF[121].

The impact of LVP on the reverse remodeling seems to be different from that during BVP. It was shown that LVP is associated with a significant increase in LVEF. However, LVP does not seem to produce such changes in LV volumes as BVP, at least not constantly[101]. The reason for these differences between both pacing strategies are not fully

understood yet, but it may be caused by a different mechanical activation and electromechanical coupling, especially in the early systole, that cause prolongation of isovolumic contraction phase, shortening of the LV filling time and higher LV preload as compared with BiV.

3.6. IMPACT OF CRT ON HOSPITALIZATION FOR HEART FAILURE AND MORTALITY

Nowadays, there is a strong evidence that CRT, in addition to above mentioned acute and long-term effects, reduces the rate of hospitalizations for heart failure and that this therapy is also associated with a decreased mortality.

Until recently, only data from meta-analyses of large clinical trials on CRT aspired to address this issue[112,123]. They suggested that BiV is able to reduce both all-cause mortality and hospitalizations for heart failure in appropriately selected population of patients with symptomatic CHF, low LVEF and prolonged QRS duration. Those meta-analyses shown that CRT is associated with a 25% relative reduction in all cause mortality, caused mainly by the 40% reduction in deaths due to progression of CHF, and a 29-35% reduction of hospitalizations for heart failure. Conclusions of these meta-analyses were recently supported by the results of the mortality trials COMPANION[6] and CARE-HF[7]. The first trial has shown a significant reduction of the combined end-point of all-cause mortality and all-cause hospitalization by approximately 20%. The CRT-associated reduction of mortality in COMPANION[6] was similar to that reported in the mentioned metaanalysis[123], 24% and 23%, respectively. In addition, it was reported comparable reduction of the hospitalization for heart failure (34% reduction in death plus heart failure hospitalizations in COMPANION trial and 29% reduction in heart failure hospitalization in the metaanalysis[6,123], respectively).

The later study, CARE-HF[7], assessed the impact of CRT on the risk of cardiovascular complications and death as compared with standard medical treatment and demonstrated clear reduction by 37% of both during CRT. The all-cause mortality was reduced by 36% and heart failure hospitalization by 52% in the CRT arm as compared to optimal medical therapy alone. Using hazard ratios, it was calculated that one death and three hospitalizations for severe cardiovascular events are prevented for every nine CRT device.

This effect of CRT is comparable with that found in beta-blockers[124], ACE inhibitors[125] and aldosterone antagonists[126]. Importantly, the efect of CRT on mortality becomes apparent by 3months after the implantation as it reflects rather impact of LV reverse

remodeling than the acute neurohormonal changes[112]. Better survival during CRT was shown to be predominantly due to the reduction in deaths for terminal progression of CHF[112].

The results of COMPANION trial[6] indicate, in addition, further reduction of mortality when combining CRT with implantable cardioverter-defibrillator (ICD) as a tool for preventing sudden cardiac death. It was shown that CRT pacemakers reduced combined end-point of all-cause mortality and all-cause hospitalization by 20%, whereas CRT defibrillators by 36%.

Such results suggest that the positive impact of CRT on morbidity and mortality may be caused by an improvement of cardiac performance and that combination of CRT with ICD may additionally reduce the risk of sudden cardiac death.

3.7. CRT NONRESPONDERS

Currently accepted criteria for selection of suitable CRT recipients (practical guidelines of *ACC/AHA, ESC and Czech Society of Cardiology*[127-129]) are based on the results of large multicenter studies and consist from:

- CHF with persistent moderate to severe symptoms (NYHA III-IV) despite optimized pharmacotherapy
- LV dysfunction (LVEF ≤ 35%)
- Presence of ventricular dyssynchrony (until now defined by QRS duration ≥ 120ms, usefulness of different echocardiographic parameters of mechanical dyssynchrony is still assessed)

In addition, concomitant dilatation of LV is ussualy present (LV end-diastolic diameter (LVEDD) ≥ 55mm) in CRT recipients.
In appropriate candidates, combined device (CRT+ ICD) is indicated.

However, despite extensive research in this field, some limitations and unresolved issues in CRT still exist. The crucial one is the identification of nonresponders to CRT as approximately 30% of CRT recipients do not respond to this therapy appropriately[130-132]. On the other hand and surprisingly, there is still not a uniform definition of CRT non-responder. In fact, different studies used different definition:

In acute hemodynamic studies, the response to CRT was qualified by the increase of pulse pressure ≥5%[133] or change of dP/dt[134]. However, as the goal of this therapy is mainly to improve the long-term outcome, most of the clinical studies have evaluated changes of some other variables. The nonresponder rate is generally lower (11-25%) in the studies

using subjective capacity (NYHA class ≥1[135,136], quality of life[136]) or exercise tolerance (peak VO2max ≥10%[135], 6-minute walk test improvement ≥10%[137]) as a definition of response. Using "harder" end-points such as LV reverse remodeling (LV end-systolic volume reduction ≥15%, relative increase of LVEF ≥25%[107,121,138,139]) or "hard" end-points (hospitalization for heart failure, mortality[6,7]), the rate of non-responders is significantly higher (up to 40-46%) suggesting presence of certain degree of placebo response to device implantation. On the other hand, the later rate may be overestimated as the duration of the follow-up may be too short for some CRT recipients to reach the target improvement in the selected parameter.

Despite that, however, as the rate of CRT non-responders represents a substantial proportion of CRT recipients, there is an effort to identify factors that can help to predict better the response to CRT. Until now, some parameters have been shown to be useful, but single, easily obtainable marker is still missing.

PREDICTORS OF RESPONDERITY TO CRT

The findings of some studies indicated that the larger the baseline mechanical asynchrony, the more significant hemodynamic benefit during CRT could be expected[91,139,140]. In addition, certain association between mechanical dyssynchrony, QRS duration and baseline contractility was suggested[91]. First acute hemodynamic studies concluded that the QRS duration ≥150ms (especially in combination with baseline LV dP/dt max <600-700mmHg/s) is able to distinguish patients exhibiting acute improvement from those who do not improve most likely during both BVP and LVP[87,89,116,134]. However, extensive research in last years demonstrated that the usefulness of QRS duration and morphology as the only parameters for identification of significant mechanical asynchrony is limited[141]. There are two main reasons for that:

1) QRS duration reflects the total ventricular activation time. Although some differences may exist between various conduction disturbances, generally, the type of bundle branch block and QRS width do not carry accurate information about the presence and the degree of mechanical inter- or intraventricular asynchrony[28,141].

2) Echocardiographic studies demonstrated that dyssynchronous LV contraction is present also in 33-58% of heart failure patients with narrow QRS complex (<120ms)[28,141-144] and that CRT is able to improve mechanical ventricular synchrony also in these patients[145-147]. Such findings suggest that the measurement of mechanical, rather than electrical dyssynchrony is more important for estimating the effect of CRT[99].

Therefore, various imaging techniques were advocated to define reliable parameters of mechanical dyssynchrony. Among them, echocardiography seems to be the most useful. Until now, many different markers of mechanical dyssynchrony were described using either standard 2D and Doppler echocardiography or tissue-Doppler-derived imaging (*Table 2*). However, usefulness of all these ECHO parameters in prediction of CRT responderity is still not completely known and has to be further evaluated in prospective multicenter trials[148].

Mechanical interventricular dyssynchrony **Table 2**

Conventional Doppler	The difference between aortic and pulmonary pre-ejection times	≥ 40ms

Mechanical intraventricular dyssynchrony		Cut-off value
Conventional Doppler	Aortic pre-ejection time	≥ 140ms
M-mode	Septal-to-posterior wall motion delay	≥ 130ms
DTI (Doppler tissue imaging) – velocity	Maximal delay between peak systolic velocities of any of the 12 LV segments	≥ 100ms
	Maximal delay between peak systolic velocities in four LV segments	≥ 65ms
	Maximal delay in time to peak systolic velocity between the anterior and posterior wall	≥ 65ms
	Standard deviation of the time to peak systolic velocity of 12 LV segments	≥ 34ms
TSI (Tissue synchronization imaging)	Time to peak velocities of opposing wall of the LV	≥ 65ms
Longitudinal strain	Temporal difference in septal-lateral peak systolic strain	≥ 50ms
Radial strain	Time difference of peak radial strain in the septum versus posterior wall	≥ 130ms
Real-time 3D ECHO	Systolic dyssynchrony index	≥ 14.7%

Mechanical ventricular dyssynchrony seems to be the most crucial prerequisite for hemodynamic improvement during CRT. However, there are some other variables modifying the final outcome of CRT such as the underlying heart disease. Specifically, patients with ischemic etiology and the presence of scar are more likely to not respond[136,149,150]. Moreover, it seems that a greater basal LV dilatation and lower LV ejection fraction are more often associated with a lack of response to CRT[121]. Besides the selection of appropriate candidates of CRT, the final effect of this therapy seems to be modified by some periimplant variables like 1/ the type of pacing strategy (BVP, LVP), 2/ selection of the optimal pacing site(s) or 3/ optimization of atrioventricular or interventricular delay.

THE AIM OF THE WORK

METHODS AND STATISTICAL ANALYSIS

SUMMARY OF RESULTS

CONCLUSIONS

THE AIM OF THE WORK

The aim of this PhD was, therefore:

1/ to compare the effect of different pacing strategies that were proposed as alternatives of CRT (biventricular (BVP), single-site left-ventricular (LVP) and bifocal pacing of the right ventricle (BFP)) on the activation sequence, hemodynamic and clinical outcome of patients with advanced CHF,

2/ to identify factors modifying the degree of CRT-related improvement.

Specifically, this PhD study addressed these issues:

1/ Description of electrical activation sequence during different pacing modes (BVP, LVP, BFP).

Until recently, there was only little known about the activation sequence of the heart in the presence of different conduction disturbances. In addition, most of these observations were based on the experimental models[44,99,151]. Introduction of new technologies, such as the electroanatomical mapping system, enables to study the activation pattern directly in the target population of patients with advanced CHF. Such studies contribute to our understanding of the pathophysiological and pacing-induced changes of electrical inter- and intraventricular dyssynchrony that are tightly related to the changes of the contraction pattern and hemodynamics.

2/ Comparison of the acute effect of BVP and LVP during exercise

Studies reporting similar effect of LVP and BVP in patients with advanced CHF and manifest dyssynchrony reflect mostly hemodynamic status at rest. However, only limited data are still available on the effect of both pacing modalities during the exercise. In fact, such studies are highly important as the aim of CRT is not only to reduce symptoms at rest, but mainly to increase the exercise tolerance of CRT recipients. Therefore, we evaluated the impact of both pacing strategies on the acute changes of cardiac output (assessed noninvasively using stress echocardiography) during symptoms-limited exercise.

3/ Importance of RV pacing site optimization in CRT

It seems that the crucial prerequisite for LV function enhancement during CRT is preexcitation of the most delayed wall by LV pacing. Therefore, the optimal pacing site within the LV was predominantly studied in the past. Most studies reported the greatest improvement during pacing from the lateral/ posterolateral LV wall[152-158]. However, optimal pacing site may vary interindividually based on the type of conduction disturbance, scar location etc. It was shown that the correspondence of the site of late electromechanical activation and site of pacing provides the greatest benefit in terms of LV reverse remodeling, whereas no effect or worsening can be present when paced from remote sites[158].

Surprisingly, there are still only limited data about the importance of RV pacing site optimization in CRT. Therefore, we assessed the impact of RV pacing site on the long-term clinical outcome of CRT recipients in our third study. We hypothesized that 1/ the selection of suitable RV pacing site may, at least partially, affect the final effect of CRT and 2/ RV lead should be rather placed in region ensuring rapid ventricular activation resembling the physiological activation pattern. We further presumed that RV midseptal (RVS) location could fulfill such criteria.

4/ Impact of different atrio-ventricular and interventricular delay setting in BVP and LVP on acute changes of cardiac output.

The importance of atrioventricular and interventricular delay (AVD and VVD resp.) optimization emerges from the physiology of the cardiac cycle: 1/ Atrial contraction contributes to the stroke volume by approximately 20-40% in the heart with either normal or depressed systolic function[159-161]. Both atrioventricular (AV) block and/or presence of LBBB (despite normal electrical AV conduction)[162,163] may cause prolongation of mechanical AVD with shortening of the LV filling time due to fusion of the early passive filling phase with the atrial systole-dependent flow[25,161,164]. As the performance of the failing heart is dependent on an elevated preload, this summation may lead to a decrease of the stroke volume. 2/ In addition, appropriate AVD setting seems to reduce LV asynchrony (both intra- and interventricular)[44,93] due to the phenomenon of fusion. 3/ Finally, AVD and VVD optimization may contribute to the improved hemodynamics due to a reduction of mitral regurgitation[165-167].

As the mechanical AVD may be longer than the corresponding electrical AVD in LBBB patients, we presumed 1/ that the shorter electrical AVD may be optimal for a prolongation of the filling phase and maximal hemodynamic improvement in CRT

recipients as compared to the optimal AVD in conventional pacemakers. In addition, some studies in patients with preserved LV systolic function suggest that the spontaneous atrial activation during atrial-triggered ventricular pacing (atrial sense followed by ventricular pacing at a predetermined AV delay, S-AVD) is hemodynamically superior to AV sequential pacing (paced both atrium and ventricle with a predetermined AV delay, P-AVD)[168]. Therefore, we assessed 2/ if it is similar in CRT recipients. Finally, 3/ need of individual AVD optimization and 4/ effect of various degree of ventricular preexcitation (VVD) on the acute hemodynamic changes were assessed in the last study of this PhD.

METHODS

Patients included in the studies fulfilled accepted criteria for CRT: advanced CHF with persistent symptoms despite optimized medical treatment (NYHA class III-IV), LV dysfunction (LV ejection fraction (LVEF) <30-35%, QRS duration >150ms (in most cases), LV dilatation (LV end-diastolic diameter (LVEDD) > 60mm). The study populations were of different size: twenty patients were enrolled in study 1, 28 patients in study 2, 99 and 19 patients were included in study 3 and 4. Underlying heart disease was either coronary artery disease or idiopathic dilated cardiomyopathy or their combination. In few cases, coincidence of previsouly corrected valvular disease and ischemic cardiomyopathy was present (study 2 and 3). The mean age of enrolled patients was close to 60 years in all studies. Patients with CHF decompensation requiring catecholamine support, those with a recent history of myocardial infarction (<6 months) and/or angina pectoris of III-IV degree were excluded from all analyses. Except study 1, presence of atrial fibrillation was another exclusion criterium. On the other hand, patients with complete AV block (either spontaneous or ablation-induced) were included in studies 1, 2 and 4. Upgrade from conventional pacemaker to CRT was performed in indicated patients based on the above mentioned indication criteria and QRS duration during right-ventricular pacing >200ms. All patients gave their informed consent.

DEVICE IMPLANTATION

Device providing CRT therapy was implanted in the left or right subclavian region. All pacing leads were implanted transvenously via subclavian route. Leads with active fixation were used for pacing of the right ventricle and right atrium in most cases.

Right-ventricular lead was inserted either into the apex (RVA) or midseptal region (RVS) of the right ventricle. In the later case, pacing lead was first introduced to the high RV outflow tract and then pulled down along the IVS. Suitable RVS site was identified using both simultaneously recorded intracardial signal from the tip of RV pacing lead and radiographic appearance in at least 3 different views.

Left-ventricular pacing lead was introduced into a suitable tributary of the coronary sinus and placed laterally or posterolaterally in most cases. Alternative LV pacing site was used in patients with no suitable vessel in this region or in those with repeated lead dislocations, high pacing threshold, pacing of the diaphragm or phrenic nerve. In such cases, LV lead was inserted predominantly more posteriorly or anterolaterally.

For selection of the optimal right- and left-ventricular pacing site, periprocedural recording of the intracardial signal from the tip of the appropriate lead was used. The site with intracardial signal recorded in the most terminal portion of the QRS complex was assigned as the target place for LV lead insertion. Vice versa, signal preceeding or coincide with the onset of QRS complex and/or displaying sharp signal of the conduction system determined region for RVS pacing *(Figure 5)*.

The third electrode was inserted in the right atrium, usually in its appendage. Biventricular pacing was set in all patients after the implantation. BVP configuration was also let in long-term follow-up in all patients with succesfull LV lead insertion. LVP was obtained by temporary reprogramming of the CRT device.

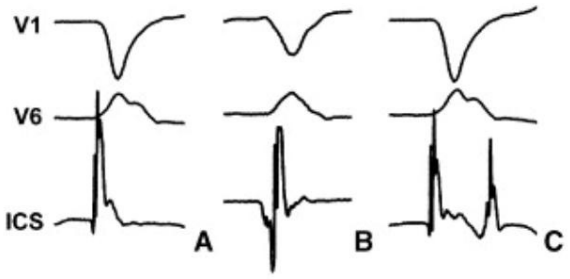

Figure 5: Relationship between the QRS complex and intracardial signal (ICS) of the RV pacing lead inserted at the midseptum (A) and in the RV apex (B). Simultaneous recording of signals from the earliest (RVS) and latest (LV lateral wall) site of ventricular activation (C).

In addition, total of 7 patients with bifocal RV pacing was included in the study 1. This pacing strategy was predominantly indicated in those patients with unsucessfull LV lead implantation. For BFP, two leads were introduced in the RV with one placed in the apex and second in the high outflow tract of the RV.

ELECTROANATOMICAL ACTIVATION MAPPING (CARTO) – STUDY 1

Four-milimeter tip mapping catheter was introduced via vena and arteria femoralis into the right and left ventricle. The LV catheter was introduced retrogradely through the aortic valve and boluses of heparin were administered during the mapping as a prevention of thromboembolic events. Detail electroanatomical activation mapping during BVP, LVP

or BFP was performed using CARTO system (Biosense Webster, Haifa, Israel). AVD was set at 120ms for sensed and 150ms for paced AVD. Four patients with no intraventricular conduction disturbance who underwent radiofrequency ablation of the accessory pathway served as a control group. There were no procedure-related complications.

All 3D isochronal activation maps were subsequently analyzed by one operator. The local activation time of each point was defined by the onset of the first high-frequency component of the bipolar signal. Analysis of the unipolar signal was additionally used if the amplitude of the bipolar signal was <0.5mV or in the presence of fragmented potentials. Low-voltage signals (<0.2mV) with uncapture were labelled as a scar.

The ventricular activation sequence was described with regard to direction and number of the activation wavefronts. Left ventricular activation time (LVAT) was defined by the interval between the earliest and the latest endocardial activation. Interventricular delaly was described as the time-difference between the earliest activation in the RV and LV respectively (negative values marked preexcitation of the LV). The transseptal time was defined by the interval between the pacing stimulus and the earliest LV endocardial activation in the septal region. Fusion between spontaneous and pacing-induced activation was considered to be present, when additional LV endocardial breakthrough corresponding with the RV pacing site was observed and was not present during the spontaneous rhythm.

STRESS ECHOCARDIOGRAPHY AND NONIVASIVE MEASUREMENT OF THE CARDIAC OUTPUT – STUDIES 2 AND 4

Impact of BVP and LVP on the acute changes of the cardiac output during exercise was assessed by stress echocardiography in study 2. The test was performed in the supine position using bicycle ergometer (Ergoline-ergometrics 900, Marquette Electroics MN, USA). After resting for 10minutes, exercise with stepwise workload increase by 25watts every 3minutes was applied. The test was performed in the mornings of 2 consecutive days and the patients were randomly allocated to either BVP or LVP with crossover on the following day.

At the end of the resting phase and at the end of each exercise level, blood pressure and heart rate were measured noninvasively. In addition, cardiac output was assessed using velocity time integral formula with the sampling volume placed in the LV outflow tract. A mean value of velocity time integral obtained by averaging of three consecutive cycles was used for calculation of the cardiac output (CO).

Similar approach to the estimation of CO was also applied in study 4. This study was focused on the impact of different AVD and VVD on the cardiac output during the following pacing modes: 1/ BiV-LV – BVP with preexcitation of the LV by 4ms, 2/ BiV-RV – BVP with preexcitation of the RV by 4ms, 3/ LVP. We tested a sequence of sensed and paced AVD (i.e. AVD during atrial-trigerred ventricular pacing and atrioventricular sequential pacing, resp.) in all three pacing modes. Range of 80-160ms for sensed and 120-160ms for paced AVD was tested. Changes of CO induced by various degree of ventricular preexcitation (interventricular delay, VVD) were then assessed during BVP with an optimal AVD. Preexcitation of either RV or LV by 4-20ms was tested *(Figure 1 in study 4)*.

LONG-TERM FOLLOW-UP – STUDIES 1-4

Following variables were evaluated every 3 months after the CRT implantation: clinical outcome including current NYHA functional class and change in exercise tolerance, medication, ECG, spiroergometry and check of the device function, pacing thresholds, sensings and impedances of all implanted pacing leads. In addition, echocardiographic evaluation assessing LVEDD and LVEF was performed routinelly every 3 months.

STATISTICAL ANALYSIS

The main findings were expressed as a mean ± standard deviation. For comparison in the group or between different groups, paired or unpaired t-test was used, when appropriate. P-value <0.05 was considered as significant. Correlation between variables was assessed using Pearson correlation coefficient, independent predictors were then identified using discriminant analysis.

RESULTS

1. ELECTRICAL ACTIVATION SEQUENCE DURING DIFFERENT PACING MODES

(STUDY 1)

Using electroanatomical mapping, activation pattern of both ventricles during different pacing modes (BVP, LVP, single-site RV pacing, BFP) was analysed. It was clearly shown that the activation sequence of the heart can be interindividually highly variable, depending on 1/ the type of conduction disturbace, 2/ pacing mode and 3/ placement of the pacing lead(s). In addition, underlying heart disease, specifically the presence and location of scar, participated on this variability of activation pattern. The conduction defect localized on the ventricular level predominantly determined the ventricular activation pattern. Moreover, this study highlighted the contribution and impact of spontaneous activation via right bundle on the degree and pattern of ventricular resynchronization, so called phenomenon of fusion. Our results indicate that the presence of fusion of spontaneous conduction with LVP-induced wavefront mimicks ventricular activation sequence observed during BVP. More importantly, this study described factors that modify the degree of this fusion. Present study further demonstrated that various pacing strategies alter the degree of both intra- and interventricular dyssynchrony. In addition, this was the first study describing activation sequence during BFP to our knowledge.

2. COMPARISON OF THE ACUTE EFFECT OF BIVENTRICULAR AND SINGLE-SITE LEFT VENTRICULAR PACING DURING EXERCISE *(STUDY 2)*

In the second study, effect of BVP and LVP on the acute, exercise-induced changes of stroke volume was assessed. The results of our study implied that similar exercise level can be reached during both BVP and LVP in most cases with preserved AV conduction. Our results also indicated that LVP is equivalent to BVP in terms of augmentation of cardiac output. In fact, LVP was associated with slightly better results at rest and during low-level exercise as compared to BVP. However, cardiac output increase did not differ between LVP and BVP during higher exercise-levels. In addition, we observed superiority of one the modes in about 80% of all cases. Interestingly, superiority of LVP was seen predominantly in patients with DCM in our study. This might be related to a different expression of the inter- and intraventricular dyssynchrony among patients with DCM and CAD.

3. VENTRICULAR PACING SITE(S) *(STUDY 3 & REVIEW)*

The aim of the third study of this PhD was to assess the importance of RV lead positioning in CRT recipients. The review summarizes current data about the hemodynamic consequences of alternative RV pacing sites that served as a rationale for study 3.

To our knowledge, our study was the first study assessing the impact of RV lead positioning on the long-term outcome of CRT. Its results confirmed our hypothesis that the selection of RV pacing site in CRT recipients affects the extent of LV reverse remodeling with more favourable results when paced from midseptal region. Less pronounced reverse remodeling was observed in patients with RV lead placed in the apical region. However, trend towards reduction of LVEDD was visible also among the later group, but after 2-3 times longer period than in the patients with midseptal pacing. This observation may suggest that CRT related reverse remodeling is also time-dependent. In addition, this study demonstrated that midseptal pacing is associated with a shortening of the total electrical activation (as expressed by the duration of QRS complex) during both single-site RV pacing and BVP. In accordance with other studies, however, we did not find relationship between the degree of reverse remodeling and either QRS duration or the extent of the QRS narrowing.

4. IMPACT OF DIFFERENT ATRIOVENTRICULAR AND INTERVENTRICULAR DELAYS ON CARDIAC OUTPUT DURING CRT *(STUDY 4)*

Our last study demonstrated that the acute hemodynamic benefit of ventricular pacing is primarily dependent on the pacing mode, but using any pacing mode or site, the benefit is titrated by selected AVD. Our results shown nonsignificantly higher CO during the atrial-trigered than during AV sequential CRT pacing. Optimal P-AVD was constantly longer than the optimal S-AVD during CRT and no significant correlation with spontaneous AV conduction was found. In addition, it was possible to identify an optimal S-AVD and P-AVD in most patients as the distribution of CO during different AVD setting was a bell-shaped curve with the maximum around 120ms for S-AVD and 140ms for P-AVD, respectively. However, CO changed only minimally in some patients and optimum value was often shifted to the right in these cases. This finding emphasized the necessity to optimize AVD individually as we have not identified any independent predictor of this AVD behavior.

Regarding VVD optimization, our findings suggest that the optimization of VVD may partially modify hemodynamics during CRT. LV preexcitation or simultaneous BVP was favorable in majority of our patients. Preexcitation of RV was constantly associated with worse hemodynamic performance.

1. ELECTRICAL ACTIVATION SEQUENCE DURING DIFFERENT PACING MODES

STUDY 1

Peichl P, Kautzner J, Čihák R, Riedlbauchová L, Bytešník J. Ventricular activation patterns during different pacing modes. An insight from electroanatomical mapping. Kardiol Pol 2005;63(6):622-632. (PMID: 16380863)

2. COMPARISON OF THE ACUTE EFFECT OF BIVENTRICULAR AND SINGLE-SITE LEFT VENTRICULAR PACING DURING EXERCISE

STUDY 2

Riedlbauchová L, Frídl P, Kautzner J, Peichl P. Performance of left ventricular versus biventricular pacing in chronic heart failure assessed by stress echocardiography. Pacing Clin Electrophysiol 2004 May,27(5):626-631. (PMID: 15125719).

3. IMPORTANCE OF RIGHT-VENTRICULAR PACING SITE IN CRT

STUDY 3 & REVIEW

Riedlbauchová L, Čihák R, Bytešník J, Vančura V, Frídl P, Hošková L, Kautzner J. Optimization of right ventricular lead position in cardiac resynchronization therapy. Eur J Heart Fail 2006 Oct;8(6):609-614. Epub 2006 Feb 28. (PMID: 16504581)

Riedlbauchová L, Kautzner J, Hatala R, Buckingham TA. Is right ventricular outflow tract pacing an alternative to left ventricular/biventricular pacing? Pacing Clin Electrophysiol 2004 Jun;27(6 Pt 2):871-877. (review, PMID: 15189518).

4. IMPACT OF DIFFERENT ATRIOVENTRICULAR AND INTERVENTRICULAR DELAYS ON CARDIAC OUTPUT DURING CRT

STUDY 4

Riedlbauchová L, Kautzner J, Frídl P. Influence of different atrioventricular and interventricular delays on cardiac output during cardiac resynchronization therapy. Pacing Clin Electrophysiol 2005 Jan;28 Suppl 1:S19-S23. (PMID: 15683494)

CONCLUSIONS

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Cardiac resynchronization therapy (CRT) represents an accepted treatment modality in patients with advance chronic heart failure, acute and long-term benefit of which was confirmed in several clinical trials. Recently, reduced mortality and rate of hospitalization for heart failure were also demonstrated. However, response to CRT is interindividually highly variable with a substantial proportion of CRT recipients who do not respond to this therapy.

Although the identification of suitable candidates is probably the most important factor in the reduction of the rate of non-responders, some other determinants, peri- and post-implant, may substantially affect the final effect of CRT. The present PhD focused on some of these variables:

1/ First of them is a selection of the appropriate pacing mode. This PhD evaluated effect of 3 pacing modalities that have been proposed as alternatives of CRT – biventricular pacing (BVP), single-site left-ventricular pacing (LVP) and right-ventricular bifocal pacing (BFP). It was clearly shown that the first two pacing strategies, BVP (i.e. simultaneous pacing of both ventricles) and LVP, cause comparable acute hemodynamic improvement at rest. Study No.2 of this PhD confirmed that the comparable effect of BVP and LVP is preserved also during the exercise.

In addition, study No.1 described the character of ventricular activation during all 3 pacing strategies and explained the reasons for comparable hemodynamic benefit of BVP and LVP by restoration of more physiological activation sequence with merge of two activation wave fronts in the middle of the left ventricle. On the contrary, based on our experience from the long-term follow-up, BFP (simultaneous pacing from the apex and outflow tract of the right ventricle) is only rarely associated with the clinical improvement. Possible reasons for the inferiority of BFP as compared to BVP and/or LVP on the electrical level is the inability to correct the intraventricular asynchrony by BFP.

2/ Besides the selection of pacing mode, the pacing site is very important determinant affecting the final outcome of CRT. Optimal regions for insertion of the left-ventricular lead were studied by many investigators in the past. However, the issue of proper right-ventricular (RV) lead positioning in BVP was not addressed before. In fact, our study was the first one

that demonstrated additional benefit when using RV midseptal region as compared to RV apex for long-term BVP (study No.3). More significant and earlier reverse remodeling of the ventricles was observed when paced from the midseptal region.

3/ Last, but not least, the final benefit of CRT is titrated, at least partially, by the atrioventricular and interventricular delay programming (AVD and VVD) due to modification of the degree of inter- and/or intraventricular resynchronization. Study No.4 of this PhD indicated that the cardiac output changes with selected AVD and VVD, with the optimum usually around 120ms and 140ms for sensed and paced AVD resp. and preexcitation of the left ventricle in range 4-12ms for the VVD. Variable response to changed AVD and VVD setting in some patients, however, suggested the superiority of their individually-based optimization.

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Reviews	- in English:	2
	- in Czech:	4
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