

# Cardiac resynchronisation – a new standard in heart failure therapy

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Chronic heart failure is a clinical syndrome and the final common pathway of different cardiac diseases. A rising incidence is reported all over the world, leading to enormous cost and spending of health care resources. Although medical therapy with beta blockers, ACE-inhibitors and spironolactone has proved to be efficacious, mortality remains high. Therefore the introduction of supplemental methods is very welcome and indeed, electrical therapies with implanted devices become increasingly important in this regard. Besides the implanted cardioverter defibrillator (ICD), cardiac resynchronisation therapy (CRT) has recently been shown not only to improve exercise tolerance, but also to prolong survival in patients with heart failure and cardiac asynchrony. Therefore, an overview of cardiac resynchronisation therapy, including additional CRT-ICD capabilities, is given herein according the literature. This includes current guidelines, our own implantation experience, and follow-up data of 500 patients during 1999 – 2007.

## Introduction

Chronic heart failure (CHF) is a clinical syndrome and the final common pathway of several different cardiac diseases. The main symptoms of CHF are breathlessness, fatigue and ankle swelling. Its diagnosis relies on history, physical examination and objective evidence of cardiac dysfunction. The most common cause of CHF is hypertension and ischemic heart disease, though diastolic HF exists with normal systolic function<sup>1-3</sup>. The prevalence in Europe is 0.4 to 2% of general population, with about ten million cases. Extrapolated from these data, Iran should have more than 1 million CHF patients<sup>4</sup>, and there is no reason to believe that numbers are lower in other Asian countries. The incidence is still

rising, as acute episodes for example of myocardial infarction, can be more often successfully treated by invasive measures<sup>5</sup>. In patients older than 65 years of age CHF is one major reason for hospitalisation and death<sup>6</sup>. Even at present the 5 years mortality is 80% despite medical therapy<sup>7</sup> and equals the mortality of aggressive malignancies<sup>1, 6</sup>. Thus, this is a major economic problem as health care costs total approximately 80 billions Euro/year worldwide and, 2.7 billions in Germany<sup>8</sup>. Therefore any measure improving prognosis and reducing adverse events and hospitalisation is very welcome, not only to provide better patient care but also to spare significant economic resources.

## CHF and asynchrony

A broadening of the QRS complex (>120ms) is a typical finding in patients with CHF. In higher NYHA classes (III, IV), its prevalence can be as high as 50% of all cases<sup>9</sup>. A wide QRS (mostly left bundle block like configurations) is

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an independent risk factor for cardiac events and death<sup>10</sup> and is an important coefficient of the heart failure survival score HFSS<sup>11</sup>. Patients with wider QRS (> 200 ms) had five times greater mortality risk than those with the narrowest QRS (< 90 ms)<sup>12</sup>. These electrical changes are associated with asynchronous contractions of the right and left ventricle<sup>13</sup> leading to mechanical stress and hemodynamic deterioration<sup>14</sup>. Asynchrony causes wall segments to contract early or late, with redistribution of myocardial blood flow, non-uniform regional myocardial metabolism, and changes in regional molecular processes<sup>15</sup>. Furthermore, intraventricular asynchrony partly favours mitral valve incompetence and shortens LV filling times. These changes seem to represent a pathophysiological process that directly depresses ventricular function causing LV remodelling and CHF, and as a consequence leading to a higher risk of morbidity and mortality.

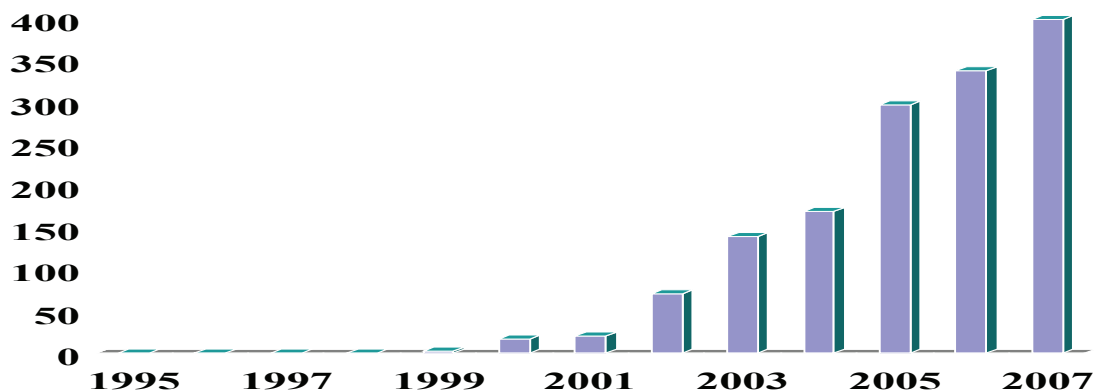
### Mechanism of CRT action

Biventricular pacing in CRT stimulates both ventricles and/or septal and lateral walls of the left ventricle near-simultaneously and improves the coordination of ventricular contraction. The contraction delays of each cardiac

segment can be lowered by CRT as measured by tissue Doppler imaging studies (TDI)<sup>16</sup>. One of the major action of CRT seem to be a reduction of the total isovolumic time (IVT) during stress<sup>17</sup> yielding an augmentation of hemodynamics predominantly at exercise<sup>18</sup>. Filling pressures decrease and systemic arterial pressures are augmented<sup>19</sup>. These beneficial hemodynamic effects lead to a process called reverse remodelling, thus lowering volumes of the left ventricle<sup>20</sup>. Clinical status (NYHA class) and exercise capacity can increase overall and dramatically in individual patients<sup>21</sup>. The worse the patient's condition, the better is the gain in oxygen uptake.

### Historical aspects and evolution of CRT

The first descriptions of hemodynamic benefits of left or of simultaneous right and left ventricular stimulation were published over 40 years ago<sup>22-24</sup>. However the current clinical application of the stimulation technique known as CRT began only in 1994, when Serge Cazeau et al.<sup>25</sup> described the first case of atrio-biventricular pacemakers implanted in a patient with severe HF, stimulating the left ventricle via epicardial leads. Since that time, an exponential interest in clinical and experimental data



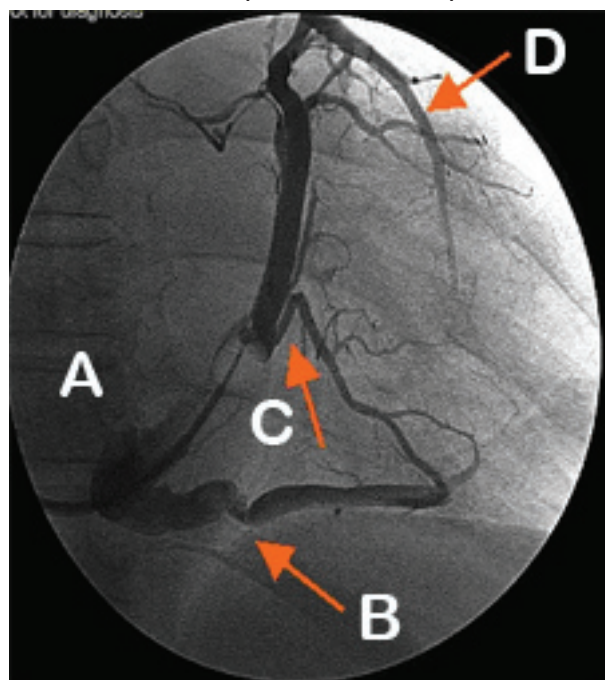
**Figure 1** Increase in MEDLINE publications addressing CRT, results of MEDLINE search using the terms “resynchronisation” in connection with heart and cardiovascular diseases

concerning this form of therapy has been noted (Figure 1). The breakthrough for CRT came along with the development of leads specially designed for the coronary sinus, especially with over the wire capabilities<sup>26</sup>. This allowed the stimulation of the left ventricle without calling the surgeon.

### Implantation techniques of CS leads

Successful CRT depends on the placement of left ventricular leads usually via the CS (Coronary Sinus), a technically more challenging procedure than regular pacemaker implantations resulting in 1-10% of implantation failures. Reasons for unsuccessful implantation procedures were mostly due to an inability to locate the coronary sinus ostium. Therefore every effort should be made to overcome this first serious implantation hindrance. Some centres prefer to perform a venous angiogram of the CS preoperatively - for example, via the femoral veins. However we prefer a one-time procedure. Sometimes it may be helpful to review a coronary angiogram of the patient in detail because the late venous phase may uncover at least the main stem of the CS (Coronary Sinus), showing its drainage site in the right atrium. Data from cardio CT or cardio MRI could also be useful in selected cases, but are rarely used in clinical practice due to enormous costs. The ostium of the CS can be finally localized in different ways, typically by use of application sheaths of different shapes. The selection of a target vein should be done by means of retrograde venous angiography using standard balloon catheters allowing temporal blockade of the surface ECG signals of the venous return of the CS (Figure 2). By correct visualization, a suitable target vein could be identified in 99% of patients<sup>27</sup>. Optimally CS

leads should be placed in the regions with the latest activations. These were mostly posterolateral or anterolateral veins. The site of latest activation can be visualized by comparing intracardiac electrograms to the surface ECG, sensing the LV late in the course of an acceptable position. Some centers perform intraoperative measurements at different lead positions using pressure volume loops obtained by the use of Millar pressure catheters in the left ventricle<sup>28</sup>. However, so far, it has never been shown conclusively that the rate of non-responders can be reduced by this invasive and expensive method. In our series, coronary sinus leads were positioned 51% in posterolateral, 38% in anterolateral and only 11% in anterior veins<sup>29</sup>. Selecting the right position visually is the most important measure needed to avoid non-responders. In our study, only 58% of the patients with anterior leads were responders while the responder rate in patients with



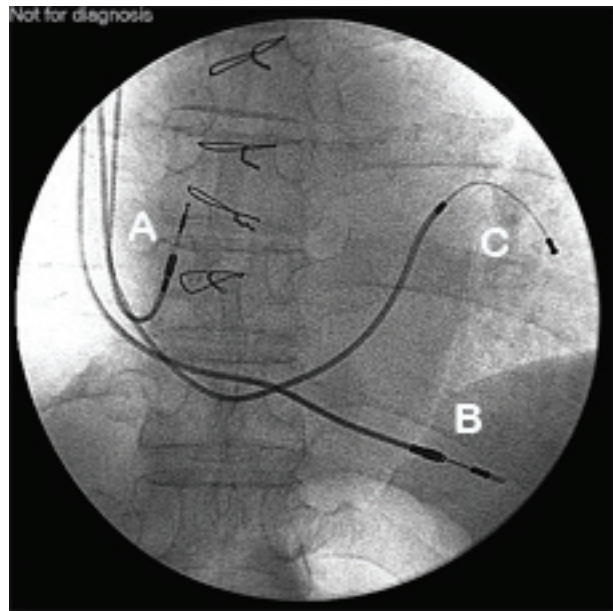
**Figure 2.** Typical retrograde CS angiography.

- A: CS main stem with cannulation sheath and balloon catheter
- B: Big middle cardiac vein
- C: Small posterolateral cardiac vein
- D: Great and anterior cardiac vein

anterolateral and posterolateral CS leads was 91%<sup>30</sup>. Once a target vein could be identified a method should be chosen for its cannulation. The availability of an over the wire lead is warranted in many cases at least in our means. Classically CS leads have to be pushed in a wedge position to yield a stable fixation. However, this goal could not be met every time due to anatomical reasons such as large venous diameters or phrenic nerve stimulation in very distal positions. However, the apparently simple solution of a proximal lead positioning is a difficult task resulting in a high number of dislocations and high stimulation thresholds, despite preshaped angulations in commercially available leads. Active fixation may be an option in this difficult situation. To date, one model of an active CS lead is available using expandable tines. First experience with this lead show a zero dislocation rate, low and stable thresholds but possible difficulties with extraction<sup>31</sup>. Procedure-related mortality should be < 1%; in our series it is 0%<sup>29</sup>. Figure 3 shows a typical pacing configuration of a transvenous CRT system with an atrial, a right ventricular and a left ventricular lead passed through a high posterolateral coronary vein.

### CRT patient studies

The clinical effects of long-term CRT were first evaluated in non-controlled studies, in which a sustained clinical benefit conferred by biventricular pacing was measured<sup>32-34</sup>. Biventricular pacing improves exercise capacity and reduces hospitalizations<sup>37-39</sup>. Prospective randomised multi- centre studies, such as the CARE-HF<sup>35</sup>-and COMPANION<sup>19</sup> trials have shown a reduction of left ventricular volumes and mitral regurgitation as well as improvements in symptoms and prognosis with CRT.



**Figure 3.** Typical CRT pacing configuration with an atrial (A), right ventricular (B) and a lead in a posterolateral branch of the CS (C)

Having established a reduction in mortality, CRT was judged to be a class 1A indication for patients in NYHA III and IV CHF in the classical situation of QRS >150ms and LVEF <35%.

### CRT Guidelines

CRT has been adopted in the guidelines of several cardiology societies. The newest guidelines published by the European Society of cardiology in 2007<sup>38</sup> favour relatively liberal inclusion criteria depending on symptoms (NYHA classes III and IV), a reduced ejection fraction (<35%) and a widened QRS-complex (>150ms class I, and 120-150ms class II). After all, it is obvious that patients have to be symptomatic despite optimal medical therapy including  $\beta$ -blockers, ACE-inhibitors or equivalents and diuretics. QRS broadening may be due to spontaneous block (class I) or chronic right ventricular stimulation (class II). There is less evidence for a therapeutic effect on patients with shorter QRS durations (120-150 ms), resulting in a lower class of indication.

However when asynchrony can be documented, for example, by means of tissue Doppler examination, CRT may be as effective as in the case of broader QRS intervals. One could also argue that the presence of objective markers of heart failure is a prerequisite for successful CRT.

### **Patient selection for CRT**

Daily clinical practice is something different from the guidelines. Selecting the right patient for cardiac resynchronisation therapy is an absolute prerequisite for a successful therapeutic response. Dyspnoea on exertion and fatigue can be caused by different mechanisms ranging from pulmonary disease to depression. In this regard we think that the determination of objective values such as the brain natriuretic peptide (BNP or NT-proBNP) in plasma is a useful tool for the differentiation of problems besides CHF. In this regard a recent publication showed that non-responders to CRT had significantly lower BNP levels than patients successfully treated with this method<sup>39</sup>. In other words patients with normal BNP levels should be carefully investigated to determine whether they have a true indication. A cardiopulmonary exercise (CPX) test is another test which proves to be very useful for patient selection. It has been shown that patients with an oxygen uptake of more than 16 ml/kg/min of body weight do not benefit from CRT, at least in the first 6 months<sup>21</sup>. With BNP and CPX testing, patients too well for CRT can be excluded from a therapy which would not improve their condition despite the fact that, a long-term beneficial effect was not impossible.

### **Echo and CRT**

In past years it was believed that the most

important investigative tool for evaluation of CRT candidates and in follow-up is TDI echo (YU 2007). Although these measurements yield fascinating pictures unravelling asynchrony in different cardiac segments (see Table 1), in the PROSPECT study, no single echocardiographic measure of mechanical asynchrony was identified as being useful for identifying patients more or less likely to respond to CRT<sup>40</sup>. Three of the echo measures (IVMD, LVFT/RR and LPEI) were predictors of a small improvement in the clinical composite score and five echo measures (SPWMD, IVMD, LVFT/RR, LPEI and Tslat-sep) were predictors of reverse remodelling in spite of the fact that all had low sensitivity and specificity. In particular the inter-core lab variability was relatively high at 6.5–72%, indicating a need for refinement of the methodology. A recent report from the CARE-HF study<sup>41</sup> suggested that patients with echocardiographic evidence of more severe dyssynchrony and low systolic blood pressure gain greater benefit from CRT, but this study also found that these relationships were weak. It is likely that asynchrony is a dynamic problem and therefore a single measurement, under one set of physiological circumstances, is not representative of the total disease burden<sup>40</sup>.

### **The surveillance of CRT patients using intra-device technology and long-distance data transmission**

As patients with CRT are surviving longer, close follow-up requires much more medical resources. It seems logical to include sophisticated technologies for patient surveillance. Up to now, several intra-device tools have been available for the assessment of each patient's heart failure status. Patients can be monitored according to their body movements, heart

**Table 1.** Echocardiographic indices of asynchrony

Acronyms	Method	Suggestive for asynchrony
SPWMD <sup>42</sup>	Septal-to-posterior wall motion delay (M-Mode)	> 130ms
LV-PEP <sup>35</sup>	Aortic preejection delay (Pulse Doppler)	>140 ms
$\Delta$ PEP <sup>43</sup>	Interventricular electromechanical delay : (Q-Ao)-(Q-Pulm) (Pulse Doppler)	77 ms for QRS >150ms
DLC <sup>44</sup>	Delayed longitudinal contraction % basal LV (Tissue doppler)	
Systolic asynchrony index <sup>45,46</sup>	Time-to-peak systolic contraction (Tissue Doppler imaging)	33 ms
Peak strain <sup>47</sup>	Peak septum strain-peak lateral wall strain (Strain rate imaging)	
LV asynchrony <sup>48</sup>	Septal to lateral delay (Tissue velocity imaging)	> 65 ms
LV-LV-RV asynchrony <sup>49</sup>	Tissue Doppler imaging	> 102 ms

rate variability or their intrathoracic impedance, which indicates fluid accumulation in the body<sup>50</sup>. However these algorithms are expensive and not fully explored and their true clinical importance has to be defined. In addition, patient surveillance over long distance, has recently become a reality. Not only simple binary data, but also complete high resolution electrograms can be transmitted worldwide<sup>43</sup>. Studies are under way to show if the individual patient really benefit from these exciting technical advances.

### **CRT pacemaker only or CRT defibrillator for every patient?**

Patients with severe HF are still threatened by the risk of sudden cardiac death and may profit from primary prophylaxis with an implanted defibrillator<sup>52</sup>. This raises the question of whether patients with a CRT indication should receive a simultaneous defibrillation capability. Despite some information in randomized studies, situations are not so clear as converging curves in the COMPANION study<sup>19</sup> after 3 years and the CARE-HF extension study showed a reduction in sudden death without defibrillators as well<sup>53</sup>. At the present,

more or even most patients are being supplied with CRT-ICDs in clinical practice<sup>54</sup>. Especially for young patients it seems to be very unfair to implant CRT-pacing devices only because they are threatened with lethal arrhythmia in the long run. Most importantly, sudden death risk remains even if the ejection fraction increased above the magical border of 35% under medical and CRT therapy<sup>55</sup>.

### **The CRT Nonresponders**

Despite its proven efficacy, the response to CRT varies substantially between patients<sup>56-58</sup>. The reasons for this remain somewhat obscure. No single parameter could be identified to predict a favourable response to therapy<sup>40</sup>. The exception is posterolateral scar tissue, which, when present in Cardio-MR is a strong predictor of non-response<sup>59</sup>. Therefore scar imaging may be an option in possible non-responders to indicate that alternative therapies should be investigated.

### **CRT in special indications**

Still remaining are the questions about CRT in patients with the following indications:

- Narrow QRS complex: There is still no

evidence that CRT is indicated in patients with HF and QRS < 120ms. However echocardiographic studies found that mechanical asynchrony correlates weakly with electrical asynchrony, and a recent report showed that 36% of patients with an LVEF < 35% could have asynchrony shown by tissue Doppler imaging measurements<sup>60</sup>. Randomised studies are still needed.

- Mild heart failure or asymptomatic left ventricular systolic dysfunction (NYHA I-II): In this population there are just a few trials with small groups and only 6 months of observation such as CONTACT-CD and MIRACLE ICD II, which showed a significant amount of reverse remodelling. Thus, at the time of this writing, no recommendation can be made regarding these patients. There is a need for larger randomised trials.
- Atrial fibrillation (AF): The prevalence of AF in patients with HF varies between 25% and 50%<sup>61</sup>. This high prevalence contrasts with the low percentage (2%) of patients with HF enrolled in randomised trials for CRT. Thus, there is less evidence-based information regarding the value of CRT in this population.
- Previously implanted conventional pacemaker and severe left ventricular dysfunction: There are scarce data concerning the effects

of device upgrading from right ventricular to biventricular pacing<sup>34</sup>. The consensus is that in patients with chronic right ventricular pacing and the presence of an indication for CRT, an upgrade is indicated.

### Future aspects of CRT

Hopefully we will have the data from studies on the above-mentioned patients with special indications in the near future. It is very likely that many more patients may benefit from this form of therapy, such as those with narrow QRS, mild CHF, atrial fibrillation, and chronic right ventricular stimulation. The question remaining is whether we have the financial power to fulfil all these needs. Promising technical developments are new implantation techniques using magnetic navigation systems<sup>62</sup>, multimodal visualization techniques of the CS, and multipolar stimulation. Whether the use of fiberoptic catheters will be useful for optical visualization of the CS entrance remains to be established by further studies<sup>63</sup>. If CRT fails another fascinating technology appears on the horizon: cardiac contractility modulation (CCM) with non-excitatory stimulation in the absolute refractory phase. This technique can be used, for example, to help CRT non-responders<sup>64</sup>.

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