

Cardiac resynchronisation therapy in chronic heart failure

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Summary

Cardiac resynchronisation therapy (CRT) has emerged as a treatment option for patients with severe, drug-refractory heart failure and signs of intraventricular dyssynchrony. In clinical trials CRT reduced the overall mortality, improved symptoms, exercise tolerance, and left ventricular function, as compared with optimised medical therapy alone. One of the challenging fields in patient selection for CRT is to identify the 20–30% of heart

failure patients with bundle branch block that will not respond to this novel therapy. Other fields of uncertainty, such as CRT in patients with atrial fibrillation or chronic right ventricular stimulation as well as the role of a back-up defibrillator will be discussed.

Key words: heart failure; cardiac resynchronization therapy; biventricular pacing; QRS duration

Introduction

Major progress has been made in the pharmacological management of patients with heart failure. The introduction and widespread use of angiotensin converting enzyme inhibitors, angiotensin II-receptor blockers, beta-blocking agents, and spironolactone improved mortality and morbidity in this population [1–4]. However, trials of new agents, such as endothelin antagonists, vasopeptidase inhibitors, and soluble tumour

necrosis factor α -antagonists, did not show further survival benefits. Cardiac resynchronisation therapy (CRT) has emerged as a highly effective treatment option in a subset of patients with marked intraventricular dyssynchrony. Eight randomised trials with more than 4000 patients have been completed and give evidence for the effectiveness of CRT [5–12].

Mechanisms of dyssynchrony and resynchronisation

Most patients with intraventricular dyssynchrony display a left bundle branch block pattern on the surface ECG. This occurs in up to 25% of all heart failure patients and confers a higher risk of both, worsened heart failure and sudden cardiac death [13]. In these patients, the left lateral wall is activated well after the septum contracts. This leads to contraction of the lateral wall during relaxation of the septum resulting in profound mechanical dysfunction. This, in turn, causes an increase in the left ventricular volume, reduction of contractility, and worsening of mitral regurgitation. Ventricular dyssynchrony on tissue Doppler studies itself predicts a worse outcome independent of the QRS duration which is only an indirect marker for dyssynchrony [14]. The dyssynchro-

nous heart exhibits marked changes in local calcium handling as exemplified by a strong decrease of the key calcium handling protein, phospholamban, in the delayed activated myocardium [15]. There is strong evidence that the mechanical dyssynchrony rather than the electrical delay is mainly responsible for the detrimental effects of the dyssynchronised heart [16]. Implementation of CRT results in an instantaneous increase of the left ventricular contractility (dp/dt) along with a rise in cardiac output. Of note, this is due to an improvement of chamber efficiency and not to an increased metabolic demand of the failing heart [17]. Although very little data is available, it appears that the favourable effects of CRT are even enhanced under stress conditions [18]. Long-term CRT re-

sults in a decrease of endsystolic and enddiastolic volumes, which has been coined “reversal of ventricular remodeling”. In an echocardiography substudy of the MIRACLE trial, CRT over 1 year led to a significant decline in these volumes, which was even more pronounced in the subgroup with non-

ischaemic origin of heart failure [19]. Our own data indicates, that this effect as well as the improvement of the ejection fraction (EF) persist for at least 30 minutes after chronic CRT has been turned “off” [20].

Effects on mortality

Initially, numerous trials with and without crossover design were able to demonstrate the symptomatic improvement of patients with CRT [8, 12]. The COMPANION trial provided the first evidence for a positive effect of CRT on mortality [7]. The trial randomised patients in sinus rhythm with left bundle branch block >120 ms, an EF <35%, and symptomatic heart failure NYHA class III or IV to optimal medical therapy, CRT, and CRT with defibrillator (CRT-D). With regards to the combined endpoint of all cause mortality and rehospitalisation for worsened heart failure CRT as well as CRT-D were significantly better than optimal medical therapy, with a relative risk reduction of 24%. All cause mortality was significantly

reduced by CRT-D whereas CRT alone was only borderline significant ($p = 0.06$).

Recently, the CARE-HF trial provided convincing evidence that CRT without defibrillator back-up reduces all cause mortality by more than 30% ($p < 0.002$) as compared to optimal medical therapy [9]. This effect became obvious 12 months after implantation and was even more pronounced in the long-term follow-up [21]. Importantly, in the CARE-HF study almost half of the patients suffered from dilated cardiomyopathy. Non-ischaemic patients have a lower risk for sudden cardiac death [22] and appear to have greater benefit from long-term CRT therapy [19].

Current indications

According to the updated ESC heart failure guidelines, CRT is now a class I indication (level of evidence A) in patients with symptomatic heart failure NYHA III or IV, reduced ejection fraction, and a QRS duration >120 ms [23]. CRT-D is a class IIa indication for patients with an EF $\leq 35\%$, symptomatic heart failure NYHA class III or IV, and a

QRS duration >120 ms. To date, these data apply to patients in sinus rhythm and there are certain areas of uncertainty which will be addressed below. The most pressing question, however, is how to identify the 25–30% of patients that will not respond to CRT.

Patient selection

Most clinical trials so far focused on the QRS width as the main parameter for cardiac dyssynchrony. However, there is little difference in QRS duration between responders and non-responders [24]. Doppler echocardiography is more suitable to identify cardiac dyssynchrony [25]. Nonetheless, so far only very few trials, including the CARE-HF trial, also used Doppler criteria to determine mechanical dyssynchrony [9]. There is growing evidence that the latter is the main determinant for cardiac dyssynchrony. Yu et al. were able to demonstrate that a considerable number of patients with a wide QRS complex display no mechanical dyssynchrony as assessed by Doppler studies whereas some of those with a narrow QRS show pronounced mechanical dyssynchrony [26]. In fact, up to 30% of heart failure patients with normal QRS complexes have signs of mechanical dyssynchrony

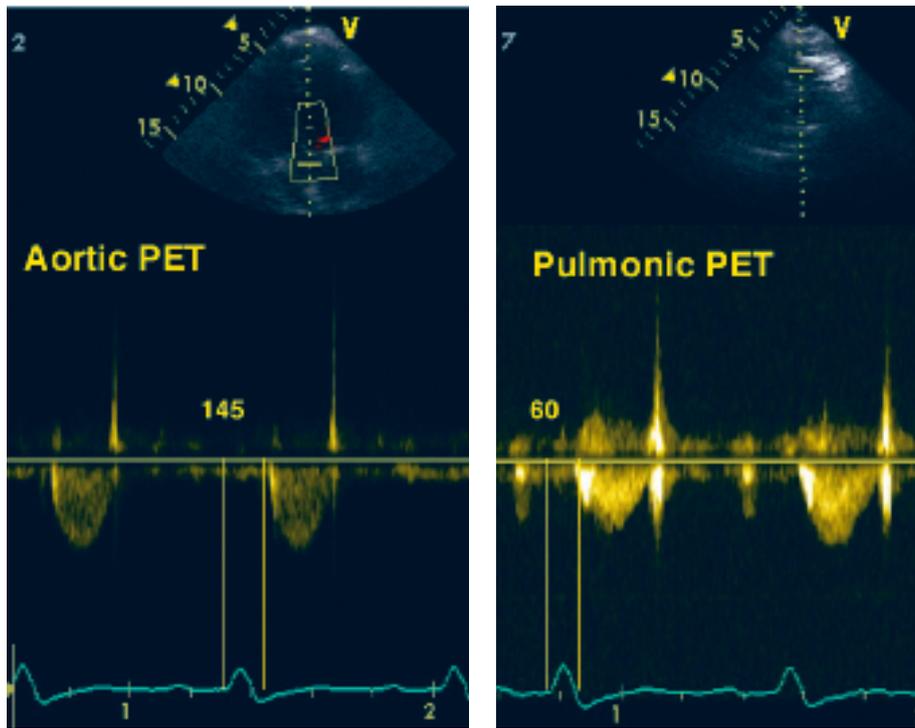
and one study demonstrated that patients with comparable mechanical dyssynchrony responded equally well to CRT regardless of the width of the underlying QRS complex [27]. One has to bear in mind, however, that to date there is conflicting data and no clear consensus as to which echocardiographic parameter predicts clinical response.

Commonly used echocardiography parameters for the assessment of mechanical dyssynchrony

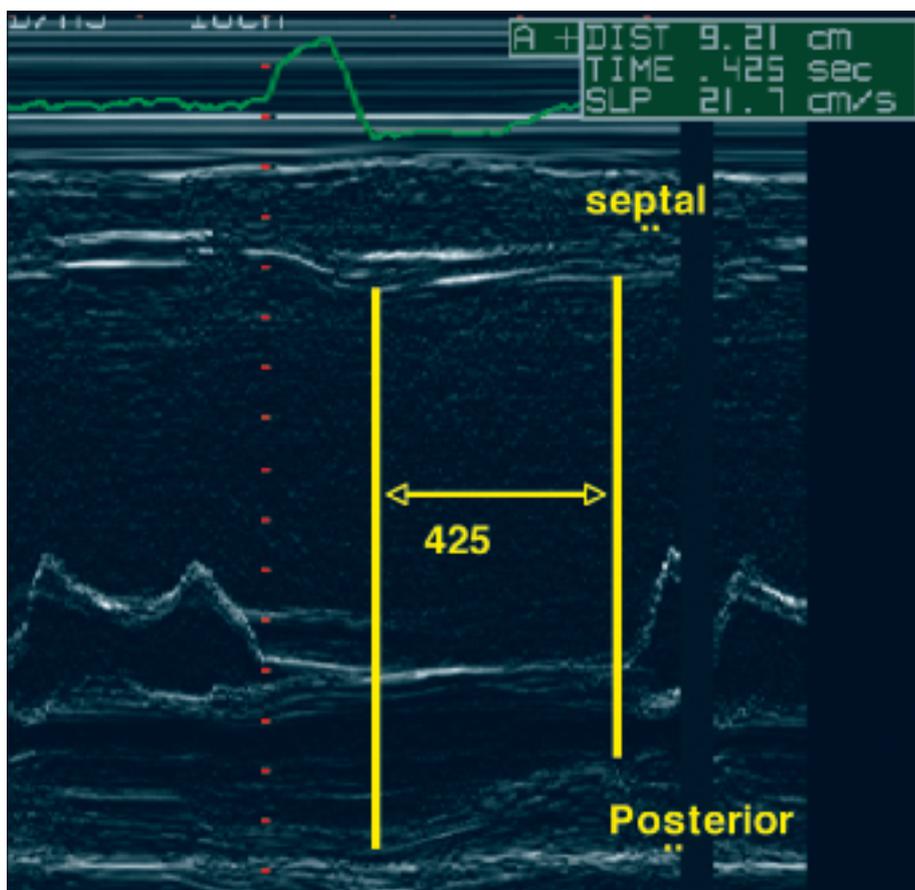
Because of its widespread availability and its ease of use, echocardiography is a very convenient tool for the assessment of intra- and interventricular dyssynchrony. There is a plethora of proposed techniques and criteria for identifying CRT responders [28]. At our institution we use the following parameters:

Figure 1

Assessment of the interventricular mechanical delay (IVMD) by Doppler echocardiography. The presystolic ejection time (PET) is calculated by measuring the time from the onset of the QRS-complex and the beginning of the Doppler-ejection signal across the aortic valve (APET) and the pulmonary valve (PPET), respectively. IVMD is then calculated by subtracting PPET from APET (here: $IVDM = 145 \text{ ms} - 60 \text{ ms} = 85 \text{ ms}$; $IVDM \geq 40 \text{ ms}$ indicative for interventricular dyssynchrony).

**Figure 2**

Assessment of the septal to posterior wall motion delay (SPWMD) using M-mode echocardiography. The time interval between maximal systolic inward motion between the septal and posterior wall is calculated (here: 425 ms; cut-off $\geq 130 \text{ ms}$).



- a) *Interventricular mechanical delay (IVMD)*: time difference between left and right ventricular pre-ejection intervals (fig. 1). An IVMD ≥ 40 msec is indicative for interventricular dyssynchrony [29, 30].
- b) *Septal to posterior wall movement delay (SPWMD)*: assessment of intraventricular mechanical dyssynchrony. From the parasternal short-axis view an M-mode at the level of the papillary muscles is used to assess SPWMD ($\geq 130 \text{ ms}$; fig. 2) [30]. Although this measure has been correlated with better clinical outcome, it is often impossible to obtain perpendicular M-mode sections or to perform accurate measurements since the septum is often akinetic [31].
- c) *Septal to lateral delay using tissue Doppler imaging (TDI)*: more accurate assessment of intraventricular dyssynchrony by placing two sample volumes on the basal part of the septum and

Figure 3

a, b: Lengthening of the diastolic left ventricular filling time by shortening of the AV-interval measured by Doppler echocardiography of the mitral inflow.

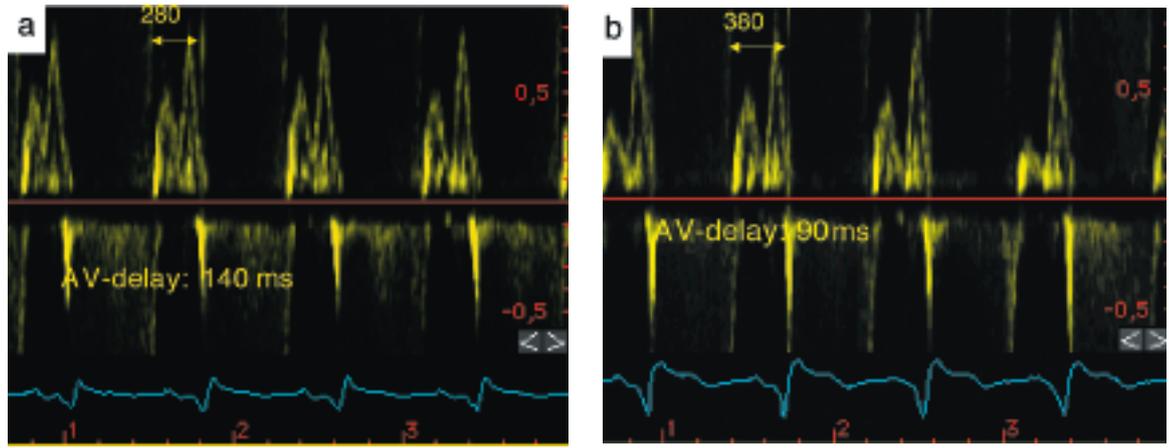
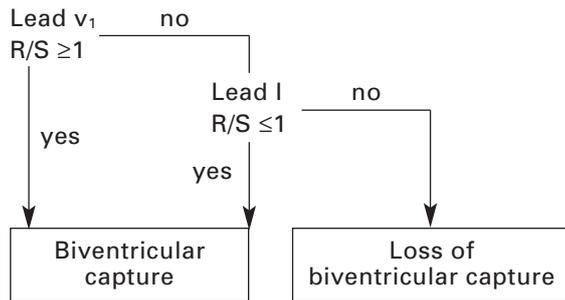


Figure 4

Algorithm for identifying biventricular pacing in patients with CRT.



lateral wall. A delay between the peak systolic velocities ≥ 60 ms was used as an indicator of substantial intraventricular dyssynchrony [32].

As with more elaborate TDI techniques, strain and strain rate, and tissue tracking, it is currently not clear which methods are the best to use. We prefer the above mentioned since they are relatively easy, not too time consuming, and readily available for screening purposes.

With regards to the non-responders, one has to bear in mind, however, that a certain percentage of these patients may have done a lot worse without CRT.

Optimal programming

Optimisation of the AV-interval is important to ensure biventricular stimulation and to prevent intrinsic conduction to attenuate the beneficial effects of CRT. A long AV interval weakens the contribution of atrial systole and can cause presystolic mitral regurgitation. Although complex methods, like the Ritter method, had been proposed earlier, easier methods may be applied in clinical practice [28]. Using Doppler mitral inflow patterns, the goal should be to maximise the diastolic filling time and to have the end of the left atrial contraction (A-wave) coincide with mitral valve closure and the onset of ventricular contraction. The impact of different AV-intervals on the left ventricular diastolic filling time is displayed in figure 3. Recently, we were able to demonstrate that the chosen pacing mode also plays an important role in prolonging the LV filling period [33]. Avoidance of right atrial pacing by choosing the VDD-mode resulted in significantly longer LV filling times and improved myocardial performance as compared to DDD-paced CRT patients. It is our policy to program an AV-delay of 100 ms until an echocardiography based optimisation can be carried out.

The ideal timing between right and left ventricular activation, the so called VV timing, is even more controversial. Unfortunately, there is no

good correlation between QRS narrowing and mechanical resynchronisation and clinical response [34, 35]. Sophisticated echocardiography methods like TDI with tissue tracking have shown that CRT improves mechanical dyssynchrony as well as decreases mitral regurgitation [36, 37]. Since there are no data demonstrating a clinical benefit of optimal VV timing to simultaneous right and left ventricular stimulation it is sensible to program the offset to 0 to -20 ms. One has to keep in mind, that all sophisticated echocardiography parameters are obtained at rest and that heart rate, body position, fluid status, and activity levels are not accounted for.

Analysis of the 12-lead ECG to detect loss of LV-capture

Although the changes in QRS duration have not been very helpful in assessing mechanical resynchronisation, the analysis of the ECG still plays an important role in the assessment of CRT patients with worsening heart failure. An easy algorithm analysing only the surface leads V1 and I permits diagnosis of loss of left ventricular capture even without the need for interrogating the device (fig. 4) [38].

Areas of uncertainty

Who needs a back-up defibrillator?

Large heart failure trials indicate that the mode of death depends on the functional NYHA class [39]. Patients with severe heart failure more often die of worsening heart failure while less symptomatic patients in NYHA class II have a higher incidence of sudden cardiac death. Nevertheless, even in patients with NYHA class III and IV the absolute number of sudden cardiac death remains high (59% and 33% of all deaths). As mentioned, in the COMPANION trial, CRT-D patients showed a somewhat better outcome than patients treated with CRT only [7]. However, this trial was not powered to show a mortality difference between CRT and CRT-D. The CARE-HF trial studied only patients without defibrillator backup [9]. In this population, the two-year-mortality was reduced by CRT compared to optimal medical therapy (18% vs. 25%). Sudden cardiac death was the blamed mode of death in 35% of the deaths in the CRT group and 32% in the medical therapy group [9]. The ICD is the best therapy for the prevention of sudden cardiac death and has been established by numerous primary and secondary prevention trials [40–43]. For primary prevention, the MADIT II trial [42] showed an benefit for patients with ischaemic cardiomyopathy and an EF $\leq 30\%$ whilst the SCD-HeFT trial suggests that patients with ischaemic and non-ischaemic cardiomyopathy and an EF $\leq 35\%$ benefit from an ICD [43]. In the CARE-HF trial, the mean EF increased from 25% at baseline to 32% after 18 months. A follow-up echocardiography study in the MIRACLE population found an improvement of the mean EF over one year from 25% to only 30% in the ischaemic CRT patients, but a more sustained improvement from 23% to 33% in the non-ischaemic CRT patients [19]. In conclusion, many of the CRT patients with ischaemic cardiomyopathy will still fall under the MADIT II criteria for primary prophylactic ICD implantation. Since this group has a higher risk for sudden cardiac death, it appears to be prudent to consider an ICD back-up. Non-ischaemic CRT-recipients appear to have a greater and more sustained effect of CRT and a lower arrhythmic risk. At the moment, the addition of a defibrillator remains an individual decision.

CRT in atrial fibrillation

Up to 40% of patients in advanced heart failure suffer from atrial fibrillation [39]. Since many of those have poor permanent ventricular rate control, full biventricular capture may be hampered by intrinsic ventricular conduction. Only one randomised CRT-study included patients with atrial fibrillation. The MUSTIC-AF trial showed promising but inconclusive results in that the intention-to-treat analysis demonstrated no difference between right ventricular and biventricular pacing

[44]. However, in 37 patients appropriate ventricular rate control was achieved, mostly by AV-node ablation. This subgroup showed a significant improvement in exercise tolerance with biventricular pacing. Similar results were reported earlier in a non-randomised study by Leon et al., which showed an improvement in LV function and symptoms after upgrade to a CRT system in patients with previous AV-node ablation and chronic right ventricular pacing [45]. In concert with these findings, the PAVE trial could demonstrate that patients who underwent AV-node ablation for rate control in atrial fibrillation showed a significant improvement in the 6-minute walking test and the ejection fraction when biventricular pacing as compared to right ventricular pacing was employed. These effects were even greater in patients with impaired systolic function and symptomatic heart failure [46]. Data on the impact of CRT on mortality in this subgroup are pending. There is also early evidence that CRT may reduce the incidence of atrial fibrillation in patients with poor left ventricular function [47].

CRT for right ventricular pacing induced dyssynchrony

In patients with the need for (mostly apical) right ventricular pacing, the LV activation sequence is altered in a fashion similar to those with a left bundle branch block. The *Dual Chamber and VVI implantable defibrillator* (DAVID) trial studied the impact of right ventricular pacing compared to intrinsic ventricular activation in ICD recipients that all had an impaired left ventricular function with an EF $\leq 40\%$ [48]. This trial showed that in this population the asynchronous LV-activation caused by apical right ventricular stimulation, even with preserved atrioventricular synchrony, was associated with an increase in the combined end point of death and hospitalisation. These findings were corroborated by data from the MOST trial, which compared DDDR pacing with VVIR pacing in patients with sinus node dysfunction, mostly preserved left ventricular function, and normal QRS duration at baseline [49]. Ventricular pacing was not only associated with a higher risk for the development of atrial fibrillation, but carried a 2.6-fold increased risk for heart failure hospitalisation if the prevalence of right ventricular pacing exceeded 40%. Consequently, contemporary pacemaker therapy strives to abstain from ventricular pacing whenever possible. The PAVE trial provided further evidence to support this concept since after AV-node ablation and consecutive 100% ventricular pacing, patients with biventricular pacing fared much better in the symptomatic outcome parameters than those with right ventricular pacing. This effect was even more pronounced in patients with an EF $\leq 45\%$ [46]. It is sensible to assume that at least in patients with impaired left

ventricular function who require frequent ventricular stimulation, biventricular pacing should be considered, although prospective trials comparing

biventricular pacing with right ventricular pacing in heart failure patients with standard pacemaker indications are pending.

Conclusion

Cardiac resynchronisation therapy has emerged as a new, device-based therapy for patients with symptomatic heart failure [25, 50]. In eligible patients with signs of intraventricular dyssynchrony, CRT reduces morbidity and mortality. Further studies need to clarify how to identify potential responders to CRT. Echocardiography is currently the technique of choice for this purpose. There are several questions that still await conclusive answers, including the role and benefit of CRT in patients with atrial fibrillation, in patients with mild-to-moderate heart failure, in right ventricular pacing induced dyssynchrony, in patients with

narrow QRS complexes as well as whether ICD back-up is always needed and the cost-effectiveness of CRT.

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