# resynchronisation

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Randomised trials involving large number of patients have demonstrated the benefits of cardiac resynchronisation therapy (CRT) in patients with heart failure who have failed optimal medical treatment. Echocardiography plays an important role in defining dyssynchrony which is key to optimal patient selection. The electrocardiographic criteria for patient selection is supplemented by the finding of dyssynchrony on Doppler myocardial imaging, and echocardiography with Doppler myocardial imaging may eventually replace the electrocardiographic criteria for selection of patients who derive benefit from CRT.

The utilisation of cardiac resynchronisation therapy (CRT) in patients with advanced heart failure (HF) and mechanical dyssynchrony is an established treatment option. The beneficial effects of CRT were first described in 1983,[1] but it took another decade before the concept of CRT was widely recognised, when several groups reported their initial experience in patients with end stage heart failure and left bundle branch block (LBBB).[2 3] What started as a clinical curiosity has now evolved into an approved indication for treatment of heart failure based on evidence from small and large trials. However, indications continue to evolve along with criteria for selection of patients amenable to therapy. Here we present the state of the literature.

## PATHOPHYSIOLOGY OF VENTRICULAR DYSSYNCHRONY

Regional myocardial ischaemia as well as a disturbed electrical activation sequence may both lead to ventricular dyssynchrony and exhibit negative effects on left ventricular performance.[4 5] As a result of the discordant contraction sequence, a significant part of the left ventricular (LV) blood volume undulates between early and late contracting regions instead of being ejected.[6] LV end diastolic pressure rises and shortens the duration of diastolic filling. This impairs cardiac efficiency and leads to an immediate reduction of stroke volume, systolic blood pressure, and pulse pressure. Another frequent finding in advanced heart failure is the presence of functional mitral regurgitation, which is mainly caused by the combination of progressive ventricular dilatation, leading to an increase in chordal tethering forces, and the reduction in LV systolic performance, reducing the mitral closing force.[7] Dyssynchronous activation of the papillary muscles and the surrounding myocardium may further aggravate functional mitral regurgitation.

In combination, these mechanisms contribute to the overall clinical benefit of CRT which is mirrored by the improvement in clinical symptoms, neurohumoral status, cardiac function, and haemodynamics.

## EVIDENCE TO SUPPORT CRT IN HEART FAILURE

Several trials have demonstrated the beneficial effects of CRT on heart failure symptoms, quality of life, exercise capacity (six minute walking test, peak oxygen consumption during exercise), hospitalisation, and echocardiographic variables (LV volumes, LV ejection fraction (LVEF), mitral regurgitation) (table 1).

The MIRACLE trial (multicenter InSync randomized clinical evaluation) was the first large placebo controlled, randomised trial to confirm the results of smaller pilot trials.[13] Based on the large body of available data, biventricular cardiac resynchronization therapy (BiV-CRT) has been added to the American Heart Association/American College of Cardiology/ North American Society of Pacing and Electrophysiology guidelines in 2002. According to these guidelines, the indication is limited to patients with drug refractory, symptomatic New York Heart Association (NYHA) functional class III–IV heart failure of either ischaemic or non-ischaemic origin with a prolonged QRS complex ($>$ 130 ms), LV end diastolic diameter $\geqslant$ 55 mm, and LVEF $\leqslant$ 35%.[14]

Despite these promising results, it is estimated that approximately up to 30% of resynchronised patients will not improve or become worse insofar as heart failure is concerned.[10 13] One of the most important reasons for this failure is probably the lack of distinct mechanical dyssynchrony before implantation. In a subgroup of patients from the InSync trial, the average interventricular delay measured by Doppler echocardiography before implantation was relatively low (mean (SD) 27.5 (32) ms) if compared to generally accepted cut-off values for dyssynchrony (40 ms).[15] In patients without underlying mechanical dyssynchrony, CRT may tend to impair LV systolic function instead of improving it. Other factors such as lead placement, programming of an adequate atrioventricular and interventricular delay, and the underlying heart disease (ischaemic or non-ischaemic) may also contribute to the treatment response.

Survival benefits have not been demonstrated with CRT. The impact of CRT on survival is still under investigation. None of the published randomised trials was adequately powered to detect changes in mortality. In a meta-analysis of 1634 patients, CRT was associated with a decrease in HF related mortality by more than 50% compared with controls.[16]

**Abbreviations:** AF, atrial fibrillation; AHI, apnoea hypopnoea index; BiV, biventricular; CHF, congestive heart failure; CRT, cardiac resynchronisation therapy; CSA, central sleep apnoea; Cum% VP; cumulative percent ventricular paced; DAVID, dual chamber and VVI implantable defibrillator; FMR, functional mitral regurgitation; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MIRACLE, multicentre InSync randomized clinical evaluation; MUSTIC, multisite stimulation in cardiomyopathy; NYHA, New York Heart Association; Path-CHF, pacing therapies for congestive heart failure; RBBB, right bundle branch block; SR, sinus rhythm; TDI, tissue Doppler imaging; VT, ventricular tachycardia

**Table 1** Cardiac resynchronisation therapy study results

| Study | Randomly selected patients | Enrolment | Inclusion criteria | End points | Results |
|---|---|---|---|---|---|
| Path-CHF I [8–10] | 42 | 1996-99 | NYHA III-IV, QRS >120 ms, PR >150ms, sinus rhythm >55 bpm | Peak $VO_2$, NYHA class, 6 min walk, QoL, hospitalisation | Improved peak $VO_2$, 6 min walk distance, NYHA class, QoL LV volumes |
| InSync[11] | 103 | 1966-67 | NYHA III–IV, LVEF <35%, LVEDD >60 mm, QRS >150 ms | NYHA class, QoL, 6 min walk, QRS width | Improved 6 min walk, NYHA, and QoL |
| MUSTIC-SR[12] | 131 | 1998-99 | NYHA III-IV, LVEF <35%, LVEDD >60 mm, QRS <150 ms, 6 min walk <450 m | 6 min walk, QoL, hospitalisation, peak $VO_2$ | Improved 6 min walk, QoL, reduced hospitalisation |
| MIRACLE[13] | 452 | 1998-2000 | NYHA III-IV, LVEF <35%, LVEDD >55 mm, QRS >130 ms, no pacemaker | NYHA class, QoL, 6 min walk, peak $VO_2$, hospitalisation, neurohormone values, echo indices, mortality | Improved NYHA class, 6 min walk, QoL, LVEF, LV volumes and MR, hospitalisation |

Path-CHF, pacing therapies for congestive heart failure; MUSTIC, multisite stimulation in cardiomyopathy; MIRACLE, multicentre InSync randomized clinical evaluation; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; QoL, quality of life; $VO_2$, oxygen consumption.

However the study did not demonstrate reduction in all-cause mortality. The COMPANION (comparison of medical therapy, pacing, and defibrillation in chronic heart failure) trial was terminated prematurely after recruiting 1600 patients, as initial results demonstrated a significant survival benefit in patients with a combined resynchronisation–defibrillator device (BiV pacemaker with defibrillator capacity). The combined end points of all cause mortality and all cause hospitalisation in patients with dilative cardiomyopathy and heart failure of poor functional class was reduced by approximately 20% with CRT with or without defibrillator capacity.[17]

These assumptions are mainly based on the conventional selection criteria applied in the large randomised trials, mainly on QRS as an identifier for cardiac dyssynchrony, but it has been demonstrated that many patients may present with areas of ventricular dyssynchrony despite a normal QRS width.[18] In particular patients with only slight QRS prolongation between 120–150 ms may present very heterogeneously with synchronous contraction or pronounced dyssynchrony. In patients with a QRS width above 150 ms, the picture appears more consistent and most patients will present with significant correctable dyssynchrony. Thus, the inclusion of echocardiographic selection criteria or fast magnetic resonance imaging to define the dyssynchronous ventricle may influence the expected numbers of eligible patients for resynchronisation therapy. Most studies excluded patients with atrial fibrillation (AF); however, it is estimated that about 30% of heart failure patients who are in NYHA class III or IV heart failure have or will develop AF.[19]

CRT devices are costly, the implantation procedure is technically demanding, and the follow up visits require more expertise and are more time consuming. Optimistic analyses indicate that CRT is a cost saving procedure since upfront costs are offset within one year, mainly based on reduced hospitalisation rate[20]; however, conclusive, up to date cost effectiveness data are not yet available. It remains to be proven that the widespread use of CRT in centres with less expertise is not associated with a higher complication rate than is reported from controlled clinical trials.

## WHO ARE CANDIDATES FOR CRT?

The current indications for implantation of a cardiac resynchronisation device are based on the presence of a prolonged QRS duration (> 130 ms) and stable sinus rhythm in patients with advanced systolic heart failure. In most studies CRT has been performed on top of an optimised drug regimen, including β blockers, angiotensin converting enzyme inhibitors, and diuretics. However, a positive effect of CRT on left ventricular reverse remodelling has also been demonstrated in patients without β blocker medication.[21] What about patients who present with normal QRS duration but mechanical dyssynchrony on echocardiography? Do patients with right bundle branch block and AF benefit from CRT? Although the currently available data are scarce, there is increasing evidence that these subgroups may equally benefit from CRT and that the presence of mechanical dyssynchrony may be more important than QRS duration alone.

## LEFT VENTRICULAR DYSSYNCHRONY AND QRS DURATION

A pilot study reported that biventricular pacing may improve the functional status of heart failure patients with normal QRS duration, provided that inter- and intraventricular asynchrony can be documented before implantation.[22] A precise evaluation of dyssynchrony appears useful because a high proportion of patients with incomplete bundle branch block, left anterior hemiblock, or ''normal'' QRS exhibit a pronounced intra-LV dyssynchrony and may respond to CRT.[23 24] Inter-or intraventricular dyssynchrony caused by structural and ultrastructural myocardial tissue damage exists. As a consequence mechanical delay in contraction in the LV free wall even in the absence of electrical delay on surface electrocardiography may occur. Beneficial effects of biventricular pacing in patients with narrow (120–150 ms) QRS can be expected, as has been seen with LBBB and QRS duration > 150 ms.[25]

Recently tissue Doppler imaging (TDI) was performed in 141 patients: 115 had coronary artery disease, 18 had dilated cardiomyopathy, six had hypertensive heart disease, and two had alcoholic cardiomyopathy.[26] The authors concluded that for patients with symptomatic LV systolic dysfunction and significant asynchrony by TDI, CRT is a viable treatment option even in the absence of electrical delay on the surface electrocardiogram.

The same authors reported another series of 67 patients with congestive heart failure and narrow QRS complexes (⩽ 120 ms) with a high prevalence of systolic and diastolic asynchrony of 51% and 46%, respectively. In comparison 45 patients with CHF and wide QRS complexes (>120 ms) had a prevalence of 73% and 69%, respectively.[18] They concluded that the echocardiographic assessment of intraventricular dyssynchrony may be more important than QRS duration in considering CRT. Furthermore, in the individual patient a salutary effect of biventricular pacing on electrical remodelling with normalisation of QRS duration could be demonstrated.[27]

Although QRS duration has been the main selection parameter for identification of dyssynchrony to date,

increasing evidence suggests that it correlates poorly with the acute and chronic response in individual patients. In contrast, direct measures of mechanical dyssynchrony based on conventional echocardiographic imaging and more complex tissue Doppler imaging based approaches appear to improve patient selection and to predict the long term response to CRT better.[6]

## RIGHT BUNDLE BRANCH BLOCK

Only few studies evaluated CRT in patients with right bundle branch block (RBBB). In the CONTAK CD trial, the patient subgroup with RBBB did not demonstrate a significant improvement in symptom status, heart size, or LVEF.[28]

More recently CRT effects have been reported in a series of seven patients with RV dysfunction demonstrating improvement of cardiac index, RV dP/dtmax, and decreased QRS duration as compared with atrial pacing or sinus rhythm.[29]

The reasons for not demonstrating overwhelming success are manifold and it might be necessary to test alternative stimulation sites (for example, right ventricular (RV) outflow tract) in these patients. Furthermore a study designed to test patients with RBBB needs to be developed.

## SHOULD AN UPGRADE OF RV PACING SYSTEM TO A BIVENTRICULAR SYSTEM BE DONE?

Dual chamber (DDD) pacing preserves atrioventricular (AV) synchrony and may reduce heart failure and AF compared with ventricular (VVI) pacing in sinus node dysfunction. However, conventional RV DDD pacing often results in delayed LV activation with prolonged QRS durations and ventricular dyssynchrony may result. The MOST (mode selection trial) investigators demonstrated that the time dependent covariate ''cumulative per cent ventricular paced'' (Cum% VP) was a strong predictor of heart failure hospitalisation in DDD (hazard ratio (HR) 2.99, 95% confidence interval (CI) 1.15 to 7,75, for Cum%VP $>$ 40%) and VVI (HR 2.56, 95% CI 1.48 to 4.43, for Cum%VP $>$ 80%).[30] The risk of AF increased linearly with Cum%VP from 0% to 85% in both groups, for each 25% increase in Cum%VP. The authors concluded that ventricular desynchronisation imposed by ventricular pacing, even when AV synchrony is preserved, increases the risk of heart failure hospitalisation and AF in sinus node dysfunction with normal baseline QRS duration.

The DAVID (dual chamber and VVI implantable defibrillator) trial randomised 506 patients with an implantable cardioverter-defibrillator (ICD) indication and an LVEF $<$ 40% and tested the hypothesis that the dual chamber pacing mode would improve cardiac function and prognosis, prevent arrhythmias, and reduce mortality in comparison to back up pacing.[31] The results were disappointing with a worse outcome in the patients randomised to dual chamber pacing, probably related to the detrimental effects of RV pacing induced dyssynchrony. This might have been prevented by a more physiological left ventricular based pacing modality.

Modification of RV pacing to a biventricular system using commercially available leads and adapters can be performed effectively and safely. This could be shown in a series of 60 consecutive patients with congestive heart failure (CHF) and conventional pacing with a low complication rate (8.3%): lead dislodgment (n = 1), pocket haematoma (n = 1), and wound infection (n = 3). At three month follow up mean (SD) quality of life scores improved 31 (28) points, ($p < 0.0001$), NYHA class improved from 3.4 (0.5) to 2.4 (0.7) ($p < 0.0001$), and ejection fraction increased from 0.23 (0.8) to 0.29 (0.11) ($p < 0.0003$).[32]

Dyssynchronous LV activation induced by RV apical pacing leads to paradoxical septal motion and inefficient ventricular contraction, similar to the effects of an LBBB.

In a chronically paced population, the majority of whom did not have pre-existing heart failure, Thackray and colleagues[33] showed that heart failure was more prevalent in patients with single chamber compared to dual chamber pacemakers, and in those with chronic AF compared to those with sinus rhythm.[33]

A head to head comparison of biventricular versus RV pacing revealed that systolic function, including ejection fraction, myocardial performance index, and isovolumic contraction time, only improved during BiV pacing as well as reduction of mitral regurgitation. LV end diastolic and end systolic volumes were only decreased during BiV pacing. A significant delay in peak systolic contraction in the lateral over the septal wall was revealed by TDI when there was no pacing. This was abolished by BiV pacing, in which septal contraction was delayed. However, RV pacing restored the lateral wall delay, and systolic asynchrony reappeared.[34]

## ATRIAL FIBRILLATION AND BIVENTRICULAR PACING

In a series of 20 consecutive patients with severe CHF, chronic AF, and RV pacing after atrioventricular junction ablation, Leon and colleagues studied the effect of BiV pacing on ventricular function, functional status, quality of live, and hospitalisation. NYHA functional classification improved, LVEF increased, LV diastolic diameter decreased, and end systolic diameter decreased. Further the number of hospitalisations decreased by 81% ($p < 0.001$) and the scores on the Minnesota living with heart failure survey improved by 33% ($p < 0.01$).[35]

As compared with conventional VVIR pacing, effective biventricular pacing seems to improve exercise tolerance in NYHA class III heart failure patients with chronic AF and wide paced QRS complexes.[36]

In another small series, 13 patients with chronic AF, severe heart failure, and QRS $\geq$ 140 ms received after His bundle ablation a pacemaker providing both LV pacing and BiV pacing.[37] LV pacing and BiV pacing provided similar haemodynamic effects at rest whereas BiV pacing was associated with better haemodynamic effects during exercise and fewer premature ventricular complexes.

The MUSTIC (multisite stimulation in cardiomyopathy) study investigated patients with sinus rhythm (SR) and AF side by side.[38] At 12 months, all SR and 88% of AF patients were programmed to BiV pacing. Compared with baseline, the six minute walked distance increased by 20% (SR) ($p < 0.0001$) and 17% (AF) ($p < 0.004$); the peak $VO_2$ by 11% (SR) and 9% (AF); quality of life improved by 36% (SR) ($p = 0.0001$) and 27% (AF) ($p < 0.0001$). The ejection fraction improved by 5% (SR) and 4% (AF).

These results are supported by others pointing out that a long term follow up CRT is beneficial in patients with CHF regardless of the presence of SR or AF and that AF is not a predictor for non-responsiveness to CRT.[39] For these reasons, patients in AF should not be excluded ''a priori'' from CRT.

In patients with paroxysmal AF, heart failure, and dyssynchrony, CRT may reduce the number of episodes probably because of improved atrial loading conditions and reverse remodelling. In 19 of 70 patients AF burden decreased from (mean (SD)) 1.77 (1) h/day after the first month to 0.18 (0.09) h/day after three months ($p < 0.05$).[40]

## VENTRICULAR ARRHYTHMIA

The hypothesis that prolonged QRS duration independently predicts long term mortality in patients who undergo risk stratification and treatment for ventricular arrhythmias has been thoroughly investigated. QRS duration $\geq$ 130 ms was associated with a twofold increase in mortality. For every

10 ms increase in QRS duration, mortality rate increased 10%.[41]

These results are supported by findings from the Ventak CHF BiV pacing study, where the frequency of defibrillation therapy has been evaluated.[42] At least one tachyarrhythmic episode was documented in 5/32 patients(16%) during BiV pacing, whereas 11 (34%) had at least one episode while programmed to no pacing. Similar observations have been found by Kies and colleagues.[43] During the year before implantation of the ICD-CRT device, 8/17 patients (47%) experienced 242 VT episodes. After implantation only 3/17 patients (18%) experienced 19 VT episodes ($p < 0.01$).

The mechanism for this improvement may be related to the beneficial effects on LV synchrony. Improved synchrony will not only improve LV haemodynamics such as LV end diastolic pressure, but it will also homogenise regional wall stress and reduce regional pre-stretch, which is potentially arrhythmogenic.[44]

Although BiV pacing does not obviate the need for an ICD, it does diminish the need for appropriate tachyarrhythmia therapy in selected patients.

Currently there is general agreement that patients undergoing CRT should receive a combined CRT-ICD device if there is a primary indication with a history of syncope, sustained VT, or survived sudden death.

## RELIEF OF DRUG REFRACTORY ANGINA PECTORIS

In coronary artery disease patients who are not amendable to myocardial revascularisation, CRT may not only improve LV function but also increase the threshold of drug refractory angina. Early experiences supports this hypothesis[45]; 8/75 patients who underwent CRT had drug refractory angina occurring daily before the procedure. None of them was able to complete a six minute walk test because of angina. All patients experienced a notable decrease in angina episodes, and completed a six minute walk test, so the beneficial effect of CRT may include a better control of angina in the group of patients with severely symptomatic angina pectoris. CRT may improve endothelial function. Baseline and maximal hyperaemic flow have been assessed by forearm venous occlusion plethysmography.[46]

## FUNCTIONAL MITRAL REGURGITATION

Acute effects of CRT on functional mitral regurgitation (FMR) have been studied by Breithardt and colleagues[47] in 24 patients with LBBB and FMR using the proximal isovelocity surface area method. Effective regurgitant orifice area and regurgitant volume decreased significantly with CRT.

The major mechanism for the reduction of FMR by CRT seems to be improvement in LV systolic pressure[47] and LV longitudinal synchronicity. As a result, LV systolic shape becomes less spherical and subvalvar traction decreases. The tethering forces on the mitral valve are reduced and the closing force is increased, causing a more effective and rapid mitral valve closure. In a series of 22 patients, decrease of FMR could be demonstrated using the vena contracta diameter.[48]

Reduction of FMR can be observed in the majority of patients according to recently completed trials and the benefits from CRT regarding FMR can be expected both in patients with non-ischemic as well as ischaemic cardiomyopathy.[49]

## MILD HEART FAILURE

The MIRACLE ICD II study enrolled NYHA II heart failure patients with LVEF $< 36\%$, QRS $\geq 130$ ms, a class I ICD indication, and optimised medical management. A total of 101 patients were randomised to control and 85 to CRT. Fifty eight per cent of the CRT group versus 36% of the control group were categorised as having improved in their composite clinical response. CRT did not alter exercise capacity but did result in significant improvement in cardiac function and composite clinical response over a six month follow up period.[50]

Obviously this was not a large trial, and it raised several issues. The conclusion as it stands today is that large scale, adequately powered clinical trials seem to be needed to assess functional outcomes in patients with less severe heart failure.[19]

## BIVENTRICULAR PACING DURING AND AFTER HEART SURGERY

CRT has the potential to simplify the management and improve the outcomes of selected patients after cardiac surgery. Cardiac dysfunction is a major cause of morbidity and mortality after congenital heart surgery. Six patients (median age 11.1 months) with congenital heart disease, poor ventricular function, and complete heart block has been converted to BiV pacing from traditional single site atrioventricular (DDD) pacing.[51] LVEF increased, five patients showed an improvement in weight for age, and one patient was removed from the transplant list.

Early results of 25 high risk cardiac surgery patients receiving permanent left ventricular free wall pacing electrodes with the intent of implanting BiV pacing devices have been reported.[52]

## CENTRAL SLEEP APNOEA AND CHEYNE-STOKES RESPIRATION

Patients with advanced heart failure often suffer from central sleep apnoea (CSA) with Cheyne-Stokes respiration. In a series of 24 patients who received a BiV pacing system because of cardiac dyssynchrony the number of apnoeas and hypopnoeas per hour (AHI) and minimal oxygen saturation ($SaO_2$min) were quantified by cardiorespiratory polygraphy.[53] CRT led to a significant decrease in AHI, and to a significant increase in $SaO_2$min in patients with CSA, suggesting a potential improvement in prognosis. These results may have implications for future devices which incorporate dedicated sensors to monitor respiration and oxygen saturation and may help to monitor CRT efficacy.

## CONCLUSION

CRT represents a giant leap in treatment of patients with advanced heart failure. What was a clinical curiosity in the mind of a single Austrian cardiologist—the treatment of advanced heart failure with a pacemaker[54]—has now become an evidence based reality. Methods to detect and quantify dyssynchrony continue to evolve and the indications for CRT expand as the body of evidence increases.

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## REFERENCES


1 **De Teresa PA**, Chamoro JL. An even more physiological pacing: changing the sequence of ventricular activation. *Proceedings of the VIIth World Symposium on Cardiac Pacing*, Vienna, 1983:95–100.
2 **Bakker PFA**, Mejburg H, de Jonge N, *et al*. Beneficial effects of biventricular pacing in congestive heart failure [abstract]. *PACE* 1994;**17**:820.
3 **Cazeau S**, Ritter P, Bakdach S, *et al*. Four chamber pacing in dilated cardiomyopathy. *PACE* 1994;**17**:1974–79.
4 **Grines CL**, Bashore TM, Boudoulas H, *et al*. Functional abnormalities in isolated left bundle brunch block. The effect of interventricular asynchrony. *Circulation* 1989;**79**:845–53.
5 **Prinzen FW**, Peschar M. Relation between the pacing induced sequence of activation and left ventricular pump function in animals. *Pacing Clin Electrophysiol* 2002;**25**:484–98.
6 **Kass DA**. Ventricular resynchronization: pathophysiology and identification of responders. *Rev Cardiovasc Med* 2003;**4**(suppl 2):S3–13.
7 **Otsuji Y**, Handschumacher MD, Schwammenthal E, *et al*. Circulation 1997;**96**:1999–2008.
8 **Auricchio A**, Stellbrinck C, Sack S, *et al*. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol*. 2002;39: 2026–2033, A small -sized study that performed elaborate haemodynamic optimization during CRT.Implantation and demonstrated the beneficial long-term effects of biventricular and univentricular CRT after 12 months of therapy..
9 **Breithardt OA**, Stellbrink C, Kramer AP, *et al*. Echocardiographic quantification of left ventricular asynchrony predicts an acute haemodanamic benefit of cardiac resynchronization therapy. *J Am Coll Cardiol* 2002;**40**:536–545.
10 **Stellbrink C**, Breithardt OA, Franke A, *et al*. Impact of cardiac resynchronization therapy using haemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. *J Am Coll Cardiol* 2001;**38**:1957–65.
11 **Gras D**, Mabo P, Tang T, *et al*. Multislice pacing as a supplement treatment of congestive heart failure: preliminary results of the Medtronic Inc. InSync Study. *PACE* 1998;**21**:2249–55.
12 **Cazeau S**, Leclercq C, Lavergne T, *et al*. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;**344**:873–80.
13 **Abraham WT**, Fisher WG, Smith AL, *et al*. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**:1845–53.
14 **Gregoratos G**, Abrams J, Epstein AE, *et al*. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices. Summary article: a report of the American College of Cardiology/ American Heart Association task force on practice guidelines (ACC/AHA/ NASPE Committee to Update the 1998 Pacemaker Guidelines), *J Am Coll Cardiol* 2002;**40**:1703–19.
15 **Gras D**, Leclerq C, Tang AS, *et al*. Cardiac resynchronization therapy in advanced heart failure: the Multicenter InSync clinical study. *Eur J Heart Fail* 2002;**4**:311–20.
16 **Bradley DJ**, Bradley EA, Baughman KL, *et al*. Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. *JAMA* 2003;**289**:730–40.
17 **Salukhe TL**, Francis DP, Sutton R. Comparison of medical therapy, pacing and defibrillation in heart failure (COMPANION) trial terminated early; combined biventricular pacemaker-defibrillators reduce all-cause mortality and hospitalization. *Int J Cardiol* 2003;**87**:119–20.
18 **Yu CM**, Lin H, Zhang Q, *et al*. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and narrow QRS duration. *Heart* 2003;**89**:54–60.
19 **Mehra MR**, Greenberg BH. Cardiac resynchronization therapy: caveat medicus! *J Am Coll Cardiol* 2004;**43**(7):1145–8.
20 **Gras D**, Banz K. Development and validation of a new decision-analytic model designed to evaluate the cost-effectiveness of cardiac resynchronization therapy. *Eur Heart J* 2003;**24**(suppl 2):5.
21 **St John Sutton MG**, Plappert T, Abraham WT, *et al*. Effect on resynchronization therapy on left ventricular size and function in chronic heart failure patients. *Circulation* 2003;**107**:1985–90.
22 **Sassara M**, Achilli A, Fucili S, *et al*. Efficacy of cardiac resynchronization in narrow QRS patients. *Europace* 2001;**2**(suppl B):B59.
23 **Fauchier L**, Marie O, Casset-Senon D, *et al*. Reliability of QRS duration and morphology on surface electrocardiogram to identify ventricular dyssynchrony in patients with idiopathic dilated cardiomyopathy. *Am J Cardiol* 2003;**92**:341–4.
24 **Turner MS**, Bleasdale RA, Vinereanu D, *et al*. Electrical and mechanical components of dyssynchrony in heart failure patients with normal QRS duration and left bundle-branch block. Impact of left and biventriclar pacing. *Circulation* 2004;**109**:2544–9.
25 **Gasparini M**, Mantica M, Galimberti P, *et al*. Beneficial effects of biventricular pacing in patients with a ''narrow'' QRS. *Pacing Clin Electrophysiol* 2003;**26**(1 Pt 2):159–64.
26 **C-M**, Yang H, Lau C-P, *et al*. Regional left ventricle mechanical asynchrony in patients with heart disease and normal QRS duration. *PACE* 2003;**26**(Pt I):562–70.
27 **Dizon J**, Horn E, Neglia J, *et al*. Loss of bundle brunch block following biventricular pacing therapy for heart failure:evidence for electrical remodeling. *J Interv Card Electrophysiol* 2004;**10**:47–50.
28 **Saxon LA**, Foster E, De Marco T, *et al*. Effect of cardiac resynchronization therapy in patients with right bundle brunch block [abstract]. *J Am Coll Cardiol* 2004;**43**(suppl A):14A.
29 **Dubin AM**, Feinstein JA, Reddy VM, *et al*. Electrical resynchronization: a novel therapy for the failing right ventricle. *Circulation* 2003;**107**:2287–9.
30 **Sweeney MO**, Hellkamp AS, Ellenbogen KA, *et al*. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation* 2003;**107**:2932–7.
31 **Wilkoff BL**, Cook JR, Epstein AE, for the Dual Chamber and VVI Implantable Defibrillator Trial Investigators, *et al*. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the dual chamber and VVI implantable defibrillator (DAVID) trial. *JAMA* 2002;**288**:3115–23.
32 **Baker CM**, Christopher TJ, Smith PF, *et al*. Addition of a left ventricular lead to conventional pacing systems in patients with congestive heart failure: feasibility, safety and early results in in 60 consecutive patients. *Pacing Clin Electriophysiol* 2002;**25**:1166–71.
33 **Thackray SD**, Witte KK, Nikitin NP, *et al*. The prevalence of heart failure and asymptomatic left ventricular systolic dysfunction in a typical regional pacemaker population. *Eur Heart J* 2003;**24**:1243–52.
34 **Yu CM**, Lin H, Fung WH, *et al*. Comparison of acute changes in left ventricular volume, systolic and diastolic functions, and intraventricular synchronicity after biventricular and right ventricular pacing for heart failure. *Am Heart J* 2003;**145**:E18.
35 **Leon AR**, Greenberg JM, Kanuru N, *et al*. Cardiac resynchronization in patients with congestive heart failiure and chronic atrial fibrillation: effect of upgrading to biventricular pacing after chronic right ventricular pacing. *J Am Coll Cardiol* 2002;**39**:1258–63.
36 **Leclercq C**, Walker S, Linde C, *et al*. Comparative effects of permanent biventricular and right univentricular pacing in heart failure patients with chronic atrial fibrillation. *Eur Heart J* 2002;**23**:1780–7.
37 **Garrigue S**, Bordachar P, Reuter S, *et al*. Comparison of permanent left ventricular and biventricular pacing in patients with heart failure and chronic atrial fibrillation: a prospective hemodynamic study. *Card Electrophysiol Rev* 2003;**7**:315–24.
38 **Linde C**, Leclerq C, Rex S, *et al*. Long term benefits of biventricular pacing in congestive heart failure: results from the multisite stimulation in cardiomyopathy (MUSTIC) study. *J Am Coll Cardiol* 2003;**41**:709.
39 **Gasparini M**, Galimberti, P, Simonini S, et al. Long term results of CRT in patients with permanent atrial fibrillation [abstract]. *Circulation* 2003;**108**(suppl IV):IV-486.
40 **Huegl B**, Mortensen P, Gasparini M, *et al*. Monitoring the burden of non-persistent atrial fibrillation in the course of biventricular pacing in patients with chronic heart failure [abstract]. *Circulation* 2003;**108**:17(suppl IV):IV–486.
41 **Kalahasti V**, Nambi V, Martin DO, *et al*. QRS duration and prediction of mortality in patients undergoing risk stratification for ventricular arrhythmias. *Am J Cardiol* 2003;**92**:798–803.
42 **Higgins SL**, Yong P, Sheck D, *et al*. Biventricular pacing dimishes the need for implantable cardioverter defibrillator therapy. Ventak CHF investigators. *J Am Coll Cardiol* 2000;**36**:824–7.
43 **Kies P**, Molhoek SG, Bax JJ, *et al*. Cardiac resynchronization therapy results in a lower arrhythmia burden [abstract]. *J Coll Cardiol* 2004;**43**(suppl A):149A.
44 **Breithardt O-A**, Stellbrink C, Herbots L, *et al*. Cardiac resynchronization therapy can reverse abnormal myocardial strain distribution in patients with heart failure and left bundle branch block. *J Am Coll Cardiol* 2003;**42**:486–94.
45 **Gasparini M**, Mantica M, Galimberti P, *et al*. Relief of drug refractory angina by biventricular pacing in heart failure. *Pacing Clin Electrophysiol* 2003;**26**(1 Pt 2):181–4.
46 **Kolokathis F**, Theodorakis GN, *et al*. Endothelial function and ventricular resynchronization in heart failure [abstract]. *Circulation* 2003;**108**(suppl IV):IV-487.
47 **Breithardt OA**, Sinha AM, Schwammenthal E, *et al*. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. *J Am Coll Cardiol* 2003;**41**:765–70.
48 **Vinereanu D**, Turner AS, Bleasdale RA, *et al*. Cardiac resynchronization therapy reduces secondary mitral regurgitation by decreasing subvalvar traction [abstract]. *Circulation* 2003;**108**(suppl IV):IV-488.
49 **Molhoek SG**, Bax JJ, van Erven L, *et al*. Comparison of benefits from CRT in patients with ischemic cardiomyopathy versus idiopathic dilative cardiomyopathy. *Am J Cardiol* 2004;**93**:860–3.
50 **Young JV**, Abraham WT, Smith AL, *et al*. for the Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial Investigators. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD trial, *JAMA* 2003;**289**:2685–94.
51 **Rosenthal DN**, Dubin AM, Geiss DM, *et al*. Use of resynchronization therapy in pediatric patients with congenital heart disease and complete heart block [abstract]. *J Am Coll Cardiol* 2004;**43**(suppl):384A.
52 **Gaudiani VA**, Castro LJ, Fisher AL, *et al*. Biventricular pacing during cardiac operations. *Heart Surg Forum* 2003;**6**(6):E126–8.
53 **Sinha A-M**, Skobel EC, Breithardt OA, *et al*. Cardiac resynchronization therapy improves central sleep apnea and Cheyne-Stokes respiration in patients with chronic heart failure. Effects of CRT on central sleep apnea. *J Am Coll Cardiol* 2004;**44**:68–71.
54 **Hochleitner M**, Hortnagel H, Hortnagel H, *et al*. Long-term efficacy of physiologic dual-chamber pacing in the treatment of end-stage idiopathic dilated cardiomyopathy. *Am J Cardiol* 1992;**70**:1320–5.

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