# Cardiac resynchronisation therapy: when the drugs don't work.

**R A Bleasdale, M P Frenneaux**

*Heart* 2004;**90**(Suppl VI):vi2–vi4. doi: 10.1136/hrt.2004.048546

Heart failure effects 1–2% of the population[1] and accounts for approximately 5% of all medical admissions[2]; despite the undoubted improvements in treatment over the past two decades, the outcome remains poor. One third of those patients admitted with decompensated heart failure die within one year of their first hospitalisation[3] and up to 50% will be readmitted within the first six months after the initial hospitalisation.[4] There appears little scope for further advances aimed at blocking neurohumoral maladaptive mechanisms, and other strategies, including cytokine blockade, have been disappointing. While cellular transplantation holds out considerable promise in the longer term, medically refractory heart failure remains a huge (and growing) clinical problem. Over the past decade an emerging body of evidence has suggested that biventricular and/or left ventricular pacing may provide effective palliation in some of these patients.

Initial attention regarding the potential use of pacing therapy in heart failure focused on short atrioventricular (AV) delay right sided pacing to reduce pre-systolic mitral regurgitation. This phenomenon is most pronounced in patients with long AV delays, especially when left ventricular end diastolic pressure is notably raised. Despite impressive improvements in acute haemodynamic measurements in selected patients,[5–7] long term results were disappointing.[8 9] The next target for pacing therapy was the dysynchronous contraction associated with the presence of left bundle branch block in patients with heart failure. Overall, approximately one third of patients with heart failure have a left bundle branch block pattern,[10] although this figure rises in patients with more severe left ventricular dysfunction.[11] By causing a dysynchronous left ventricular activation sequence, left bundle branch block impairs left ventricular contractile performance.[12] It is not surprising, therefore, that the presence of left bundle branch block is associated with more severe symptoms and greater mortality in heart failure patients.[10] This led to the hypothesis that simultaneously pacing the two ventricles with biventricular pacing would reduce the dysynchrony, hence the term ''cardiac resynchronisation therapy'' (CRT), and improve cardiac contractile performance and symptoms. Early acute haemodynamic studies were promising.[13–15] In subsequent long term studies CRT has been shown to induce reverse remodelling and significantly reduce morbidity and re-hospitalisation in heart failure patients with prolonged QRS durations who remain severely symptomatic despite optimal medical treatment, including an angiotensin converting enzyme inhibitor/angiotensin receptor blocker, a β blocker, digoxin, and diuretics.[16–18] These three large studies have shown a trend to improved survival in patients who receive CRT; however, none of these studies were appropriately powered to directly address this question. However the COMPANION study did report that combined biventricular pacing with an implantable cardioverter-defibrillator is associated with a significant reduction of total mortality.[18] The available data from these studies has resulted in biventricular pacing being granted a class IIa indication, with a level A evidence base in the American College of Cardiology/American Heart Association/North American Society of Pacing and Electrophysiology guidelines,[19] for heart failure patients with medically refractory, symptomatic New York Heart Association (NYHA) class III or IV limitation and prolonged QRS duration ($\geqslant$ 130 ms), coupled with left ventricular dilatation (end diastolic diameter $\geqslant$ 55 mm) and an ejection fraction $\leqslant$ 35%.

## PROPOSED BENEFICIAL MECHANISMS

The evidence to date suggests that several mechanisms may be responsible for the benefits of biventricular (and left ventricular) pacing in heart failure. These will be briefly reviewed.

### Electrical resynchronisation

Several acute haemodynamic studies have compared the main two forms of CRT, biventricular pacing and left ventricular pacing. These studies have shown either similar improvements between the two modalities or a greater improvement with left ventricular pacing. Kass and colleagues showed notably greater haemodynamic improvement with left ventricular pacing compared to biventricular pacing despite the fact that left ventricular pacing produces a considerably wider QRS duration.[20] While left ventricular pacing worsened electrical synchrony acutely in an animal model of heart failure, it improved mechanical synchrony and correction of a prolonged QRS duration did not correlate with mechanical or haemodynamic improvement.[21] The recently reported BELIEVE study demonstrated similar overall chronic results from biventricular and left ventricular pacing in patients with medically refractory heart failure.[22] Improvement in left ventricular systolic function seems to depend on improving the timing of regional contraction events in the left ventricle rather than electrical resynchronisation.

### Systolic mechanical resynchronisation

Both radionuclide and echocardiographic techniques have been applied to study the timing of regional contraction within the left ventricle (intraventricular synchrony)[15 23] and between the left and right ventricles (interventricular synchrony).[24 25] While heart failure patients with left bundle branch block tend to have greater mechanical dysynchrony than those with normal QRS durations, there is considerable overlap and indeed some patients with left bundle branch block appear to have degrees of mechanical intraventricular dysynchrony which lie within the ''normal range''.[26] Our recent work demonstrated that mechanical dysynchrony was reduced similarly by both left and biventricular pacing and

**Abbreviations:** AV, atrioventricular; CRT, cardiac resynchronisation therapy; NYHA, New York Heart Association

that this occurred irrespective of the presence of QRS widening or not.[27]

### Reduction of systolic mitral regurgitation

Several studies have confirmed that CRT reduces secondary systolic mitral regurgitation both acutely and chronically. The acute effects appear to relate to an increase in the mitral closing pressure and/or a reduction in systolic sphericity of the left ventricle.[28] Reverse remodelling may also contribute to the chronic effects.[29]

### Improved diastolic filling

Diastolic filling of the left ventricle may potentially be improved by resynchronisation therapy by three mechanisms.

Improving synchrony might be anticipated to increase the rate of active relaxation of the left ventricle and to reduce the ''wasted'' time spent during the isovolumic periods. Despite these theoretical considerations, Kass and colleagues observed no acute effects of CRT on Tau, passive left ventricular compliance, or on left ventricular end diastolic pressure.[20]

As noted above, short AV delay pacing reduces pre-systolic mitral regurgitation, prolonging the effective diastolic filling period. Many workers in the field advocate that the paced AV interval should be tailored for each patient to optimise the effective diastolic filling period. It is not clear whether these adjustments, carried out with the patient supine and resting, translate into clinical benefits given that the situation may be very different when the patient is erect and exercising.

We have recently shown that at least part of the acute haemodynamic benefit from left ventricular pacing may be caused by reduced external constraint to left ventricular filling.[30] In previous work we demonstrated that, in congestive heart failure patients with high pulmonary capillary wedge pressure, left ventricular filling was notably impeded by external constraint from the right ventricle via the shared interventricular septum (direct diastolic ventricular interaction)[31] and from the stretched pericardium (pericardial constraint). Lower body negative pressure reduced right ventricular volume but increased left ventricular volume and stroke volume. We showed that this was because the reduction in external constraint from the right ventricle and the pericardium was greater than the fall in left ventricular end diastolic pressure, resulting in an increase in the ''effective filling pressure''.[32 33] Left ventricular pacing induces a phase shift such that left ventricular contraction and filling both occur earlier than right ventricular events.[24 25 34] Since pericardial stretch (and therefore pericardial pressure) depends on total cardiac volume, a smaller right ventricular volume during left ventricular filling would result in less constraint to left ventricular filling, a greater left ventricular end diastolic volume, and (by the Frank Starling mechanism) greater left ventricular stroke work. Our recent work confirms Kass' observations that left ventricular pacing does not significantly affect Tau or left ventricular end diastolic pressure across a group of patients. Nevertheless we have shown pronounced effects on diastolic filling, which were caused by a reduction in external constraint to left ventricular filling; hence at the same left ventricular pressure there was a greater effective left ventricular preload.[30] External constraint to left ventricular filling is linearly related to the pulmonary capillary wedge pressure or the left ventricular end diastolic pressure.[35] Our acute temporary pacing data shows that the acute haemodynamic benefit of left ventricular pacing can be predicted by higher pulmonary capillary wedge pressure, but not by QRS duration.[36] Indeed even patients with a high pulmonary capillary wedge pressure and a normal QRS duration derived acute haemodynamic benefit.[37]

## FUTURE DIRECTION

From the above it is clear that the major trials of resynchronisation were designed on a false premise—that is, that this therapy would be effective only in patients with left bundle branch block, and that by pacing the two ventricles simultaneously, the QRS duration would be shortened, improving global left ventricular performance. Accordingly, recruitment for the major trials has included only patients with left bundle branch block, and in the major studies biventricular rather than left ventricular pacing was assessed. At present this is the evidence base on which funding of device therapy must be based. However, nearly 30% of patients derive no detectable benefit from this relatively costly treatment.[18] Furthermore, from the foregoing, it seems likely that a proportion of patients with short QRS duration may benefit, although they do not meet the current criteria. The challenge for the future is to identify which patients are most likely to benefit and those who are unlikely to do so. Furthermore, it is possible that the optimal pacing strategy (that is, biventricular or left ventricular) may differ from patient to patient depending on the dominant pathophysiological mechanisms operating in each patient.


### Authors' affiliations

**R A Bleasdale,** Department of Cardiology, Royal Glamorgan Hospital, Llantrisant, UK
**M P Frenneaux,** Department of Cardiovascular Medicine, University of Birmingham, Birmingham, UK


The British Heart Foundation supports Professor Frenneaux

Correspondence to: Dr R A Bleasdale, Department of Cardiology, Royal Glamorgan Hospital, Ynysmaerdy, Llantrisant, CF72 8XR; bleasdalera@aol.com

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