The interaction of interventricular pacing intervals and left ventricular lead position during temporary biventricular pacing evaluated by tissue Doppler imaging

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The interaction of interventricular pacing intervals and left ventricular lead position during temporary biventricular pacing evaluated by tissue Doppler imaging

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Objective: To determine the effects of interventricular pacing interval and left ventricular (LV) pacing site on ventricular dyssynchrony and function at baseline and during biventricular pacing, using tissue Doppler imaging.

Methods: Using an angioplasty wire to pace the left ventricle, 20 patients with heart failure and left bundle branch block underwent temporary biventricular pacing from lateral (n = 20) and inferior (n = 10) LV sites at five interventricular pacing intervals: +80, +40, synchronous, −40, and −80 ms.

Results: LV ejection fraction (EF) increased (mean (SD) from 18 (8)% to 26 (10)% (p = 0.016) and global mechanical dyssynchrony decreased from 187 (91) ms to 97 (63) ms (p = 0.0004) with synchronous biventricular pacing compared to unpaced baseline. Sequential pacing with LV preactivation produced incremental improvements in EF and global mechanical dyssynchrony (p < 0.0001 and p = 0.0026, respectively), primarily as a result of reductions in inter-LV–RV dyssynchrony (p = 0.0001) rather than intra-LV dyssynchrony (NS). Results of biventricular pacing from an inferior or lateral LV site were comparable (for example, synchronous biventricular pacing, global mechanical dyssynchrony: lateral LV site, 97 (63) ms; inferior LV site, 104 (41) ms (NS); EF: lateral LV site, 26 (10)%; inferior LV site, 27 (10)% (NS)).

ECG morphology was identical during biventricular pacing through an angioplasty wire and a permanent lead.

Conclusions: Sequential biventricular pacing with LV preactivation most often optimises LV synchrony and EF. An inferior LV site offers a good alternative to a lateral site. PACing through an angioplasty wire may be useful in assessing the acute effects of pacing.

Interventricular pacing is an effective adjuvant treatment for selected patients with chronic refractory heart failure and left bundle branch block.1,2 Around 20–30% of patients implanted on conventional indications fail to improve clinically.3 The selection of the relative timing of left ventricular (LV) and right ventricular (RV) stimulation, and left ventricular lead position may be important in optimising cardiac performance.4,5

Using tissue Doppler derived measures of ventricular dyssynchrony and an angioplasty wire pacing technique, we examined the combined influence of temporary left ventricular pacing from different coronary sinus tributaries over a range of interventricular pacing intervals, in the same patients.

METHODS

All patients had severely impaired left ventricular function (ejection fraction ≤30%), heart failure (New York Heart Association functional class III–IV), and sinus rhythm with left bundle branch block (QRS ≥120 ms). Each patient gave informed consent for this study, which was approved by the local ethics committee.

Temporary pacing protocol

Quadripolar catheters were positioned at the high right atrium and right ventricular apex. A 6 F ALI guide catheter was used to cannulate the coronary sinus from a femoral approach. Coronary sinus angiography was acquired in three orthogonal views. A 0.014 inch angioplasty wire (Choice, Scimed) insulated with an uninflated angioplasty balloon (Maverick Scimed) advanced to expose <1 cm terminal tip, was used to pace the lateral free wall (n = 20). The quadripolar catheters and angioplasty wire were connected to a biventricular pacemaker (Medtronic InSync III 8042). Each electrode was tested in VVI or AAI mode. Bipolar configurations were used for atrial and right ventricular pacing. The right ventricular ring was the indifferent electrode for the unipolar left ventricular lead for left ventricular sensing and pacing. Biventricular VDD pacing with an output twice the capture threshold, or below the anodal capture threshold, was programmed to ensure continuous pacing. Biventricular pacing at five different interventricular pacing intervals (−80, −40, synchronous, +40 and +80 ms referenced to right ventricular pacing) was carried out with continuous recording of surface and intracardiac electrograms.

Mean unpaced PR interval was 188 (30) ms. Atroventricular delays of 80–120 ms were programmed during synchronous biventricular pacing,5,7 but were not individually optimised. The pacemaker used in this study delivers the first ventricular stimulus at the programmed atroventricular interval and delivers the second stimulus at the programmed interventricular interval. During left ventricular preactivation, the second right ventricular stimulus is delayed with a constant left sided atroventricular delay. During right ventricular preactivation, the second left ventricular stimulus is delayed and the atroventricular delay shortened to maintain left sided atroventricular synchrony. With each pacing configuration, a progressive change in QRS morphology confirmed ventricular capture, while comparison with QRS morphology during VVI and VDD pacing excluded the possibility of fusion. After five minutes of pacing for each configuration, echocardiographic data were acquired.

A second inferior left ventricular site was paced through an angioplasty wire in the middle cardiac vein (n = 10) and the
Doppler evaluation of temporary biventricular pacing

protocol was repeated. The anatomical site of pacing (lateral or inferior) was defined by the final wire tip position determined by orthogonal fluoroscopic projections. The calibrated surface measurement of distance between left ventricular tip positions confirmed that left ventricular pacing was from disparate sites.

In four patients, the anterior left ventricular wall was paced through the great cardiac vein and the protocol was repeated.

Angioplasty wire
Temporary pacing using an angioplasty wire has been described during coronary intervention, and recently during biventricular pacing. The angioplasty wire is insulated along the shaft with impedance >20 megaohms to the distal 3 cm tip. The balloon was advanced to cause a unipolar electrode. Pacing from the wire was validated during pacing from the wire and through an over-the-wire lead (4193 Medtronic) advanced under fluoroscopy to the same position. Diaphragmatic pacing was not observed in any of these five implants.

Echocardiographic data acquisition
All echocardiographic data were acquired using an ATL 5000 ultrasound system. Patients had a baseline conventional echocardiographic examination. The ejection fraction was calculated using Simpson’s equation and the apical four chamber view. Tissue Doppler imaging enables quantitative assessment of regional systolic function and ventricular dyssynchrony. Pulsed wave tissue Doppler traces were recorded with a surface electrocardiogram during end expiration, using apical four, two, and three chamber views with a 5 mm sample volume on the basal septum, lateral, anterior, inferior, and posterolateral left ventricular walls, and from the right ventricular free wall at the level of the tricuspid valve annulus. Tissue Doppler imaging was undertaken at baseline, during each different pacing configuration, and at each left ventricular pacing site. Data were analysed offline using HDI lab software (ATL Corporation).

Tissue Doppler imaging measurements
From each tissue Doppler trace, peak systolic velocity and electromechanical delay were measured, with mean values calculated from 3 cardiac cycles. A single, blinded operator analysed all data.

Electromechanical delay was defined as the time from QRS onset to the beginning of systolic contraction (S wave). The longest electromechanical delay within the left ventricle defined the latest site of left ventricular contraction. Maximum dispersion in electromechanical delay between different left ventricular segments defined individual intra-LV dyssynchrony. Inter-LV–RV dyssynchrony was calculated as maximal dispersion in left and right ventricular electromechanical delay. The sum of inter-LV–RV and intra-LV dyssynchrony provides a measure of global mechanical dyssynchrony and is a good predictor of left ventricular functional recovery and reverse remodelling after biventricular pacing. Systolic velocity was measured as the peak of the S wave (cm/s).

Reproducibility
The reproducibility of systolic velocity, electromechanical delay, and ejection fraction were assessed in 15 random examinations as the mean difference between two independent measurements carried out on different occasions by one observer (intraobserver variability) and between two independent blinded observers (interobserver variability).

Statistical analysis
Continuous data are expressed as the mean (SD) unless specified otherwise. To compare effects of interventricular pacing intervals for each pacing site, we used repeated measures analysis of variance (ANOVA) and the paired t test. Correlation coefficients were calculated by the Pearson product-moment method. Statistical analyses were made with SPSS version 10.0 and Statview version 5.0. A probability (p) value of <0.05 was considered significant.

RESULTS
Patient characteristics
The baseline characteristics of twenty patients are summarised in table 1. Ninety five per cent of the patients were on either angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers, 50% were on ß blockers, and 65% were on spironolactone. All the patients required oral diuretics.

All patients were paced from a lateral left ventricular site, and 10 of 20 (50%) were paced from a second inferior left ventricular site. In a left anterior oblique projection, the mean separation between lateral and inferior pacing sites was 39 (8) mm. Four patients were paced from an anterior left ventricular site; owing to the small numbers, only limited data are presented. In all patients, right ventricular pacing was from the right ventricular apex.

Reproducibility
There was good reproducibility of measurement for electromechanical delay, systolic velocity, and ejection fraction, with intraobserver coefficient of variance of 3.2%, 6.0%, and 9.0%, respectively, and interobserver coefficient of variance of 7.7%, 8.3%, and 13%.

Effect of pacing configuration on left ventricular ejection fraction
Left ventricular ejection fraction increased between unpaced and synchronous biventricular pacing with a lateral left ventricular pacing site (from 18 (8)% to 26 (10)%, p = 0.016). From an inferior left ventricular pacing site, the ejection fraction increased to 27 (10)% (NS). There was no significant difference in ejection fraction between lateral and inferior left ventricular pacing sites. During pacing there was a gradual increase in ejection fraction with increasing left ventricular preactivation (p<0.0001 by ANOVA), the increases in ejection fraction during left ventricular preactivation being significantly greater than synchronous biventricular pacing (fig 1). Left ventricular end diastolic diameter was unchanged from baseline during each of the pacing configurations.

Effect of pacing configuration on regional electromechanical delay and mechanical dyssynchrony
During the baseline unpaced state, mean right ventricular contraction occurred notably ahead of left ventricular contraction. Within the left ventricle, mean septal contraction occurred earliest, followed by anterior and inferior left ventricular wall contraction, with posterior and lateral left ventricular walls significantly delayed, accounting for inter-LV–RV, intra-LV, and global mechanical dyssynchrony.

During biventricular pacing with right ventricular preactivation from both lateral and inferior left ventricular pacing sites, mean right ventricular contraction was modestly delayed by approximately 20 ms, while mean lateral left ventricular wall contraction was advanced. Onset of mean septal contraction was unchanged during pacing from a lateral left ventricular pacing site but was advanced during pacing from the inferior left ventricular wall.
### Table 1: Patient baseline demographic variables

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<td>164</td>
<td>202</td>
<td>29</td>
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</table>

Mean (SD): 67 (12) years, 3.3 (0.5) NYHA class, 166 (23) QRS, 188 (30) PR, 41 (13) MS, 18 (8) EF, 111 (47) EDD.

DCM, dilated cardiomyopathy; EDD, end diastolic diameter; EF, ejection fraction; F, female; HF, heart failure; IHD, ischaemic heart disease; LV, left ventricular; M, male; NYHA, New York Heart Association; RV, right ventricular.

During synchronous biventricular pacing from a lateral or inferior left ventricular site, mean right ventricular contraction was delayed by approximately 50 ms. With an inferior left ventricular pacing site, mean septal contraction was delayed while electromechanical delays in other regions were virtually unchanged. With a lateral left ventricular pacing site, mean septal contraction was substantially delayed, lateral left ventricular wall contraction was minimally delayed, while mean electromechanical delay for the remaining left ventricular regions increased by approximately 15 ms.

With left ventricular preactivation from an inferior left ventricular pacing site, mean right ventricular contraction was significantly delayed, with a small advance in mean lateral left ventricular wall contraction and little change in the remaining left ventricular regions. With a lateral left ventricular pacing site there was a marked delay in mean right ventricular contraction, beyond that seen during synchronous pacing. There was a minor delay in mean lateral wall electromechanical delay, with significant delays in the remaining left ventricular regions.

These changes in mean regional electromechanical delays explain the reductions in intra-LV, inter-LV–RV, and global mechanical dyssynchrony observed with different pacing configurations when compared with the baseline unpaced state (figs 2 and 3; table 2).

Intra-LV and inter-LV–RV dyssynchrony were significantly reduced with synchronous biventricular pacing from both left ventricular pacing sites. Altering the interventricular pacing interval made no significant difference to intra-LV dyssynchrony, but inter-LV–RV dyssynchrony decreased with increasing left ventricular preactivation ($p = 0.0001$ by ANOVA). There was no significant difference between lateral and inferior left ventricular pacing sites for any interventricular pacing interval. (table 2)

Global mechanical dyssynchrony (sum of inter-LV–RV and intra-LV dyssynchrony) significantly decreased with synchronous biventricular pacing, independent of left ventricular pacing site ($187 (91)$ ms, unpaced, to $97 (63)$ ms, $p = 0.0004$, lateral left ventricular site; and $104 (41)$ ms, $p = 0.018$, inferior left ventricular site). There was a gradual decrease in global mechanical dyssynchrony with increasing left ventricular preactivation, with no significant difference between lateral and inferior left ventricular pacing sites (fig 3).

### Optimal resynchronisation

From a lateral left ventricular pacing site, biventricular pacing with left ventricular preactivation provided optimal mechanical resynchronisation or lowest global mechanical dyssynchrony in 15 of the 20 patients (75%) and in eight of 11 patients (73%) with dilated cardiomyopathy. Optimal resynchronisation occurred in a minority of patients (3/20 or 15%) during synchronous biventricular pacing, and in two of 20 patients (10%) with right ventricular preactivation, both of whom had ischaemic heart disease. From an inferior left ventricular pacing site the interventricular pacing interval producing optimal resynchronisation was more variable: three of 10 (30%) with right ventricular preactivation; two of 10 (20%) with synchronous pacing; and five of 10 (50%) with left ventricular preactivation. In all patients with ischaemic heart disease paced from a lateral left ventricular site, optimal resynchronisation occurred during sequential biventricular pacing (two of nine (22%) with right ventricular preactivation, and seven of nine (78%) with left ventricular preactivation).

During synchronous biventricular pacing from an anterior left ventricular site (n = 4) there was no significant difference in ejection fraction, intra-LV, inter-LV–RV, or global mechan-
patients who underwent this temporary pacing study.

biventricular pacemaker insertion are presented for 12 of 20 pacing study. Chronic follow up data at six months post-

had been identified as a likely problem during the temporary owing to the small calibre of suitable venous tributaries, which extraction at two months, and in one patient coronary sinus before permanent pacing from a non-cardiac cause, one medical treatment. Of the remaining nine patients, one died with six patients randomised to biventricular pacing and five to were subsequently enrolled in the CARE-HF multicentre trial, 15 Following this temporary pacing study, 11 of 20 patients (55%)

Follow up data

Following this temporary pacing study, 11 of 20 patients (55%) were subsequently enrolled in the CARE-HF multicentre trial, 16 with six patients randomised to biventricular pacing and five to medical treatment. Of the remaining nine patients, one died before permanent pacing from a non-cardiac cause, one developed a device related infection necessitating system extraction at two months, and in one patient coronary sinus lead placement at permanent implantation was not possible owing to the small calibre of suitable venous tributaries, which had been identified as a likely problem during the temporary pacing study. Chronic follow up data at six months post-

Individual data acquired during the temporary pacing study were used to guide left ventricular lead placement at implant, and in the programming of interventricular pacing intervals. Eleven of the 12 patients (92%) had implantation at a lateral left ventricular pacing site. Before discharge, the interventricular pacing interval was programmed according to the lowest measure of global mechanical dysynchrony for the implanted left ventricular site during the acute study. At six months post-

implant, 11 of the 12 patients (92%) were symptomatically improved, with a significant reduction in mean baseline NYHA functional grade from (mean (SD)) 3.5 (0.5) to 2.4 (0.5) during biventricular pacing (p<0.001). Chronic follow up data appeared to correspond well with acute data presented in this study. The left ventricular ejection fraction was significantly increased from baseline (18 (6)% to 24 (8)%, p<0.001), while intra-LV, inter-LV–RV, and global mechanical dys synchrony were significantly reduced from baseline (79 (60) to 42 (24) ms, p = 0.04; 123 (52) to 62 (34) ms, p<0.001; and 202 (107) to 104 (59) ms, p = 0.03, respectively). In the patient with no symptomatic improvement at follow up who was enrolled in the CARE-HF study (patient 7 in table 1), there was minimal evidence of baseline dys synchrony with no significant changes in these variables, either during the temporary pacing study or at follow up.

**DISCUSSION**

Several studies have now shown sequential biventricular pacing may be superior to simultaneous right ventricular and left ventricular stimulation. 7–10 There has been conflicting evidence over the importance of left ventricular lead position in studies which have largely compared lateral versus anterior left ventricular sites. 4–8 However, the combined effects of different interventricular pacing intervals and left ventricular stimulation sites have yet to be fully defined. This study provides a direct comparison within the same patients of different interventricular pacing intervals, suggesting that sequential biventricular pacing, most often using left ventricular preactivation, may further optimise the effects on mechanical dysynchrony and systolic performance. In addition, it directly compares the effect on mechanical function of biventricular pacing from lateral and inferior left ventricular pacing sites, without evidence that one left ventricular site is more favourable than the other.

**Effect of interventricular pacing intervals**

Sogaard et al 5 found that sequential biventricular pacing was superior to synchronous biventricular pacing in enhancing left ventricular systolic and diastolic performance: nine of 20 patients had delayed contraction of the posterolateral wall and improved with left ventricular lead preactivation, and 11 of 20 had delayed contraction of the septum or inferior wall and showed optimal benefit with right ventricular lead preactivation. The benefits were shown within a small range of interventricular pacing intervals from +20 to −20 ms, and further increases in preactivation were deleterious to left ventricular function. In contrast, our mean data suggest that sequential biventricular pacing with right ventricular lead preactivation was typically better than unpaced, but less beneficial than synchronous biventricular pacing, while the greatest mechanical benefit was seen with left ventricular lead preactivation. One explanation for these discrepancies may be differences in baseline patient characteristics. In the study by Sogaard, despite having left bundle branch block, fewer than 50% of patients showed delayed lateral or posterior left ventricular wall contraction (and those that did, benefited from left ventricular lead preactivation), whereas 75% of our patients had this pattern at baseline. From either left ventricular pacing site the lowest mean measures of dys synchrony and hence the most optimally coordinated contractions were seen with left ventricular preactivation.

During atrio-biventricular pacing there is fusion between intrinsic excitation of the septum along the native right bundle branch and excitation of the distal septum from right
ventricular pacing, combined with the premature pacing of the left ventricle. The pattern of electrical activation is dependent on propagation of the three wavefronts, regions of slow conduction, with spread of excitation within the left ventricle through both specialised and non-specialised conducting tissue. The resulting mechanical contraction is further influenced by heart failure aetiology, myocardial architecture, the presence of scar tissue, the position of the pacing electrodes, and the atrioventricular and interventricular pacing intervals.

Biventricular pacing with left ventricular preactivation was seen to maximally enhance mean left ventricular ejection fraction and septal systolic velocity, without significant effect on other left ventricular and right ventricular systolic velocities. Isolated left bundle branch block is known to reduce septal regional ejection fraction while sparing that of the apex and lateral walls, and biventricular pacing may simply correct contractility in the regions in which it is impaired. During biventricular pacing there is slow progression of anterolateral wall shortening, with more prominent septal wall shortening, which may arise as a result of preloading and prestretching of septal regions remote from the site of preactivation. Adjustment of the interventricular pacing interval may help to optimise septal myocardial stretch and hence contractility.

Influence of left ventricular pacing site
Consistent with previous studies, we found that the lateral and posterior left ventricular walls were the most frequent sites of delayed regional contraction (100% of patients with idiopathic dilated cardiomyopathy and 50% of patients with ischaemic heart disease). Published data suggest that the greatest improvement in left ventricular performance is seen when the site of left ventricular pacing is concordant with the site of latest left ventricular contraction. Consequently, left ventricular pacing from the lateral free wall has been shown to be superior to an anterior site, where stimulation has been thought to provide the least haemodynamic benefit in the majority of patients. In this study, the limited pacing data for four patients from an anterior left ventricular site also failed to show improvement in measures of ventricular dyssynchrony or cardiac function.

Although the inferior left ventricular wall has previously been considered a suboptimal site for left ventricular lead placement, we have demonstrated improvements in both mechanical dyssynchrony and systolic performance.

Temporary left ventricular pacing through an angioplasty wire
Most left ventricular lead delivery systems use over-the-wire angioplasty technology. This acute study using an angioplasty
guidewire technique provided information about coronary venous anatomy, local capture thresholds, and phrenic nerve stimulation. Previous studies using this technique have shown that individualisation of pacing site configuration can maximise haemodynamic responses and reduce non-responders. This study has further increased our understanding of the mechanisms by which variations in left ventricular pacing site combined with sequential pacing influence mechanical resynchronisation and could be used to guide lead placement and pacemaker programming. The use of non-invasive tools to reliably predict response to biventricular pacing is still evolving. Performing such a pre-implant study may enhance the prediction of clinical response. However, reverse remodelling occurs as a chronic process and an apparent lack of acute response assessed by non-invasive data should be interpreted judiciously.

Study limitations

This study design requires device implantation as a separate procedure to avoid compromising echocardiographic data collection and an increased risk of infection. In our study, as in previous studies, short atrioventricular delays were programmed. These aimed to minimise fusion, although some degree of fusion cannot entirely be excluded during extreme sequential pacing, while lack of individual optimisation may have had a negative influence on haemodynamic improvement.

The technique of tissue Doppler imaging has some inherent limitations. Traces acquired from an apical view only assess longitudinal axis motion and cannot distinguish between active and passive wall motion. This study used only echocardiographic indices for comparing different pacing configurations. Bordachar et al recently showed that haemodynamic and electromechanical responses may vary with pacing configuration; and without haemodynamic data, it is uncertain whether reductions in dysynchrony would yield an equivalent haemodynamic response.

Reducions in dysynchrony indices have been observed in patients with reverse remodelling after biventricular pacing. In our study, with limited chronic data, we speculate that acute reductions in ventricular dysynchrony will persist chronically and may be used as a guide to predict long term clinical response.

**CONCLUSIONS**

In this acute temporary pacing study of patients with severe heart failure and left bundle branch block, biventricular pacing reduced intra-LV, inter-LV–RV, and global mechanical dysynchrony, and increased septal systolic velocity and left ventricular ejection fraction.

The optimal interventricular pacing interval varies between patients and is ideally assessed on an individual basis. Sequential biventricular pacing with left ventricular preactivation most often achieves maximal mechanical synchronicity and systolic function, particularly when the left ventricular lead is placed laterally.

Pacing from an inferior left ventricular site provides improvements in mechanical dysynchrony and may offer an alternative when lateral left ventricular lead implantation is not possible.

A new temporary angioplasty wire pacing technique is described, which may have clinical value in assessing the response to biventricular pacing before permanent pacing.

**Table 2 Effects on left ventricular pacing site and interventricular pacing interval on intra-LV and inter-LV–RV dysynchrony**

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<td>Unpaced LV pacing site</td>
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<tr>
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<td>51 (36)</td>
<td>43 (27)</td>
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<tr>
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<tr>
<td>44 (21)</td>
<td>41 (26)</td>
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<td>39 (18)</td>
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<tr>
<td>NS</td>
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<tr>
<td>Mean intra-LV dysynchrony (ms)†</td>
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<tr>
<td>77 (50)</td>
<td>51 (36)</td>
<td>43 (27)</td>
<td>39 (30)</td>
</tr>
<tr>
<td>Inferior</td>
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<td>44 (21)</td>
<td>41 (26)</td>
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<tr>
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<tr>
<td>Mean inter-LV–RV dysynchrony (ms)‡</td>
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<td>68 (37)</td>
<td>67 (38)</td>
<td>54 (40)</td>
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<tr>
<td>Inferior</td>
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<tr>
<td>70 (16)</td>
<td>58 (19)</td>
<td>57 (27)</td>
<td>57 (23)</td>
</tr>
<tr>
<td>NS</td>
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</table>

Data are mean (SD); p values shown are for comparisons with baseline, un paced data. *p<0.01, **p<0.001 for comparison of sequential and synchronous biventricular pacing for the same LV pacing site. †ANOVA, NS when compared at all of the interventricular pacing intervals. ‡ANOVA, p=0.0001 when compared at all of the interventricular pacing intervals.

**Authors’ affiliations**

R E Lane, J Mayet, D P Francis, N S Peters, D W Davies, International Centre for Circulatory Health, St Mary’s Hospital and Imperial College, London, UK
A W C Chow, The Heart Hospital, Westmoreland Street, London, UK
R J Schilling, Department of Cardiology, St Bartholomew’s Hospital, London, UK

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**REFERENCES**


