

## CARDIOVASCULAR MEDICINE

# Comparison of permanent left ventricular and biventricular pacing in patients with heart failure and chronic atrial fibrillation: prospective haemodynamic study

S Garrigue, P Bordachar, S Reuter, P Jaïs, A Kobeissi, G Gaggini, M Haïssaguerre, J Clementy

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**Objective:** To compare clinical and haemodynamic variables between left ventricular and biventricular pacing in patients with severe heart failure; and to analyse haemodynamic changes during daily life and maximum exercise during chronic left ventricular and biventricular pacing.

**Design:** Prospective single blinded randomised study with crossover.

**Setting:** University hospital (tertiary referral centre).

**Patients and methods:** 13 patients (mean (SD) age, 62 (6) years) with chronic atrial fibrillation, severe heart failure (mean ejection fraction 24 (8)%), and QRS prolongation of  $\geq 140$  ms had His bundle ablation and installation of a pacemaker providing left ventricular and biventricular pacing. The pacemaker was equipped with a peak endocardial acceleration (PEA) sensor. The PEA pattern was used as a haemodynamic marker during exercise as it is highly correlated with left ventricular dP/dt. After a baseline period of right ventricular pacing, all patients had two months of left ventricular pacing and two months of biventricular pacing in random order. At the end of each phase, an echocardiogram, a haemodynamic analysis at rest and on exercise during a six minute walk test, and a cardiopulmonary exercise test were performed.

**Results:** PEA values were higher with left ventricular pacing (0.58 (0.38) m/s) and biventricular pacing (0.62 (0.24) m/s) than at baseline (0.49 (0.18) m/s) ( $p < 0.05$ ). The six minute walk test showed similar performance in both pacing modes, but patients had more symptoms with left ventricular pacing at the end of the test ( $p = 0.035$ ). On cardiopulmonary exercise testing, there was a greater increase in mean percentage variation of PEA with biventricular pacing than with left ventricular pacing (12.5 (1.8)% v 9.7 (3.6)%, respectively;  $p = 0.048$ ) and better performance figures (92 (34) W v 77 (23) W;  $p = 0.03$ ).

**Conclusions:** During symptom limited and daily life exercise tests, chronic biventricular pacing provides better haemodynamic performance than left ventricular pacing. In heart failure patients with wide QRS complexes, the interventricular dyssynchronisation induced by left ventricular pacing may impair myocardial function during exercise.

See end of article for authors' affiliations

Correspondence to:  
Dr Stephane Garrigue,  
Clinical Cardiac Pacing  
and Electrophysiology  
Department, Hôpital  
Cardiologique du  
Haut-Leveque, 19 avenue  
de Magellan, Pessac  
33600, France;  
stgarrigue@aol.com

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**B**iventricular pacing (BVP) is a novel and promising form of treatment for patients with severe chronic heart failure. This type of pacing has been shown to reduce pulmonary capillary wedge pressure and to increase cardiac output.<sup>1,2</sup> Left ventricular pacing (LVP) alone has also been shown to improve cardiac function in patients with heart failure, but results in a longer QRS duration than BVP, or even than spontaneous rhythm.<sup>2,4</sup> These studies reported that left ventricular free wall pacing acutely enhanced femoral systolic pressure while lowering pulmonary wedge pressure, and the responses from single left ventricular sites were similar to BVP.<sup>2,4</sup> LVP tended to result in a greater increase in stroke work than BVP, along with lower end systolic volumes.<sup>2,4,5</sup> Several studies have also emphasised that the improvement in cardiac function in heart failure is not dependent upon QRS narrowing in patients with baseline intraventricular conduction delay.<sup>2,6</sup>

There has been no assessment of chronic LVP compared with chronic BVP. An ideal chronic assessment would consist of repeated invasive catheterisation procedures and measurement of the first derivative of left ventricular pressure (left ventricular dP/dt) during follow up, with the aim of correlating variations in dP/dt with the clinical status of the patient.

New non-invasive tools for the mid and long term assessment of cardiac function are needed to clarify which patients can benefit from multisite ventricular pacing. One such tool is an implantable intracardiac accelerometer (connected to a pacemaker), which is suitable for non-invasive monitoring of myocardial contractility.<sup>7,8</sup> This sensor provides intracavity recordings of the maximum amplitude of the vibrations produced by the first heart sound (peak endocardial acceleration (PEA)), using an implantable micromass tip-mounted accelerometer. The recorded changes in PEA are highly correlated with changes in left ventricular dP/dt in humans.<sup>8</sup>

Our first aim in this study was to compare clinical and haemodynamic variables during LVP and BVP at mid term follow up in patients with severe heart failure. Our second objective was to analyse haemodynamic changes during daily life and maximum exercise with the two pacing modes, using the PEA data provided by the pacemaker sensor.

**Abbreviations:** BVP, biventricular pacing; LVP, left ventricular pacing; NYHA, New York Heart Association; PEA, peak endocardial acceleration

**Table 1** Clinical, echocardiographic, and haemodynamic variables at baseline in the study population

Patient	Age (years)	Sex	Cardiac disease	PEA (G)	QRS duration* (ms)	Aortic TVI (mm)	Aortic pre-ejection time interval (ms)	Aortic ejection duration (ms)	Left ventricular ejection fraction (%)
1	42	M	Ischaemic	0.49	220	133	203	221	37
2	63	M	Idiopathic	0.74	230	81	261	178	21
3	64	M	Idiopathic	0.80	225	106	240	215	21
4	76	M	Ischaemic	0.35	210	109	248	232	37
5	49	M	Idiopathic	0.33	220	82	240	247	22
6	76	M	Idiopathic	0.52	220	180	235	272	18
7	78	M	Ischaemic	0.46	210	102	198	228	17
8	58	M	Ischaemic	0.55	210	124	206	204	33
9	79	M	Ischaemic	0.18	200	130	213	223	24
10	46	M	Idiopathic	0.38	195	109	221	198	15
11	76	M	Idiopathic	0.70	190	125	186	203	24
12	64	M	Idiopathic	0.31	185	155	228	330	38
13	63	M	Ischaemic	0.60	190	90	283	255	18
Mean (SD)	64 (12)			0.49 (0.18)	208 (15)	117 (28)	228 (27)	231 (39)	25 (08)

\*QRS duration during right ventricular pacing alone.  
M, male; PEA, peak endocardial acceleration; TVI, time-velocity integral.

## METHODS

Patients were considered for inclusion in the study if they presented with the following:

- Functional class III or IV (New York Heart Association, NYHA) congestive heart failure despite treatment with diuretics, angiotensin converting enzyme inhibitors, and  $\beta$  blockers at the maximum tolerated doses
- a left ventricular ejection fraction of < 40% assessed by radionuclide angiography
- a left ventricular end diastolic diameter of  $\geq 60$  mm
- QRS duration of > 140 ms (recorded at 50 mm/s)
- chronic atrial fibrillation.

Patients were also required to have a suitable acoustic window for reliable echocardiographic analysis. All patients received a pacemaker providing both LVP and BVP, after providing written informed consent. The study was approved by our local ethics committee. Patients were excluded if they were less than 18 or more than 80 years of age, if they had unstable angina pectoris within two months of the start of the study, if they had acute myocardial infarction within six months of the study, or if they had had percutaneous coronary angioplasty or coronary artery bypass grafts within the preceding year.

The study population consisted of 13 men (mean (SD) age, 64 (12) years) with severe chronic heart failure and chronic atrial fibrillation with a long QRS (168 (15) ms). Eight patients had left bundle branch block and five had a non-specific intraventricular conduction block. The mean left ventricular ejection fraction was 24 (8)%. Ten patients were in NYHA functional class III and three were in class IV. We selected patients with chronic atrial fibrillation who had undergone His bundle ablation so as to exclude the possibility that atrioventricular delay or intra-atrial/interatrial conduction block influenced the haemodynamic measurements.

## Implantation technique

The 13 patients presented with an intermittent symptomatic rapid ventricular rate despite the maximum tolerated treatment with amiodarone, calcium channel blockers,  $\beta$  blockers, or combinations of these. All patients underwent His bundle ablation followed by DDDR pacemaker implantation (Living Plus, Sorin Biomedica, Saluggia, Italy). This pacemaker is equipped with an intracardiac accelerometer sensor recording the PEA variations and thus provides the facility for continuous monitoring of myocardial contractility.<sup>7,8</sup>

A specific lead configuration was designed to provide left ventricular pacing, right ventricular pacing, and simultaneous

left and right ventricular pacing.<sup>6</sup> The left ventricular lead was successfully implanted transvenously in all patients. The left ventricle was paced with a specially designed lead for pacing through the coronary sinus (model 2188, Medtronic, Minneapolis, Minnesota, USA). The lead was positioned at the base/ anterolateral left ventricular wall through the great cardiac vein (at its proximal part) in all patients to allow reproducible interpretation of the effects of left ventricular pacing. A bipolar pacing lead was then positioned at the right ventricular apex, and both leads were connected to the atrial port using a Y adapter. Programming the pacemaker to unipolar AAI mode resulted in left ventricular pacing, while a bipolar AAI pacing mode provided biventricular pacing.

A second bipolar pacing lead was positioned at the right ventricular apex and connected to the ventricular port to provide back up right ventricular pacing alone.<sup>6</sup> The latter was a specific lead with an accelerometer incorporated at its tip allowing continuous measurement of PEA variations.<sup>7,8</sup>

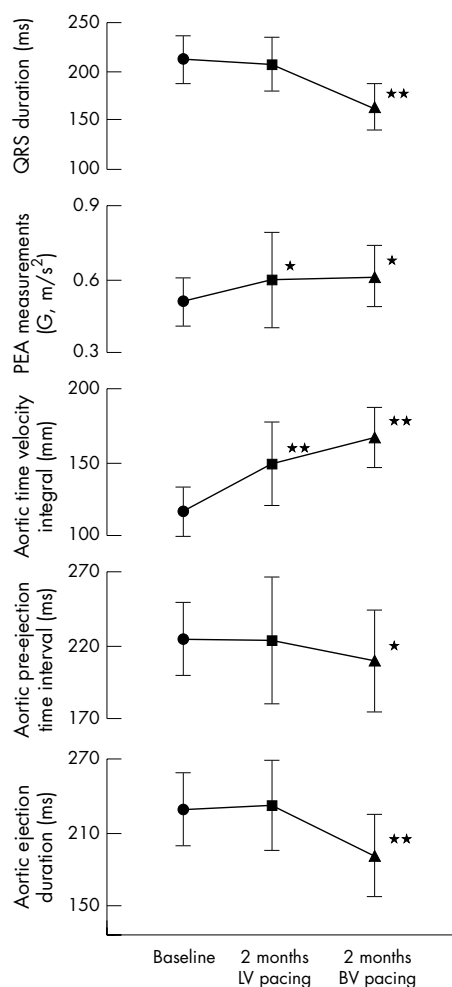
## Study protocol

Baseline measurements (table 1) were obtained after one month of right ventricular apical pacing following the His bundle ablation. After this there were two randomised phases with crossover: two months of BVP (phase 1) and two months of LVP (phase 2). Seven patients underwent LVP during the first phase, while six underwent BVP. Radionuclide left ventricular ejection fraction, QRS duration, echocardiographic measurements (aortic ejection duration, aortic pre-ejection time interval, and aortic velocity-time integer), and PEA measurements (averaged over a 10 minute period during each phase) were recorded at the end of each phase (including the baseline) at a fixed pacing rate of 70 impulses/min. In addition, all patients underwent a six minute walking test and a symptom limited bicycle ergometer test with peak oxygen uptake ( $\dot{V}O_2$ ) calculation. The two exercise tests were performed at a fixed heart rate (70 impulses/min), and the memory function of the pacemaker recorded the number of premature ventricular complexes.

## Statistical analysis

The sample size ( $n = 13$ ) was determined as the following: a statistical power reaching 80% with an  $\alpha$  risk of 0.05 when the difference between the two pacing modes reaches 25% (that is, a difference of 25% in PEA variation measurements between BVP and LVP at rest and/or on exercise).<sup>9</sup>

Results are expressed as mean (SD). Multivariate analysis of variance with repeated measurements was performed to



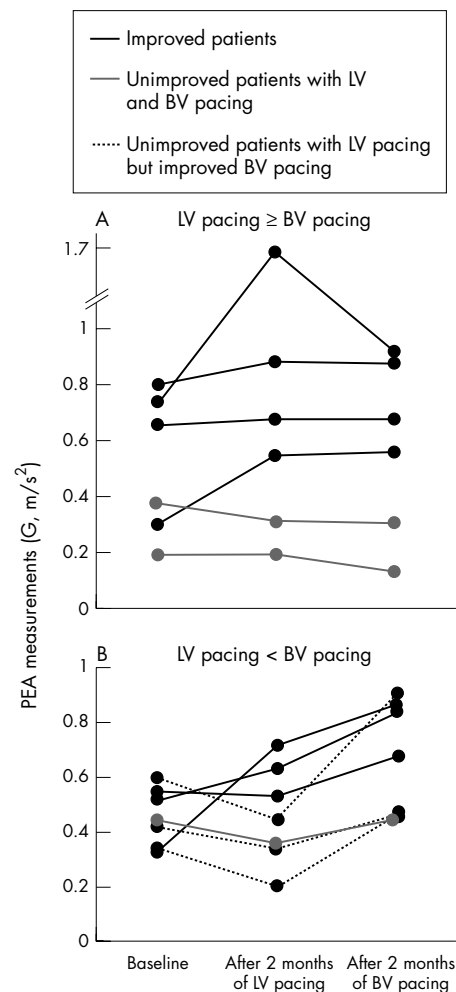
**Figure 1** Electrical, haemodynamic, and echocardiographic variables during left ventricular (LV) and biventricular (BV) pacing compared with baseline. BV pacing resulted in a significantly narrower QRS, a shorter aortic pre-ejection time interval, and a shorter aortic ejection duration than at baseline or during LV pacing. Despite a similar QRS duration between baseline and LV pacing, LV pacing provided higher peak endocardial acceleration measurements and aortic time-velocity integral values. PEA, peak endocardial acceleration,

compare the data between the baseline (right ventricular pacing after His bundle ablation), left ventricular pacing, and biventricular pacing. The Schieffer test was used for ad hoc comparisons. Variables obtained during exercise between left ventricular and biventricular pacing were analysed by using the non-parametric Mann-Whitney test for paired data. The significance threshold was set at  $p < 0.05$ .

## RESULTS

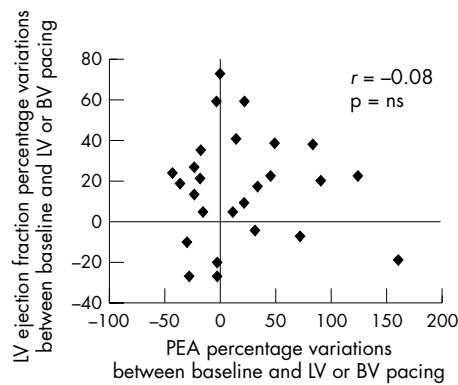
### Rest

After two months of LVP, QRS duration was similar to the value at baseline (205 (23) ms *v* 208 (15) ms, respectively; NS), while after two months of BVP, QRS duration was significantly shorter than at baseline (153 (21) ms;  $p < 0.01$ ) (fig 1). PEA measurements gave higher values with both LVP and BVP than at baseline (0.49 (0.18) m/s at baseline *v* 0.58 (0.38) m/s with LVP, *v* 0.62 (0.24) m/s with BVP;  $p < 0.05$ ) (fig 1). Similar results were observed for the aortic time-velocity integral (fig 1). The aortic pre-ejection time interval and ejection duration shortened significantly only with BVP (fig 1). The left ventricular ejection fraction increased from 25 (8)% at baseline to 29 (10)% after two months of LVP ( $p < 0.05$ ) and to 30 (11) after two months of BVP ( $p < 0.05$ ).

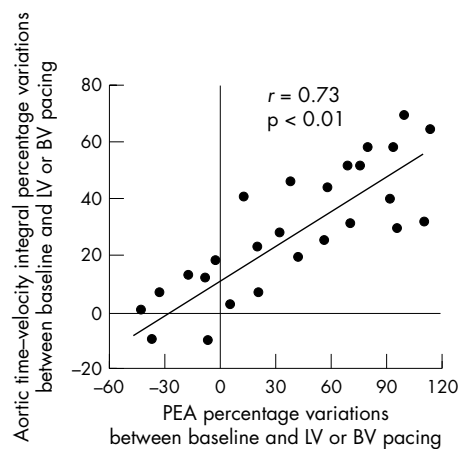


**Figure 2** Variations in peak endocardial acceleration (PEA) measurements between baseline, left ventricular (LV) pacing, and biventricular (BV) pacing. (A) Six patients had higher PEA values with LV than with BV pacing. Two of these were not clinically improved (shown in grey) by LV or BV pacing. The absence of clinical improvement was associated with absence of haemodynamic improvement, as PEA values were decreased with both LV and BV pacing compared with baseline. (B) Seven patients had higher PEA measurements with BV than LV pacing. One patient did not improve either clinically or haemodynamically (shown in grey). This patient had a decrease in the PEA values during LV pacing as well as during BV pacing compared with baseline. Three patients (dashed lines) were not clinically or haemodynamically improved by LV pacing, while BV pacing resulted in significantly higher PEA values associated with clinical improvement compared with baseline.

Ten patients improved both clinically (by NYHA functional class) and haemodynamically (as shown by an increased left ventricular ejection fraction and aortic time-velocity integral and by the PEA measurements) (fig 2A). Four patients had higher PEA values during LVP (fig 2A) and six patients had higher values during BVP (fig 2B). Three patients were not improved by LVP but were clinically and haemodynamically improved by BVP (fig 2, dashed lines), while seven patients were improved by both LVP and BVP (fig 2, continuous lines). Three patients were not clinically improved by either pacing mode (fig 2); these patients had lower PEA values compared with baseline, as well as a decrease in aortic time-velocity integral and left ventricular ejection fraction. No correlation was found between variations in the left ventricular ejection fraction and variations in the PEA measurements ( $r = -0.08$ ; NS) (fig 3). However, variations in the PEA measurements were highly correlated with variations in the aortic time-velocity integral ( $r = 0.73$ ;  $p < 0.01$ ) (fig 4).



**Figure 3** Correlation between the percentage variations in left ventricular ejection fraction and peak endocardial acceleration (PEA) values after two months of biventricular (BV) or left ventricular (LV) pacing compared with baseline.



**Figure 4** Correlation between the percentage variations in the aortic time-velocity integral and peak endocardial acceleration (PEA) values after two months of biventricular (BV) or left ventricular (LV) pacing compared with baseline.

## Exercise

### The walking test

Eleven patients underwent this protocol. The remaining two were in NYHA functional class IV despite cardiac resynchronization and were unable to accomplish this part of the protocol. Performance in the six minute walk test was similar with LVP and BVP (table 2). However, more patients with LVP were symptomatic at the end of the test ( $p = 0.035$ ; table 2). During the walking test, there were more premature ventricular complexes with LVP than with BVP ( $p = 0.04$ ; table 2).

Figure 5 shows an example of the walking test results in the same patient on LVP and BVP. It is apparent that with BVP (panel A), the PEA values increased from the onset of exercise and then progressively returned to the resting value at the end of the exercise. In contrast, with LVP there was a decrease in the PEA values during the entire exercise test, with a return to the resting value within one minute of the end of the exercise. Figure 6 shows the percentage variation in PEA values in the 11 patients compared with the baseline values. During LVP, there was a decrease in the mean percentage variation in PEA ( $-14$  (42)%), compared with a significant increase during BVP ( $+44$  (37)%;  $p = 0.028$ ).

### The bicycle ergometer

Patients performed better on the bicycle ergometer during BVP than during LVP (92 (34) W v 77 (23) W, respectively;  $p = 0.03$ ), without a significant increase in peak oxygen uptake (table 2). The number of premature ventricular complexes during the exercise testing tended to decrease with BVP compared with LVP, but the difference did not reach significance (table 2). Figure 6 shows that patients had a greater increase in the mean PEA percentage variation with BVP than with LVP (125 (18)% v 97 (36)%; respectively;  $p = 0.048$ ).

## DISCUSSION

Multisite ventricular pacing to treat severe heart failure was first investigated haemodynamically using invasive catheterisation protocols.<sup>1-5</sup> The initial acute studies also used temporary leads. We were interested to discover whether PEA recordings might be useful in the long term non-invasive monitoring of patients during chronic multisite ventricular pacing.

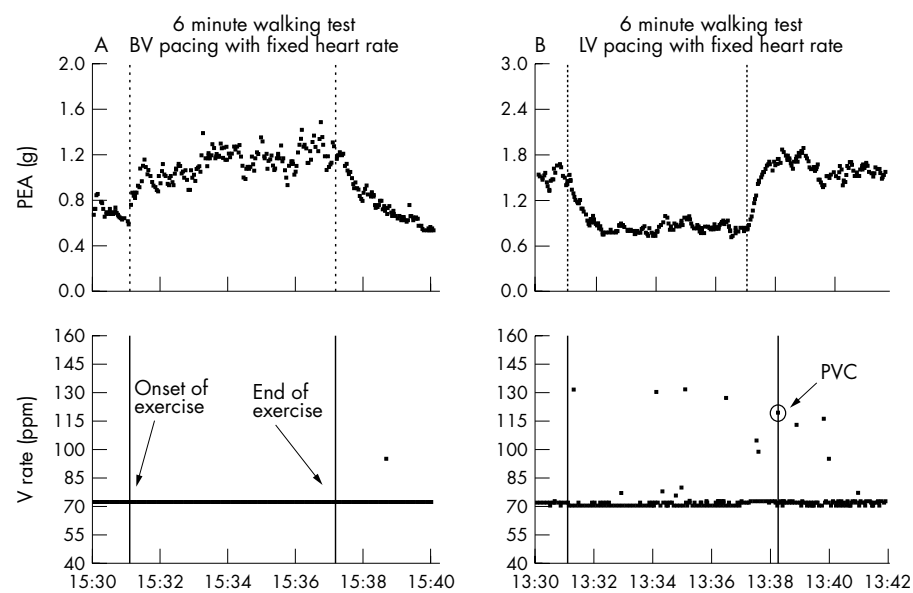
In our patients, all of whom had His bundle ablation and so no atrioventricular delay that might influence haemodynamic measurements, we placed the left ventricular pacing lead at the base of the anterolateral left ventricular wall. In our experience, this site can be reached in all patients and our main goal was to study a population with standardised pacing lead location. Choosing the mid lateral left ventricular wall would have been more difficult, as four patients had small calibre lateral branches of the coronary sinus. Although results from short term studies suggest that the lateral left ventricular wall—midway between base and apex—is optimal,<sup>2 10 11</sup> this remains to be confirmed in mid and long term follow up. In addition, a recent study<sup>12</sup> showed that pacing the left ventricle at the base/anterior wall provided the highest dP/dt and cardiac output when compared with the mid lateral wall and the mid posterior wall; this haemodynamic study was further supported by electrophysiological experiments showing that the shortest left ventricular activation time was observed when pacing the left ventricle at the base/anterior wall rather than at the posterior or the lateral wall.<sup>13</sup>

**Table 2** Comparison of effects of left ventricular pacing and biventricular pacing on exercise

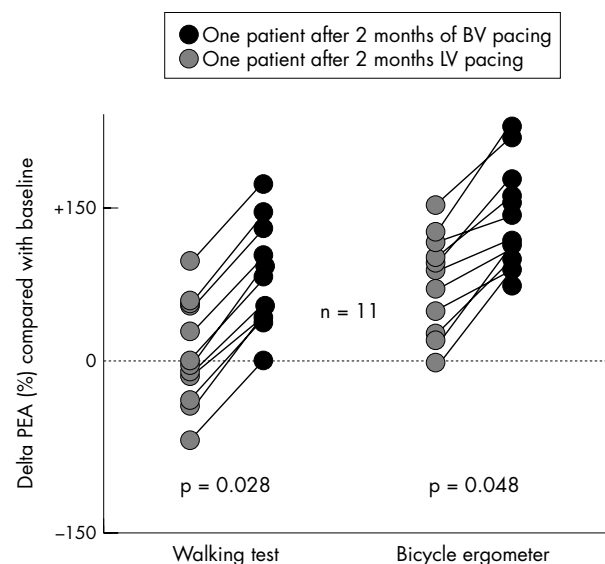
Variable	After 2 months of LVP	After 2 months of BVP	p Value
<i>Six minute walk test</i>			
Performance (m)	428 (68)	437 (59)	0.88
Patients with heart failure symptoms after the test (%)	64	18	0.035
Number of PVCs during the test	49 (71)	10 (23)	0.04
<i>Symptom limited cardiopulmonary exercise test</i>			
Performance (W)	77 (23)	92 (34)	0.03
Peak $\dot{V}O_2$ (ml/kg/min)	16.5 (3.6)	18.5 (4.2)	0.11
Number of PVCs during the test	64 (74)	25 (29)	0.09

Data are mean (SD).

BVP, biventricular pacing; LVP, left ventricular pacing; PVCs, premature ventricular complexes;  $\dot{V}O_2$ , oxygen consumption.



**Figure 5** Example of a peak endocardial acceleration (PEA) recording in one patient during a six minute walk test at the same pacing rate (70 impulses/min) with biventricular (BV) pacing (panel A) and left ventricular (LV) pacing (panel B). Note that at the onset of exercise, BV pacing caused an increase in the PEA values compared with baseline (panel A), whereas LV pacing resulted in lower PEA values (panel B). As soon as exercise ended, PEA values returned to baseline with both LV and BV pacing. LV pacing resulted in more premature ventricular complexes during and after exercise. PVC, premature ventricular complex.



**Figure 6** Comparison of individual percentage variations in peak endocardial acceleration (PEA) measurements during exercise between biventricular (BV) pacing and left ventricular (LV) pacing, compared with baseline values. At maximum exercise or during a daily life physical activity (walking test), each patient had a proportionally greater increase in PEA with BV than with LV pacing.

Our data on mid term BVP assessments are consistent with recent studies showing a significant clinical and haemodynamic improvement.<sup>14–17</sup> Although Edner and colleagues suggested that His bundle ablation can influence left ventricular ejection fraction for at least three months,<sup>18</sup> our protocol started only one month after His ablation. The pacing mode randomisation used in our study controlled for the influence of postablation time interval on the results, as seven patients had initial left ventricular pacing while six had initial biventricular pacing. Irrespective of the initial pacing mode, every patient had a lower percentage increase in PEA measurements during exercise with LVP than with BVP. In our study, a lack of clinical improvement correlated with lower or similar PEA values compared with baseline, regardless of the pacing mode (LVP or BVP). Three of the 13 patients had no haemodynamic and clinical improvement compared with baseline, even with BVP. A recent study supports these observations in a larger population.<sup>19</sup> In patients showing no

improvement, it is possible that the left ventricular pacing lead may not have been optimally located, or that BVP effects can vary from patient to patient and that a longer follow up is required to observe objective improvement.

The variations in the PEA results showed a high correlation with the variations in the aortic time–velocity integral. However, neither the absolute value nor the percentage variation in PEA measurements was correlated with isotopic left ventricular ejection fraction. It is possible that PEA measurements are more sensitive to cardiac output variations than to myocardial contractility in an altered myocardium. A recent study by Blanc and colleagues reported that LVP was clinically comparable to BVP in long term follow up,<sup>20</sup> which is consistent with the present data at rest. This supports the view that acute observations made with single site left ventricular pacing remain valid on long term follow up.

Our study achieved a non-invasive assessment of both LVP and BVP during exercise. With LVP, a decrease in the PEA measurements during the walk test was consistent with the greater proportion of patients who were symptomatic at the end of the test. The bicycle ergometer test showed a worse performance with LVP than with BVP, along with lower PEA values during the test. Thus, despite the fact that LVP and BVP provided similar haemodynamic improvement at rest, the right bundle branch block induced by LVP may be detrimental in heart failure patients during exercise. These data are consistent with a recent study emphasising that right bundle branch block is an independent factor in mortality in patients with severe heart failure.<sup>21</sup> In our study, as BVP resulted in better clinical performance than LVP and in higher PEA values, we suggest that right ventricular workload or right to left ventricular timing may be more important during exercise than previously realised. As Kass and colleagues have suggested,<sup>2</sup> it is likely that at rest, myocardial conduction of impulses originating from left ventricular epicardial pacing is slow compared with intrinsic conduction through the conducting fasciculae, so mechanical forces remain synchronous even with early activation. However, this slowing of conduction could worsen on exercise owing to the emergence of regional ischaemic areas. In that case BVP would provide better right and left electromechanical synchrony than LVP. In fig 6 it can be seen that the difference in percentage variation in the PEA pattern between LVP and BVP appears to be similar in all the patients during exercise. We performed a separate analysis for patients with ischaemic cardiomyopathy ( $n = 6$ ) and idiopathic cardiomyopathy ( $n = 7$ ) to try to characterise a

specific category of patients benefiting to a greater extent from BVP than from LVP. Patients with ischaemic heart failure showed a somewhat greater difference in the measurements of PEA variation between LVP and BVP than patients with idiopathic heart failure (62 (16)% *v* 54 (18)%, respectively), but this did not reach significance. Our study was only designed to investigate whether or not BVP was better than LVP; splitting the 13 patients into smaller groups is unlikely to provide sufficient statistical power for further analyses.

The fact that during exercise there were more premature ventricular complexes with LVP than with BVP suggests an increased catecholamine release resulting from a temporary, more pronounced disturbance of myocardial function. Whether the haemodynamic difference between LVP and BVP on exercise will influence long term mortality remains to be determined. In the present study, there was a tendency toward an increase in peak  $\dot{V}O_2$  with BVP compared with LVP. However, it is likely that the sample size was too small for the difference in peak  $\dot{V}O_2$  (+2 ml/kg/min for biventricular pacing) to reach significance. On the other hand, we cannot exclude the possibility that biventricular pacing increases exercise duration but not specifically the peak  $\dot{V}O_2$ . Our patients all had very disturbed cardiac function and it is possible to increase the anaerobic performance with only a slight improvement in aerobic performance, as shown in larger randomised prospective studies.<sup>20–22</sup>

### Conclusions

These data, along with results of other recent studies,<sup>6–12</sup> support the view that chronic LVP can provide similar haemodynamic and clinical improvement as BVP at rest. However, during activities of daily living and during symptom limited exercise, BVP allowed better performance than LVP, along with improved haemodynamic measurements and significantly fewer ventricular arrhythmias. It seems that the right bundle branch block induced by LVP may have a detrimental effect on daily living activities in patients with heart failure.

### Authors' affiliations

S Garrigue, P Bordachar, S Reuter, P Jaïs, M Haïssaguerre, J Clementy, Hôpital Cardiologique du Haut-Leveque, University of Bordeaux, Bordeaux-Pessac, France  
A Kobeissi G Gaggini, Sorin Biomedica, 9, rue Georges Besse, Bat.4, 92160 Antony, France

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