Clinical Research

Biventricular Versus Conventional Right Ventricular Stimulation for Patients With Standard Pacing Indication and Left Ventricular Dysfunction

The Homburg Biventricular Pacing Evaluation (HOBIPACE)

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OBJECTIVES
The Homburg Biventricular Pacing Evaluation (HOBIPACE) is the first randomized controlled study that compares the biventricular (BV) pacing approach with conventional right ventricular (RV) pacing in patients with left ventricular (LV) dysfunction and a standard indication for antibradycardia pacing in the ventricle.

BACKGROUND
In patients with LV dysfunction and atrioventricular block, conventional RV pacing may yield a detrimental effect on LV function.

METHODS
Thirty patients with standard indication for permanent ventricular pacing and LV dysfunction defined by an LV end-diastolic diameter ≥60 mm and an ejection fraction ≤40% were included. Using a prospective, randomized crossover design, three months of RV pacing were compared with three months of BV pacing with regard to LV function, N-terminal pro-B-type natriuretic peptide (NT-proBNP) serum concentration, exercise capacity, and quality of life.

RESULTS
When compared with RV pacing, BV stimulation reduced LV end-diastolic (−9.0%, p = 0.022) and end-systolic volumes (−16.9%, p < 0.001), NT-proBNP level (−31.0%, p < 0.002), and the Minnesota Living with Heart Failure score (−18.9%, p = 0.01). Left ventricular ejection fraction (+22.1%), peak oxygen consumption (+12.0%), oxygen uptake at the ventilatory threshold (+12.5%), and peak circulatory power (+21.0%) were higher (p < 0.0002) with BV pacing. The benefit of BV over RV pacing was similar for patients with (n = 9) and without (n = 21) atrial fibrillation. Right ventricular function was not affected by BV pacing.

CONCLUSIONS
In patients with LV dysfunction who need permanent ventricular pacing support, BV stimulation is superior to conventional RV pacing with regard to LV function, quality of life, and maximal as well as submaximal exercise capacity. (J Am Coll Cardiol 2006;47:1927–37)

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Cardiac resynchronization therapy has been evaluated mainly in heart failure patients without the indication for antibradycardia pacing (1). Only in few controlled trials on patients with atrial fibrillation and spontaneous (2) or ablation-induced bradycardia (2–4) the need for permanent pacing was not an exclusion criterion.

Although it is known that interventricular and intraventricular impulse conduction and biventricular (BV) contractility and relaxation might be impaired (5–8) and adverse myocardial remodeling might occur (9–11), the standard approach for patients with symptomatic bradycardia and atrioventricular (AV) malconduction is a pacing system that includes a right ventricular (RV) apical lead. Right ventricular outflow-tract pacing appears to convey a modest hemodynamic benefit over RV apex pacing (12), but its role still remains to be defined.

The detrimental effect of RV pacing is probably most important in patients with pre-existing left ventricular (LV) dysfunction (13–15) and may lead to aggravation of heart failure. In small uncontrolled trials, upgrading of RV pacing to BV stimulation significantly improved functional status and LV performance in patients with congestive heart failure (16–18). However, the three published randomized trials on BV pacing for patients with permanent atrial fibrillation (2–4) showed only modest favorable effects of BV as compared with RV pacing. In view of these controversial data, the optimal pacing configuration for patients with LV systolic dysfunction who need permanent ventricular pacing support is still unknown. This is the scope of the Homburg Biventricular Pacing Evaluation (HOBIPACE).

METHODS

Study population. Thirty-three patients with symptomatic bradycardia and impaired AV conduction that required
permanent ventricular pacing were enrolled in the study. Only patients with an LV end-diastolic diameter ≥60 mm and an LV ejection fraction ≤40% were included. Enrollment was independent of etiology of LV dysfunction, functional status, and presence of sinus rhythm. After three deaths during the study, complete data sets were available for 30 patients. Baseline characteristics of these patients are presented in Table 1. The study was approved by the local ethics committee (Ärztekammer des Saarlandes No. 112/98). All patients gave informed consent before device implantation.

**Device implantation.** Atrioventricular devices were implanted in 24 patients. The remaining six patients had permanent (duration >1 year) atrial fibrillation and got a conventional dual-chamber pacemaker with the atrial port connected to the LV lead and the ventricular port receiving the RV lead. Figure 1 gives an overview of the devices used. The RV lead was attached to the RV septum in 17 cases; the remaining 13 leads were positioned in the RV apex. Left ventricular leads were introduced transvenously through a coronary sinus venous branch and placed in a lateral, posterior, or posterolateral position in 20 patients and in an anterolateral position in 10 patients.

**Study protocol.** HOBIPACE was a monocentric, prospective, randomized, single-blinded crossover comparison between RV and BV pacing. It was an investigator-driven trial without industrial sponsorship. A flow chart of the study protocol is given in Figure 2. As it was the objective of the study to evaluate the net effect of BV over RV pacing on the background of optimal pharmacological therapy, the randomization phase was preceded by a run-in period of three months, which was utilized to tailor drug therapy according to guideline recommendations. In patients with atrial fibrillation, attempts were made to restore sinus rhythm using direct current cardioversion and antiarrhythmic drug therapy including amiodarone. The run-in phase was also intended to detect and correct any device or lead-related malfunction before patients entered the randomization phase. To rule out early LV lead problems (dislodgement, loss of capture, occasional diaphragmatic stimulation), devices were programmed to the BV mode in the lead-in period.

After three months, each patient was familiarized with quality-of-life assessment and cardiopulmonary exercise testing and underwent a test run of each procedure. The results of these tests were not used for further data analysis.

After randomization to one of the two pacing modes (RV vs. BV), the patients were followed for two three-month study periods with crossover to the complementary pacing mode after the first three-month interval. In patients without atrial fibrillation, the programmed AV delay was optimized at the beginning of each study period using Ritter’s approach (19).

Outcome measures were assessed at the end of each three-month period. The study had three primary end points: LV end-systolic volume, LV ejection fraction, and peak oxygen consumption. Functional class according to the New York Heart Association (NYHA), quality of life as assessed with the Minnesota Living with Heart Failure questionnaire (20), serum concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP), and parameters derived from cardiopulmonary exercise testing and Doppler echocardiography were classified as secondary end points.

Although the study was primarily designed to contrast RV to BV stimulation, a comparison was included between pre- and post-pacing echocardiographic parameters and NYHA functional classification. This analysis was intended to investigate how RV pacing together with optimal pharmacotherapy influences LV structure and function in patients with pre-existing LV dysfunction.

**NT-proBNP measurements.** Venous blood samples were taken from the resting and sitting patient at the beginning of each follow-up visit. The samples were centrifuged within 1 h and stored at −70°C for a maximum of one

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**Table 1. Pre-Operative Baseline Characteristics of the Study Patients (n = 30)**

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>69.6 ± 8.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, n (%)</td>
<td>23 (77)</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>3.0 ± 0.6</td>
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<tr>
<td>Ischemic etiology, n (%)</td>
<td>17 (57)</td>
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<tr>
<td>Patients in sinus rhythm, n (%)</td>
<td>19 (63)</td>
</tr>
<tr>
<td>With AV block only, n (%)</td>
<td>11 (37)</td>
</tr>
<tr>
<td>With AV block and sinus bradycardia, n (%)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Atrial fibrillation and AV block, n (%)</td>
<td>11 (37)</td>
</tr>
<tr>
<td>Left bundle branch block pattern, n (%)</td>
<td>19 (63)</td>
</tr>
<tr>
<td>Duration of the QRS interval (ms)</td>
<td>174 ± 42</td>
</tr>
<tr>
<td>LV end-diastolic dimension (mm)</td>
<td>69.9 ± 8.5</td>
</tr>
<tr>
<td>LV end-systolic dimension (mm)</td>
<td>59.0 ± 9.6</td>
</tr>
<tr>
<td>LV end-diastolic volume (ml)</td>
<td>236.1 ± 74.8</td>
</tr>
<tr>
<td>LV end-systolic volume (ml)</td>
<td>177.3 ± 68.7</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>26.1 ± 7.8</td>
</tr>
<tr>
<td>Grade of mitral regurgitation</td>
<td>1.5 ± 0.6</td>
</tr>
</tbody>
</table>

*Includes six patients with permanent and five patients with persistent atrial fibrillation; †refers to the intrinsic, un paced QRS complex and includes ventricular escape rhythms with left bundle branch block pattern in seven cases.

AV = atrioventricular; LV = left ventricular; NYHA = New York Heart Association.
week. Serum concentrations of NT-proBNP were measured using an Elecsys NT-proBNP sandwich electrochemiluminescent immunoassay carried out on an Elecsys 2010 bench top analyzer (Roche Diagnostics, Mannheim, Germany).

**Echocardiography.** All measurements were performed according to the guidelines of the American Society of Echocardiography using M-mode recordings for unidimensional parameters and Simpson’s biplane method for LV volumes. Left ventricular muscle mass index was calculated using the formula of Devereux et al. (21). The LV hypertrophy index (22) was calculated as the sum of LV end-diastolic septal and posterior wall thickness divided by end-diastolic diameter and given as a percentage. Left and right ventricular heart cycle intervals were measured by pulsed Doppler echocardiography as illustrated in Figure 3. Two Doppler indexes of cardiac mechanical function were calculated for patients in sinus rhythm: the Tei index (23), which is inversely correlated to LV systolic as well as diastolic function and the Z-ratio (24), which is reduced particularly in patients with electromechanical asynchrony.

Color Doppler tissue velocity imaging (frame rate $\geq 100$/s) was used for quantification of LV synchrony. From the apical four-chamber, two-chamber, and long-axis views, a six-basal and six-mid-segmental model was obtained in the LV. Myocardial pulsed Doppler velocity profiles were reconstituted off-line from the tissue velocity imaging color images (25). In each of the 12 segments, the duration of ejection phase velocities $\geq 0.5$ cm/s was measured and normalized to ejection time (Fig. 3). The average value of all

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**Figure 1.** Device types, number of first-time implantations, and upgrade procedures. ICD = implantable cardioverter defibrillator.

**Figure 2.** Flow chart of the study protocol. *At three months, the patients underwent a trial procedure of QoL testing and CPET, which were not used for further data analysis. AVDO = optimization of the programmed atrioventricular delay; BV = biventricular; CPET = cardiopulmonary exercise testing; Echo = echocardiography; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PM-FU = pacemaker follow-up; QoL = quality of life as assessed by the Minnesota Living with Heart Failure questionnaire; RV = right ventricular.
were stored on magneto-optical hard disks and analyzed off-line on an EchoPac workstation (GE Medical Systems) using the average value of eight consecutive measurements for each parameter.

Cardiopulmonary exercise testing. All patients underwent symptom-limited cardiopulmonary exercise testing with breath-by-breath gas exchange analysis using a MedGraphics CPX/D spiroergometry system (Medical Graphics Corporation, St. Paul, Minnesota). Patients performed bicycle exercise in a 45°, semisupine position lying on an Ergometrics 900EL reclining ergometer (Ergoline, Bitz, Germany). After adaptation to the mouthpiece in resting conditions, workload was increased continuously by 15 W/min (ramp protocol) starting at zero load. In each patient, maximum workload achieved, peak oxygen consumption, and oxygen uptake at the ventilatory anaerobic threshold were measured. Peak oxygen consumption was defined as the highest oxygen uptake rate observed during the exercise test using a running average of seven breaths. The anaerobic threshold was determined according to the V-slope method (28). Peak circulatory power was calculated as the product of peak oxygen consumption and systolic arterial pressure (29). The slopes of the linear regression between oxygen uptake (VO$_2$) versus workload (aerobic work efficiency) (30) and minute ventilation versus carbon dioxide output (VCO$_2$) (ventilatory efficiency) (31) were calculated.

Statistics. A two-tailed p value of <0.05 was considered significant. Differences between pre-operative data, RV and BV pacing periods were assessed using a two-way univariate analysis of variance (ANOVA) for repeated measurements with post-hoc Student-Newman-Keuls test. The stimulation mode (pre-operative vs. RV vs. BV pacing) was defined as within-subjects factor. The randomization sequence (RV→BV vs. BV→RV) was entered as a between-groups factor to allow for testing on treatment-period interaction (residual or carryover effect); ANOVA assumptions of normality and homoskedasticity were checked with the Kolmogorov-Smirnov and Levene tests. Parameters that met these assumptions are given as mean ± 1 SD. For parameters, which passed the tests only after logarithmic transformation (e.g., NT-proBNP concentration), the geometric mean with the back-transformed asymmetric standard deviation is given. Analysis of variance results were adjusted by Greenhouse-Geisser’s epsilon if a deviation from the sphericity assumption was found. Proportions and frequency distributions were analyzed using the chi-square test. For multiple pairwise comparisons of relative drug doses, the Friedman test was used. For the tissue-Doppler–derived parameters of LV synchrony, the intra- and inter-observer repeatability of the measurement was calculated as twice the SD of pairwise differences. Correlations between parameters were assessed by calculating Pearson’s product moment correlation coefficient.

Sample size calculations were focused on primary end points assuming an absolute 4% increment in LV ejection fraction, a relative decrease in LV end-systolic volume of

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12 segments (LVS) and its standard deviation (LVS-SD) were calculated as indexes of LV synchrony.

Mitrail valve regurgitation was graded from 0 to 4 using a combination of the proximal isovelocity surface area method and the vena contracta width approach (26). Left ventricular dp/dt was estimated from mitral regurgitation flow (27).

Echocardiography was performed using a Vingmed Vivid Five ultrasound system capable of second harmonic imaging and equipped with a 2.5-MHz transducer (GE Medical Systems, Milwaukee, Wisconsin). Echocardiographic data
15%, and an increase in peak oxygen uptake of 1.5 ml/min/kg with BV compared with RV pacing. Considering an estimated coronary sinus lead failure rate of 10% and a lost-to-follow-up rate of an additional 10%, the minimum number of patients required to detect a highly significant ($p < 0.01$) difference between RV and BV pacing with a power of 90% was 21.

RESULTS

Treatment period interaction. There was no significant effect of the randomization sequence (RV $\rightarrow$ BV vs. BV $\rightarrow$ RV) on any of the parameters evaluated. Likewise, no interaction between randomization sequence and the within-subjects factor could be detected.

Study dropouts, re-operations, and premature crossover. Three of 33 patients (9%) died during the course of the study, one of them during the run-in period, the other two patients after randomization to RV ($n = 1$) and BV pacing ($n = 1$), respectively. Causes of death were sudden cardiac death, fatal cerebral stroke, and suicide. Because end points could only be assessed in patients without missing data after completion of both crossover phases, all results are based on the 30 patients who completed the study.

Re-operations were required in three of these patients (10%) due to dislodgement of the LV lead in two cases and due to a device defect in another case. All corrections were successfully performed during the run-in period. In one patient who followed the BV $\rightarrow$ RV randomization sequence, the RV phase had to be terminated prematurely (after one month) because of clinical deterioration. There was no premature crossover or study termination in any other patient.

Atrial fibrillation management and device programming. At study entry, six patients had permanent and five had persistent atrial fibrillation. During the lead-in phase, one patient changed from sinus rhythm to atrial fibrillation. Thus, a total of six patients were considered amenable to cardioversion and were treated with amiodarone and direct current shock during the lead-in phase. In three patients, atrial fibrillation recurred within days, and sinus rhythm was stable for the rest of the study in the remaining three. No cardioversion attempt was made in the six patients with permanent atrial fibrillation who had undergone BV pacemaker implantation without an atrial lead. As a result, nine patients were in permanent atrial fibrillation at randomization and for the rest of the study. Their devices were programmed to RV or BV pacing only (depending on randomization). In the remaining 21 patients with sinus rhythm, atrial-based RV or BV pacing was implemented. The devices were programmed to an average LV pre-excitation of $19 \pm 14 \text{ ms}$. Rate adaption was turned on in 19 patients (63%) with chronotropic incompetence. Optimal paced and sensed AV delays were significantly ($p < 0.01$) shorter for RV pacing (paced: $142 \pm 40 \text{ ms}$; sensed: $81 \pm 39 \text{ ms}$) than for BV stimulation (paced: $155 \pm 39 \text{ ms}$; sensed: $99 \pm 36 \text{ ms}$).

Optimization of drug therapy. Due to bradycardia, beta-blockers were underutilized before device implantation. Three months thereafter, nearly every patient was on medication with beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. Drug therapy did not change during the two crossover periods (Table 2).

Effects of lead-in phase and RV pacing. In conjunction with optimized pharmacotherapy, RV pacing alone improved LV end-diastolic ($-9\%$, $p = 0.017$) and end-systolic volume ($-10\%$, $p = 0.025$) as well as LV ejection fraction ($+9\%$, $p = 0.048$) over pre-implant conditions. New York Heart Association functional class was reduced by an average of $0.5$ ($p < 0.003$). Right ventricular pacing also improved the Tei index and the $Z$-ratio for the LV (Tei index: $p < 0.010$; $Z$-ratio: $p < 0.005$) and RV (Tei index: $p < 0.001$; $Z$-ratio: $p < 0.003$). QRS duration ($+11\%$, $p = 0.002$) and the pre-ejection intervals for the LV ($+17\%$, $p = 0.003$) and RV ($+26\%$, $p = 0.002$) were prolonged by RV pacing. Left ventricular diameters, LV muscle mass index, LV hypertrophy index, cardiac index, LV dp/dt, left atrial diameter, degree of mitral regurgitation, and parameters of LV synchrony remained unchanged during RV pacing (Table 3).

Impact of BV pacing. PRIMARY END POINTS. All three primary end points for the comparison between RV and BV pacing were met (Figs. 4A, 4B, and 5). When compared with RV pacing, BV stimulation reduced LV end-systolic volume by $17\%$ ($p < 0.001$), increased LV ejection fraction by $22\%$ ($p < 0.0002$), and peak oxygen consumption by $12\%$ ($p < 0.0003$).

LV function and structure. In comparison with RV pacing, BV stimulation improved all parameters of LV dimension and function as well as left atrial diameters (Table 3). The reduction in mitral regurgitation and LV muscle mass index reached significance only for the pre-postoperative

| Table 2. Heart Failure Medication During the Course of the Study |
|-------------------|--------------------|----------------|----------------|----------------|
| % of Patients Taking | Pre-Operative | Run-In | RVP | BVP |
| ACEI/ARBs | 93 | 100 | 100 | 97 |
| Beta-blockers | 67 | 100$^*$ | 97$^+$ | 97$^+$ |
| Aldosterone antagonists | 43 | 57 | 60 | 57 |
| Diuretics | 90 | 97 | 97 | 93 |
| Digitalis | 37 | 47 | 57 | 53 |
| Amiodarone | 30 | 43 | 43 | 40 |

% of Max. Target Dose Achieved (According to Guideline Recommendations)

| % of Max. Target Dose Achieved (According to Guideline Recommendations) |
|----------------|----------------|----------------|----------------|
| Beta-blockers | 28 $\pm$ 30 | 58 $\pm$ 31$^+$ | 67 $\pm$ 28$^+$ | 65 $\pm$ 34$^+$ |
| ACEI/ARBs | 52 $\pm$ 41 | 58 $\pm$ 39 | 64 $\pm$ 48 | 67 $\pm$ 48 |

$^+$< $0.005$ vs. pre-operative; $^+$< $0.02$ vs. pre-operative; $^+$< $0.01$ vs. pre-operative; $^+$< $0.001$ vs. pre-operative. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BVP = biventricular pacing; RVP = right ventricular pacing.
Comparison (Table 3). The improvement in LV function with BV versus RV pacing was paralleled by an increase in cardiac index (+16%, $p < 0.010$) and LV dp/dt (+27%, $p < 0.020$). The decrease in LV mass index during BV pacing ($p < 0.010$ vs. pre-operative; $p = 0.051$ vs. RV pacing) was mirrored by an increase of 10% ($p < 0.002$ vs. RV pacing) and 13% ($p < 0.001$ vs. pre-operative) in LV hypertrophy index. Thus, reverse LV remodeling as induced by BV pacing led to smaller LVs with thicker walls and improved systolic contraction.

**Biventricular stimulation completely reversed the prolongation of QRS width and LV pre-ejection period precipitated by RV pacing.** In comparison with both pre-implant data and RV pacing, BV stimulation reduced the difference between the RV and LV pre-ejection period ("interventricular delay"—a surrogate parameter of interventricular dysynchrony) by 83% ($p < 0.001$) (Table 3). Right ventricular pre-ejection period was prolonged by BV pacing ($p < 0.010$ vs. pre-implant; $p = 0.026$ vs. RV pacing). Switching from RV to BV pacing further improved Doppler indexes of LV electromechanical activation (Z-ratio, $p = 0.015$) and global LV performance (Tei index, $p < 0.003$). In contrast, RV Z-ratio and Tei index were not different for RV and BV pacing.

**NT-proBNP concentration.** The NT-pro-BNP serum concentrations were severely elevated in the study population with a wide range for individual values during each of the two pacing periods (Table 4). When compared with RV pacing, BV stimulation reduced NT-proBNP concentration by 31% ($p < 0.002$). The reduction in NT-proBNP levels was significantly correlated with the decrease in LV end-diastolic ($p = 0.012$) and end-systolic volumes ($p = 0.001$), the decrease in LV end-diastolic ($p < 0.001$) and end-systolic diameters ($p = 0.008$), the increase in LV hypertrophy index ($p = 0.032$), and the increase in LV ejection fraction ($p = 0.004$). Beyond this, NT-proBNP changes from RV to BV pacing were correlated with the improvements in peak oxygen consumption ($p < 0.0002$), peak circulatory power ($p = 0.003$), aerobic work efficiency ($p < 0.010$), and ventilatory efficiency ($p < 0.002$).

**Functional class and quality of life.** As compared with pre-implant values and RV pacing, BV stimulation improved NYHA functional class by an average of 1.1 ($p < 0.001$ vs. pre-implant) and 0.6 ($p = 0.015$ vs. RV pacing) (Table 3). The Minnesota Heart Failure score was six points lower with BV versus RV pacing ($p = 0.010$) (Table 4). At the end of the crossover phase, patients (unaware of the order of pacing modes) were asked for preferences of either three month period. Twenty patients (67%) preferred the period with BV pacing ($p < 0.0002$), two (7%) preferred the period with RV pacing, and eight patients (26%) had no preference.

**Exercise capacity.** Beyond the increase in peak oxygen consumption, a higher maximum workload ($p = 0.015$) and peak circulatory power ($p < 0.0002$) were achieved with BV stimulation as compared with RV pacing (Table 4). Switching from RV to BV pacing also improved submaximal exercise capacity: oxygen uptake and workload at the ven-
Tissue Doppler echocardiography. For tissue Doppler parameters of left intraventricular synchrony, the coefficients of intra-/interobserver repeatability were 3.3%/4.7% for LVS and 1.5%/2.6% for LVS-SD, respectively. While RV pacing did not change LV synchrony, BV stimulation was associated with a highly significant increase of LVS and a decrease of LVS-SD (Figs. 6A and 6B). When switching from RV to BV pacing, the decrease of LVS-SD was linearly correlated with both the reduction in LV end-systolic volume (p = 0.0001) and the increase in LV ejection fraction (p = 0.0002). Likewise, the decrease of LV end-systolic volume and the increase of LV ejection fraction with BV stimulation showed a linear correlation with LVS-SD during RV pacing (p < 0.001), indicating that higher values of LVS-SD during RV pacing predicted more benefit from BV stimulation. Between preoperative data and BV pacing, a linear correlation was found for the reduction of LV end-systolic volume and LVS-SD (p < 0.002).

Heart cycle intervals. A systematic analysis of heart cycle intervals was restricted to patients in sinus rhythm. Compared with pre-operative values, the main effect of RV pacing on left and right heart cycle intervals was a clear-cut reduction of isovolumic contraction times by 46% (in LV: p < 0.0003) and 63% (in RV: p < 0.0001) as well as a prolongation of diastolic filling times by 15% (in LV: p < 0.005; in RV: p = 0.016) (Fig. 7). Although BV stimulation yielded a greater reduction of LV isovolumic contraction time (−62%, p < 0.0002) and a greater prolongation of LV filling time (+21%, p < 0.0005) than RV pacing, the difference between both pacing modes was not significant. Only BV pacing led to a modest but significant (p = 0.019) prolongation of ejection times in both ventricles, which is probably due to the increase in cardiac output. There was a trend toward a prolongation of isovolumic relaxation times with RV pacing (−18% in LV, p = 0.495; +9% in RV, p = 0.364), which was partly reversed by BV stimulation.

Patient subgroups. Although patients with LV leads placed in a lateral, posterolateral, or posterior position did not differ from patients with anterolateral LV leads regarding improvements in LV volumes, ejection fraction, peak oxygen uptake, NT-proBNP, and quality of life, the increase of LV synchrony when switching from RV to BV pacing was more pronounced in patients with coronary sinus leads outside the anterolateral region (LVS increase: 21.3 ± 14.0% vs. 11.5 ± 8.2%; p = 0.050). In the 17 patients with septal RV leads, RV pacing significantly improved LV synchrony (LVS: +8.8 ± 13.5%, p = 0.043; LVS-SD −4.9 ± 7.2%, p = 0.033) as compared with pre-operative values. With RV apical leads (n = 13), parameters of LV synchrony remained unchanged (LVS: −5.7 ± 12.6%, p =
0.148; LVS-SD −0.1 ± 6.0%, p = 0.973). Only with septal lead placement, RV pacing was able to reduce LV end-systolic volumes from pre-pacing values (27.2 ± 36.5 ml, p < 0.010) while apical RV pacing did not (3.8 ± 30.1 ml, p = 0.695). If primary end point analysis was confined to the 17 patients with RV septal leads, BV stimulation was still significantly superior to RV pacing (LV ejection fraction: p < 0.001; LV end-systolic volume: p = 0.003; peak oxygen uptake: p = 0.005). Neither atrial fibrillation nor a pre-operative left bundle branch block pattern had a significant impact on the benefit of BV pacing.

**DISCUSSION**

This is not just a low-powered reduplication of earlier cardiac resynchronization therapy trials in patients with advanced LV disease. Rather, HOBIPACE compares the alternative of BV stimulation with standard RV pacing in the setting of primary antibradycardia indication for patients with depressed LV function. While reducing the desynchronizing effect of conventional RV stimulation, BV pacing was expected to be beneficial in patients with LV disease.

Indeed, BV pacing was superior to RV pacing because it induced significant reverse LV remodeling with a reduction in LV end-diastolic and end-systolic volumes and an increase in ejection fraction as compared with pacing the RV alone. The relation between LV wall thickness and LV diameter was increased by BV pacing, which—according to the law of Laplace—implies a reduction in LV wall stress. Consistent with reduced wall stress, NT-proBNP levels were lower during BV pacing as compared with RV pacing.

Of note, RV pacing alone offered a modest but significant benefit in some parameters of LV and RV function when compared with pre-operative values. The improvement of heart cycle intervals (reduction of isovolumic contraction time, increase of ventricular filling time) and of Doppler echocardiographic indexes of ventricular function (Tei index, Z-ratio) that were achieved with RV pacing are thought to be (at least in part) a consequence of better AV sequencing after dual-chamber pacemaker insertion for AV block (32). Because short-term studies on dual-chamber RV pacing in congestive heart failure did not show any significant hemodynamic improvement (33), it is more likely, however, that RV septal pacing (in half of the patients), optimization of drug therapy, and cardioversion of atrial fibrillation altogether account for the improvement achieved by RV pacing.

**Table 4.** Effect of RVP Versus BVP on NT-proBNP Release, Quality of Life, and Exercise Capacity

<table>
<thead>
<tr>
<th>Parameters</th>
<th>RVP</th>
<th>BVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP concentration (pg/ml)*</td>
<td>2,405 (743–7,783)</td>
<td>1,667 (521–5,334)‡</td>
</tr>
<tr>
<td>MLHFQ score points</td>
<td>31.2 ± 20.7</td>
<td>25.3 ± 18.1‡</td>
</tr>
<tr>
<td>Peak oxygen consumption (ml/min/kg)</td>
<td>12.5 ± 2.9</td>
<td>14.0 ± 3.0§</td>
</tr>
<tr>
<td>Peak circulatory power (mm Hg×ml/min/kg)</td>
<td>1,684 ± 591</td>
<td>2,038 ± 646§</td>
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<tr>
<td>Ventilatory anaerobic threshold (ml/min/kg)</td>
<td>8.0 ± 2.0</td>
<td>9.0 ± 1.7§</td>
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<tr>
<td>Maximum workload achieved (W)</td>
<td>80.5 ± 27.1</td>
<td>86.3 ± 25.4§</td>
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<td>Workload at ventilatory anaerobic threshold (W)</td>
<td>34.6 ± 17.3</td>
<td>40.1 ± 15.2‡</td>
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<tr>
<td>Slope of regression VO₂ vs. workload (ml/min/W)</td>
<td>7.98 ± 1.37</td>
<td>8.51 ± 1.63‡</td>
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<tr>
<td>Slope of regression minute ventilation vs. VCO₂ (l/l)</td>
<td>39.0 ± 11.1</td>
<td>37.1 ± 11.0§</td>
</tr>
<tr>
<td>RER at maximum workload (l/l)</td>
<td>1.17 ± 0.12</td>
<td>1.17 ± 0.10</td>
</tr>
</tbody>
</table>

*For NT-proBNP the geometric mean with the back-transformed standard deviation is given; ‡ p < 0.01 for right ventricular pacing (RVP) vs. biventricular pacing (BVP); § p < 0.05 for RVP vs. BVP; † p < 0.001 for RVP vs. BVP.

MLHFQ = Minnesota Living With Heart Failure questionnaire; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RER = respiratory exchange ratio, defined by VCO₂/VO₂; VCO₂ = carbon dioxide output; VO₂ = oxygen uptake.

**Figures 6.** (A and B) Tissue-Doppler–derived parameters of left intraventricular synchrony. LVS = duration of systolic ejection velocities >0.5 cm/s averaged for 12 myocardial segments and given in percent of ejection time; LVS-SD = standard deviation of 12 segmental measurements of LVS; other abbreviations as in Figure 4. For description of the box plot design, see legend to Figure 4.
Data from two controlled studies, the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial (34) and the Mode Selection Trial (MOST) (35) indicate that RV pacing is associated with adverse outcome. In patients with preserved LV function (MOST), RV pacing increased the risk for heart failure hospitalization. In LV dysfunction (DAVID), the detrimental effect of RV stimulation was even worse with a risk increase of 60% for the combined end point of heart failure hospitalization or death. Although these studies were conducted in patients without AV block, they confirm observational studies that report adverse LV remodeling during chronic RV pacing in patients with congenital AV block (9,11).

Despite the evidence for its detrimental effect, RV pacing has remained the standard treatment of impaired AV conduction. With the advent of dual-chamber pacing, AV desynchronization was abolished, but LV desynchronization by unphysiological impulse conduction from the RV apex continues to be a problem that is unsolved. Because AV conduction defects (including atrial fibrillation with slow response) account for 50% of pacemaker implants and because about one-third of pacemaker patients have LV systolic impairment (36), additional dysfunction induced by RV pacing is an issue of clinical importance.

Right ventricular outflow tract pacing is the most feasible alternative to RV apical pacing (37) and appears to offer a small hemodynamic improvement over RV apical pacing (12). In the present study, therefore, attempts were made to attach the RV lead to the interventricular septum in all primary implants. Using this approach, it was shown that septal but not apical RV pacing improved LV synchrony as well as LV end-systolic volume in comparison with pre-operative data. However, even in the subgroup of patients with septal RV leads, LV function and exercise capacity were significantly better with BV than with RV pacing, suggesting that BV stimulation is superior to any RV pacing configuration.

In former studies on LV-based pacing, the acute hemodynamic benefit of LV pacing alone was comparable to BV pacing (38), and it was suggested that LV pacing without an additional RV pacing lead would be the simplest and most effective approach for cardiac resynchronization therapy. Although transvenous LV lead technology has greatly improved in recent years, it was not felt to be acceptable in the present study to randomize patients with AV block to LV pacing alone, because lead dislodgement rates and loss of ventricular capture are still higher for LV than for RV leads (39). Moreover, recent studies that compared LV and BV pacing yielded worse results for single-site LV pacing with regard to LV filling time, exercise capacity, and provocation of ventricular ectopy (40,41).
The results of the present study extend those of previous trials on cardiac resynchronization therapy using BV pacing in patients with LV dysfunction and increased QRS duration (1). HOBIPACE showed similar improvements in LV function, neurohumoral activation, functional class, quality of life, and exercise capacity, but the setting was different; BV pacing was not tested against optimal pharmacological therapy, but was compared with RV pacing on top of optimal drug therapy. This notion is still valid in view of 19 patients who showed a left bundle branch block pattern before implantation. However, seven of these had ventricular escape rhythms in the setting of AV block, which fulfilled the formal criteria of left bundle branch block.

It may be argued that RV pacing is just an experimental model for left bundle branch block and both have the same impact on LV activation and function (42). Despite a similar broadening of the QRS complex, however, RV pacing seems to have less detrimental effects on LV synchrony than left bundle branch block (43). It seems, therefore, unacceptable to extrapolate the benefits of BV pacing from heart failure patients with left bundle branch block to those who need ventricular pacing support. This is why dedicated studies are warranted.

So far, three published trials on BV versus RV pacing in patients with permanent atrial fibrillation (2–4) yielded no or only a modest benefit of BV pacing. Interpretation is hampered by a 42% drop-out rate in the Multisite Stimulation in Cardiomyopathies-Atrial Fibrillation (MUSTIC-AF) trial (2), which rendered the intention-to-treat analysis negative and a dominant effect of rate control as compared with resynchronization in the Optimal Pacing Site Study (OPSITE) (3). The results of the Post-AV nodal Ablation Evaluation (PAVE) (4), essentially a significant better 6-min walk distance and ejection fraction with BV versus RV pacing six months after AV node ablation, support the findings of the present study. However, quality of life was not different between RV and BV pacing in the PAVE study.

As in other trials on cardiac resynchronization, the effect size of BV pacing in HOBIPACE showed a wide scatter from absent to huge (Figs. 4 and 5). Because the implantation of an atrioventricular pacing system requires specialized skills, is time consuming and implies additional risks, it cannot be recommended as a universal approach for each pacemaker clinic. It is an important issue for future research to develop reliable predictors of a favorable response to BV pacing. New echocardiographic techniques have yielded promising results (44), but their availability and applicability in clinical practice is still limited.

Study limitations. HOBIPACE was an investigator-driven, single-blind trial. Although a double-blinded design would have excluded any investigator bias, its feasibility in a device trial seems questionable. Blinding of the investigator would have been jeopardized with one accidental look at the electrocardiogram, and the complex set of echocardiographic parameters did not allow for shielding the electrocardiographic tracing. Actually, parts of the study (measurement of NT-proBNP by laboratory staff, self-assessed quality-of-life questionnaire) were double-blinded and yielded consistent results. The analysis of echocardiographic data was performed with unnamed storage media. Cardiopulmonary exercise testing used a protocol for standardized motivation of the study patients and worked successfully, as may be inferred from identical respiratory equivalent ratios at peak exercise for both pacing periods. Crossover designs are prone to period and carryover effects. These could be excluded by the two-way ANOVA design that tested for sequence and interaction effects. As subgroup analyses in small studies are usually underpowered, negative findings for subgroup comparisons in this study should be interpreted with caution.

Conclusions. In patients with LV dysfunction who require ventricular pacing support for bradycardia with impaired AV conduction, the alternative approach of atrioventricular or BV pacing should be considered. Biventricular rather than RV pacing is associated with better LV function, better quality of life, and better exercise capacity.

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