Optimal Right Ventricular Pacing Site in Chronically Implanted Patients
A Prospective Randomized Crossover Comparison of Apical and Outflow Tract Pacing
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OBJECTIVES
To evaluate the long-term functional and hemodynamic effects of right ventricular outflow tract (RVOT) pacing by comparison with right ventricular apical (RVA) pacing.

BACKGROUND
Acute studies have suggested that RVOT pacing could significantly improve cardiac performance in comparison with RVA pacing but no data are available in chronically implanted patients.

METHODS
Sixteen patients with chronic atrial tachyarrhythmia and complete AV block were included. Left ventricular ejection fraction (LVEF) was ≥40% in ten and <40% in six. Patients were implanted with a standard DDDR pacemaker connected to two ventricular leads. A screw-in lead was placed at the RVOT and connected to the atrial port. A second lead was positioned at the RVA and connected to the ventricular port. Right ventricular outflow tract and RVA pacing was achieved by programming either the AAIR or the VVIR mode respectively. Four months later patients were randomized so as to undergo either RVOT or RVA pacing for three months according to a blind crossover protocol. Apart from the pacing mode, programming remained unchanged throughout the study. At the end of each period, NYHA class, LVEF, exercise time and maximal oxygen uptake were assessed.

RESULTS
No significant difference was observed between the two modes for all the parameters analyzed. These identical results were observed in all patients globally, in patients with LVEF ≥40% as in those with LVEF <40%.

CONCLUSIONS
Within the limits of this study, no symptomatic improvement or hemodynamic benefit was noted after three months of RVOT pacing, by comparison with RVA pacing.

One of the main objectives of modern cardiac pacing is to optimize, or at least to stabilize, cardiac performance which is dependent on three main parameters: chronotropic function, quality of AV synchrony when applicable and ventricular activation sequence in relation to the site selected for implanting the ventricular lead. For 35 years, the right ventricular apex (RVA) has been the elective pacing site (1). Experimental (2,3) and clinical studies (4,5), however, suggest that this site is not optimal in terms of cardiac function. Other sites have recently been proposed for right ventricular implantation: right ventricular outflow tract (RVOT), either septal (6) or in the right ventricular free wall (7,8), and the His-bundle area (9,10). Among these alternative sites, only RVOT was evaluated for feasibility and safety using chronically implanted screw-in leads (11).

Results of acute hemodynamic studies, although controversial (12), have shown increased cardiac output as a result of RVOT pacing, relatively to RVA pacing (7,8). Some authors therefore have hypothesized that RVOT could become the elective site for ventricular pacing (13), subject to obtaining positive results from chronic comparative assessments.

The aim of this study was to evaluate the long-term effects of RVOT pacing and of RVA pacing on symptoms, exercise tolerance and left ventricular function in an intra-patient comparison.

PATIENTS AND METHODS
The inclusion criteria were: first, the existence of a chronic atrial tachyarrhythmia, to rule out any potential hemody-
namic influence of the atrial systole and any further need to optimize AV delay in case of dual chamber pacing. Second, the existence of a complete AV block, either spontaneous or induced by radiofrequency ablation of the AV junction, to ensure permanent and complete ventricular capture during pacing. Third, the possibility for each patient to perform an exercise test. All patients gave their informed consent and the study protocol was approved by the local ethics committee.

**Pacing configuration.** Two ventricular leads were implanted in each patient. A passive lead (any commercially available lead could be used) was conventionally placed at the RVA. A screw-in lead (any commercially available screw-in lead could be used) was implanted at the RVOT free wall, as shown in Figure 1. The positions of the leads were controlled by fluoroscopy and surface ECG confirmed QRS axis normalization (0 to 90°) during RVOT pacing. The two ventricular leads were connected to a conventional DDDR pacemaker (Medtronic Elite or Thera DR, Medtronic Inc, Minneapolis, Minnesota). The RVA lead was connected to the ventricular port and the RVOT lead to the atrial port. Single site right ventricular apical programming thus provided single site VVIR pacing at the apex and AAIR programming ensured single site VVIR pacing at the RVOT. DDDR programming with the shortest programmable AV delay value (30 ms) provided dual site right ventricular and almost simultaneous pacing. The lower and upper rate limits were individually programmed depending on the estimated needs in each patient. The lower rate limit was set between 60 and 75 bpm and the upper rate limit from 120 to 140 bpm. However, the programmed values of lower and upper rate limits remained unchanged all along the study. The activity response curve (sensor) was programmed and set at “7” in all patients. Finally the sensitivity on the atrial channel (connected to the RVOT lead) was set at a low value (2 mV) in order to prevent the potential risk of cross-talk and of pacemaker mediated tachycardia, during the “wash-in” period with the pacemaker programmed in the DDDR mode with a short AV delay.

**Study design.** Because all patients presented with chronic atrial tachyarrhythmia at inclusion and because ventricular rate control was achieved by AV junction ablation, the crossover study only started four months later to rule out any hemodynamic improvement that could potentially be due to the regression of a tachycardia-induced cardiomyopathy. During the first four months, the pacemaker was programmed in the DDDR mode. This “wash-in” period was used to clear any carry-on effect of the pacing site during the crossover study. The crossover study included two periods of three months each, randomized as single site VVIR-RVA or single site VVIR-RVOT mode. Throughout the crossover study, the pacing parameters remained unchanged, resting and maximal heart rate and sensor programming in particular. Patients were their own control. The physicians performing the different tests were unwise to the current programming or to the results of the preceding assessment. Pharmacological treatment remained unchanged through-

### Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AV</td>
<td>atrioventricular</td>
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<tr>
<td>CO</td>
<td>cardiac output</td>
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<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
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<tr>
<td>RVA</td>
<td>right ventricular apex</td>
<td></td>
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<tr>
<td>RVOT</td>
<td>right ventricular outflow tract</td>
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<tr>
<td>VVIR-RVA pacing</td>
<td>single site right ventricular apical pacing</td>
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<tr>
<td>VVIR-RVOT pacing</td>
<td>single site right ventricular outflow tract pacing</td>
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**Figure 1.** Chest X ray, (A) frontal and (B) sagittal projections showing the position of the two ventricular leads: the passive lead at the right ventricular apex and the screw-in lead at the RVOT free wall.
At the end of each three months period spent, either in VVIR-RVA or VVIR-RVOT mode, the pacing system was verified as working well before evaluation. Lead impedance and pacing threshold were measured via telemetry on the two ventricular leads. Permanent ventricular pacing (100% paced cycles) was confirmed by pacemaker data (rate histogram) interrogation. Symptoms were evaluated by history according to the NYHA classification. QRS axis and duration were measured from a standard 12 leads surface ECG recording. Cardiac output (CO) was determined by Doppler ultrasonography (Hewlett Packard, Sonos 1000, Boston, Massachusetts, 2.5 MHz probes) (14). Left ventricular ejection fraction (LVEF) was measured at rest by radionuclide angiography (Sopha medical, DSX rectangular camera). Cardiac output and LVEF were measured at rest and at the same heart rate for each evaluation. Exercise test with oxygen consumption measurement (Eos Sprint Jaeger and Oxycon) was carried out for study requirements according to the same standardized protocol within symptom limitations, using the same equipment and under similar conditions for each evaluation. After the “wash-in” period, a run-in test in the DDDR mode was designed to familiarize the patients with the equipment and the whole procedure. Measuring oxygen consumption ensured that the test was actually maximal. Continuous ECG recording controlled that pacing was permanent with a full ventricular capture.

Statistical analysis used a nonparametric comparison. Results are expressed as mean ± standard deviation. A Kruskall and Wallis analysis of variance was performed to compare the distribution of either treatment group. When significant differences were found, a Wilcoxon signed rank test compared each pacing configuration. Each patient being their own control, a value of p < 0.05 was considered significant. Finally a Spearman rank test evaluated the correlation between the different results according to the treatment regimen.

RESULTS

Patients. Sixteen patients aged 53 to 80 (mean age 69 ± 7.5 years) were included in the study. Baseline clinical characteristics are reported in Table 1. At the end of the “wash-in” period in DDDR mode (before starting the crossover study) ten patients were in New York Heart Association (NYHA) class I, three in class II and three in class III. The mean LVEF was ≥40% in ten patients and <40% in six. Patients with LVEF <40% were significantly older and their cardiac output was significantly lower than in patients with LVEF ≥40%. Atrial fibrillation was present in 15 patients and atrial flutter was found in only one. Intrinsic ventricular conduction, as documented on the last ECG recorded before implantation, could be considered as normal in 12 patients (QRS duration ≤120 ms). Four patients had a right bundle branch block. No left bundle branch block was observed.

Implantation procedure and pacing system. Atrioventricular junction ablation was performed in 15 patients. One patient had spontaneous complete heart block and was already implanted with a standard VVIR pacemaker. The additional RVOT lead was implanted at the time of elective pacemaker replacement. No complication linked to the pacing system was noted at implantation and throughout a mean follow-up duration of 10.4 ± 3.6 months. In particular, there was no dislodgement of RVOT leads. Chronic pacing thresholds did not differ significantly between RVA and RVOT leads (1.19 ± 1.00 V vs. 1.33 ± 1.01 V, pulse width 0.5 ms).

Table 1. Patients’ Characteristics Before Randomization

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n = 16)</th>
<th>LVEF ≥40% (n = 10)</th>
<th>LVEF &lt;40% (n = 6)</th>
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<tr>
<td>Age (years)</td>
<td>69.7 ± 7.5</td>
<td>66.7 ± 7.8</td>
<td>74.7 ± 3.6*</td>
</tr>
<tr>
<td>Male/Female</td>
<td>14/2</td>
<td>8/2</td>
<td>6/0</td>
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<tr>
<td>Associated heart disease</td>
<td>n = 7</td>
<td>MVR (n = 1)</td>
<td>IHD (n = 2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DCM (n = 3)</td>
<td>MR (n = 1)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>42 ± 13</td>
<td>51 ± 5</td>
<td>27 ± 9**</td>
</tr>
<tr>
<td>CO (l/min)</td>
<td>4.6 ± 1.9</td>
<td>5.3 ± 1.9</td>
<td>3.4 ± 0.8*</td>
</tr>
<tr>
<td>A fibrillation/A flutter</td>
<td>15/1</td>
<td>10/0</td>
<td>5/1</td>
</tr>
</tbody>
</table>

*p = p < 0.05; **p = p < 0.01. Comparisons are made between patients with LVEF ≥40% and LVEF <40%.

LVEF = left ventricular ejection fraction; CO = cardiac output; A = atrial; MVR = mitral valve replacement; IHD = ischemic heart disease; DCM = dilated cardiomyopathy; MR = mitral regurgitation.
LVEF produced the same results in the ten patients whose cardiac
LVEF and CO are shown in Figures 2 and 3, respectively.

With regard to symptoms, each patient retained their
initial NYHA functional status in both pacing configurations.

Global results concerning the effects of RVA and RVOT pacing on LVEF, CO, exercise time and peak oxygen consumption are shown in Table 2. Individual changes for LVEF and CO are shown in Figures 2 and 3, respectively. Considering the patient population as a whole, no significant differences in the various parameters were noted between the two pacing configurations. Subgroup analysis produced the same results in the ten patients whose cardiac function was normal or slightly impaired, as defined by an LVEF ≥40% before the crossover study. In the patients whose LVEF was <40% before the crossover study, there was no difference either in LVEF, CO, exercise time and peak oxygen consumption, regardless of the pacing site, either RVA or RVOT.

DISCUSSION

This study did not elicit any difference between chronic RVA pacing and RVOT pacing in terms of NYHA classification, LVEF, cardiac output, exercise time and peak oxygen consumption. Nonetheless, the effectiveness and safety of RVOT pacing at ten months were confirmed.

Hemodynamic effects of RVA pacing. The right ventricular apex remains the elective site for implanting permanent ventricular leads. However, by modifying the normal activation and contraction sequence, RVA pacing has been demonstrated to alter both systolic and diastolic cardiac function. In patients with normal intrinsic conduction and without structural heart disease, the effects of pacing on cardiac performance have been assessed by Rosenqvist et al. (4) and Leclercq et al. (5). In these studies atrial pacing produced a significant improvement in systolic left ventricular function as compared with atioventricular pacing at the optimal AV delay in each patient. This benefit was observed for global and regional LVEF by radionuclide angiography (4,5), and for hemodynamics both at rest and during exercise (5). The effects on diastolic function were studied by Bedotto et al. (15) who showed significant alteration during RVA pacing in patients with low LVEF.

In patients with severe left ventricular systolic dysfunction and without conventional indication for pacing, permanent short-AV delay DDD pacing with the ventricular lead placed at the right ventricular apex was proposed as an adjunctive treatment for advanced heart failure (16,17). The clinical value of this new therapeutic approach was not confirmed in a controlled study (6). There is, however, a strong presumption of short and long term efficacy in some subgroups of patients, in particular in patients with long PR interval in spontaneous sinus rhythm (18). The results of the acute hemodynamic study by Nishimura et al. (18) clearly show that a positive response from short AV delay DDD pacing resulted from optimization in left ventricular filling by correction for mechanical AV dyssynchrony in the left heart. At that time the general view was that the potential detrimental effects of ventricular pacing at the right ventricular apex on the left ventricular function were largely counterbalanced by the benefits of extended filling time (17) in that particular subgroup of responder patients. Further studies assessed the potential interest of improving both the

Table 2. Results for the Principal Analyzed Parameters

<table>
<thead>
<tr>
<th></th>
<th>RVA (n = 16)</th>
<th>RVA (n = 10)</th>
<th>RVOT (n = 10)</th>
<th>RVOT (n = 6)</th>
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<tbody>
<tr>
<td>LVEF (%)</td>
<td>40 ± 12</td>
<td>48 ± 7</td>
<td>30 ± 10</td>
<td>42 ± 12</td>
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<tr>
<td>CO (l/mn)</td>
<td>4.5 ± 2.1</td>
<td>5.2 ± 2.3</td>
<td>3.4 ± 0.9</td>
<td>4.4 ± 1.8</td>
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<td>ED (mn)</td>
<td>12.2 ± 4.4</td>
<td>13.6 ± 3.8</td>
<td>9.4 ± 4.5</td>
<td>12.6 ± 4.8</td>
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<tr>
<td>VO2 max</td>
<td>16.2 ± 3.8</td>
<td>17.2 ± 4.1</td>
<td>14.3 ± 2.6</td>
<td>16.2 ± 4.7</td>
</tr>
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RVA = right ventricular apex pacing; RVOT = right ventricular outflow tract pacing; LVEF = left ventricular ejection fraction; CO = cardiac output; ED = exercise duration; VO2 max = peak of oxygen consumption.

![Figure 2.](image-url) Individual patient evolution for LVEF.
Gold et al. (6) RVOT pacing was sited on the septal wall of those reported by Giudici et al. (7) where RVOT pacing the two pacing modes. These findings are consistent with configurations. Only the QRS axis was different between duration was not significantly different between the two during RVA pacing than during RVOT pacing, QRS although it was slightly greater His area pacing, in terms of safety for the patients. choice of other right ventricular alternative sites, for exam- ever, because the mechanical stresses imposed on the leads in RVOT position may be greater, a longer follow-up period will provide a better assessment of the very long-term reliability of that configuration. This also may limit the choice of other right ventricular alternative sites, for example His area pacing, in terms of safety for the patients.

QRS axis and duration. Although it was slightly greater during RVA pacing than during RVOT pacing, QRS duration was not significantly different between the two configurations. Only the QRS axis was different between the two pacing modes. These findings are consistent with those reported by Giudici et al. (7) where RVOT pacing was sited on the free wall of the RVOT. In the series of Gold et al. (6) RVOT pacing was sited on the septal wall of the RVOT and the mean paced QRS duration was 151 ± 44 msec. In that study, although RVOT pacing was not compared with RVA pacing, it was suggested that the exact position of RVOT leads influences the QRS duration. In the studies of Buckingham et al. (12), the QRS duration was identical in RVA and RVOT pacing. Only dual site synchronous pacing (i.e., simultaneous RVA and RVOT pacing), provided thinner QRS complexes (12).

The baseline LVEF did not influence that parameter in subgroup analysis. Four acute studies explored cardiac output during RVOT pacing with controversial results. In the series of Giudici et al. (7), RVOT pacing at the free wall was significantly better than RVA pacing in terms of cardiac output. That study was not randomized and it is not specified whether the physician who performed the tests was aware of the pacing mode. In any case, that study constituted the most comprehensive experiment in that field, involving 89 patients. De Cock et al. in a randomized blind acute study observed higher cardiac indexes during RVOT pacing than in RVA pacing at 85, 100 and 120 bpm in patients without structural heart disease (8). In contrast, in five out of eight patients with LVEF ≤50% or significant coronary artery disease, RVOT pacing at 120 bpm decreased cardiac index. Gold et al. compared cardiac output during RVOT DDD septal pacing in relation to intrinsic heart rate in patients whose LVEF was <30% (6). The randomized study design partially made up for the restricted number of patients. In addition, the tests were carried out without knowing the pacing mode used. In that study, no difference was noted between RVOT pacing and intrinsic heart rate. Buckingham’s study (12), which assessed cardiac output under RVA, RVOT and dual site (RVA + RVOT) pacing modes only elicited a trend in favor of simultaneous dual site right ventricular pacing.

All these studies were conducted acutely and mainly differed from ours because all patients had normal sinus rhythm or were placed in the atrium. Evaluation was conducted during ventricular asynchronous pacing (7,8), or during atrioventricular synchronous pacing with fixed (12) or variable AV delay (i.e., 100 ms to 175 ms) (6). Cowell et al. (23) noted the need for a shorter AV delay for septal
right ventricular DDD pacing to be optimal as compared with apical right ventricular DDD pacing. With this optimized programming, septal short AV delay VDD pacing provided higher cardiac output as compared with spontaneous rhythm and RVA VDD pacing.

In our study, all patients presented with chronic atrial tachyarrhythmia which rules out any potential influence of the atrial systole on cardiac output and the necessity for atrioventricular optimization depending on the ventricular pacing site. Our observations therefore only apply to a purely ventricular output and should be limited to these particular patients. Nonetheless, in the present series, changing the QRS axis implicating inverted ventricular contraction sequences without modification of the QRS width did not modify cardiac performance at rest and during exercise.

Limitations of the study. These results are to be interpreted in consideration of the small population of patients although, under the methods used, each patient was his or her own control. The pacing mode selection was randomized and the tests were conducted without knowing the programmed mode and in awareness of the results from the previous evaluation (RVA or RVOT). This small number of patients was, however, considered as relevant on the basis of a Spearman rank correlation test ($r'$ ranging from 0.75 to 0.91).

Conclusions. This study confirmed the reliability and safety of chronic RVOT pacing with screw-in leads, but no significant improvement in symptoms and exercise tolerance or hemodynamic benefit was noted after three months of permanent RVOT pacing, compared with RVA pacing in patients with chronic atrial tachyarrhythmia and complete heart block. The study did not bring about any fact to encourage changing the usual pacing site on the right ventricle. Finding alternative ventricular pacing sites or other configurations to optimize cardiac performance may therefore require further investigations.

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REFERENCES