Safety and feasibility of a novel rate-smoothed ventricular pacing algorithm for atrial fibrillation

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Objectives This study was conducted to establish the safety and performance of a new rate-smoothing pacing algorithm for patients with atrial fibrillation (AF).

Background Irregularity of the ventricular response is a hallmark of AF. This irregularity may contribute to symptoms and hemodynamic compromise in patients with AF. Interventions designed to reduce irregularity have not previously been evaluated in a long-term, clinical setting.

Methods We designed a prospective, double-blind study with randomized crossover. Patients with either paroxysmal or chronic AF whose conditions were medically refractory and who were referred for an atrioventricular node ablation procedure all underwent pacemaker implantation. Subjects were then randomly assigned to either DDD mode with the rate-smoothing algorithm (RSA) on, or to OOO mode. After 2 months they were crossed over to the other arm.

Results Fourteen patients (9 with paroxysmal AF and 5 with chronic AF) were enrolled. There were no significant differences between the group randomly assigned to RSA first versus the group assigned to OOO first. The mean left ventricular ejection fraction with the RSA was not significantly different than it was in OOO mode [45.1 ± 18.6 vs 51.9 ± 12.3; P = .11], although some individuals with uncontrolled ventricular rates did have a large decrease in ejection fraction with rate smoothing. One developed overt heart failure. One quality-of-life instrument detected a significant improvement in the “physical limitations” domain with the rate-smoothing mode. Eleven of 14 patients preferred the RSA ON arm, and 6 of those 11 elected to defer the ablation procedure.

Conclusions Long-term rate-smoothed pacing is feasible. Because of concerns about pacing-induced heart failure in some patients with rapid ventricular rates, rate-smoothed pacing should be reserved for those who remain symptomatic despite adequate control of the ventricular rate. The RSA may help to reduce symptoms in patients with medically refractory AF; more study is required to define its efficacy in reducing symptoms and morbidity in this population. [Am Heart J 2001; 142:294-300.]

Atrial fibrillation (AF) is characterized by a rapid, irregular ventricular response; symptoms are thought to primarily result from the rapidity of the ventricular rate and the hemodynamic consequences of the loss of the atrial kick. Long-term management of AF has traditionally been focused on the establishment of adequate ventricular rate control, the restoration of sinus rhythm, or both. Although the contribution of a rapid ventricular response to symptoms and hemodynamic deterioration is widely acknowledged, the relative role of the irregularity of the ventricular response is unknown. Few therapeutic interventions have been able to address the contribution of ventricular irregularity to symptoms and hemodynamic status. Atrioventricular node-blocking agents reduce ventricular response but appear to have minimal effects on irregularity. Catheter atrioventricular node–His bundle ablation with permanent pacemaker implantation accomplishes both goals, but the patient is permanently dependent on a pacemaker.

Previously we evaluated a new pacemaker-based algorithm that is capable of reducing ventricular irregularity in AF by using a novel “rate-smoothing” function.1 In the acute setting, rate-smoothed pacing effectively reduced R-R interval variability. In this pilot study, we sought to establish the short-term safety and performance of this algorithm. An additional secondary goal was to determine how a reduction in irregularity affects symptoms, quality of life, functional capacity, and ventricular function in patients with AF.
Methods

Rate-smoothing algorithm

The rate-smoothing algorithm (RSA) was created on the Vitatron Diamond pacemaker platform (DDDR, Vitatron, Dieren, The Netherlands). This dual-chamber rate-responsive pacemaker contains 2 features that were customized to derive the RSA: the physiologic band and the flywheel mode. The physiologic band is a symmetric window above and below the physiologic rate and is normally fixed at 15 beats/min. For the RSA, this value was decreased to 2.5 beats/min. Any sudden decrease in ventricular rate of greater than 2.5 beats/min would be interrupted by ventricular pacing at a rate equal to the physiologic band lower limit (Figure 1). The rate of pacing then gradually decreases or “flywheels” at 0.25 beats/min per beat toward the programmed lower rate limit. The flywheel mode feature determines the rate at which the rate of pacing decrements. The existence of the physiologic band and flywheel mode effectively prevents any abrupt decrease in heart rate.

The RSA minimizes sudden decreases in ventricular rate (increases in cycle length) or “pauses” that characterize the irregular ventricular response of AF. Rate smoothing (RS) does not use overdrive pacing in the conventional sense to suppress and regularize the ventricular response; rather, it makes calculations based on the immediately preceding R-R intervals and invokes dynamic pacing interventions designed to ease or blunt sudden reductions in rate.

Optimal functioning of the RSA requires that the implanted device be programmed to the DDD mode with mode switching activated.

Study design

This pilot study was prospective, double-blind, and used a randomized crossover design. The study protocol was approved by the University Research Ethics Board. Men and women older than 18 years were considered for enrollment in the study if they had drug-refractory paroxysmal or chronic AF sufficient to warrant consideration of an atrioventricular node–His ablation procedure with permanent pacemaker implantation. Enrolled subjects agreed to delay the ablation procedure for the duration of the study, with the possibility that significant symptom improvement might allow the ablation procedure to be deferred indefinitely. Baseline measurements included a 24-hour Holter monitor recording, a bicycle exercise stress test (EST) with myocardial oxygen consumption (MV02) measurements, a 2-dimensional echocardiogram with Doppler measurements, and a multiple gated acquisition blood pool scan (MUGA) study. In addition, subjects completed 2 quality-of-life questionnaires, the short form (SF) 36 and the Pacemaker Symptom Scale. Both of these questionnaires are validated quality-of-life measures. After data collection the pacemaker was implanted. A standard percutaneous subclavian vein approach was used. After a stabilization phase of 1 month, patients were randomly assigned to either DDD with mode switch and RS ON or to OOO mode. After 2 months, they were crossed over to the other arm of the study.

Analysis

Continuous variables were analyzed with standard t tests. Time, phase, and the carryover effect of the crossover design were accounted for in the analysis.

Results

Fourteen patients (9 with paroxysmal AF and 5 with chronic AF) were enrolled. The 12 men and 2 women (62.9 ± 8.5 years) all had drug-refractory symptoms; that is, all patients continued to be symptomatic despite the best medical therapy, or had significant drug intolerance necessitating drug discontinuation. Baseline characteristics are shown in Table I. There were no significant differences in sex, age, or type of AF (chronic or paroxysmal) between the group assigned to RS ON first versus those assigned to RS OFF first. All patients were taking rate-controlling agents, antiarrhythmic drugs, or both at baseline. Nine patients were taking digoxin, 5 were taking diltiazem, and 2 were taking amiodarone; verapamil, sotalol, and propafenone were taken by 1 patient each. None of the patients had any change in drug regimen during the study.

Ventricular response data were recorded at baseline, with RS ON and with RS OFF for all patients (Figure 2). The mean heart rates did not differ (88.6 ± 21.5 beats/min for RS ON vs 81.0 ± 15.4 beats/min for RS OFF; P = .4). Because of the large number of patients enrolled who had paroxysmal AF, almost half of the heart rate measurements were recorded when the subject was in normal sinus rhythm rather than AF. The heart rate range was slightly smaller with RS ON than with RS OFF (76.5 ± 21.0 beats/min vs 92.4 ± 37.8 beats/min) with a P value that did not quite reach statistical significance (P = .09).

No significant difference was found between the 2 groups in measures of left ventricular function. How-
ever, there was a reduction in left ventricular ejection fraction (LVEF) for many individual subjects with RS ON versus RS OFF (Figure 3). Overall, a strong trend toward reduction in left ventricular systolic function with RS ON was found (Figure 4). The mean LVEF was 45.1% ± 18.6% with RS ON versus 51.9% ± 12.3% with RS OFF ($P = .11$). Mean fractional shortening (left ventricle) was 0.309 ± 0.075 with the RS ON mode; it was 0.371 ± 0.121 with the RS OFF mode ($P = .07$).

Neither exercise time nor MVO$_2$ was significantly changed with RS ON versus RS OFF mode (Figure 5). Exercise time was $15.5 ± 7.7$ minutes with the RS ON mode and $14.7 ± 7.4$ minutes with the RS OFF mode (difference not significant); maximum VO$_2$ was $22.9 ± 6.9$ versus $21.9 ± 7.4$ (difference not significant).

Quality-of-life assessment was performed by evaluation with both the SF 36 and the Pacemaker Symptom Scale. The SF 36, a generic health scale that is used widely to assess general health, showed no significant differences on any of the 8 domains (Figure 6). However, the Pacemaker Symptom Scale (Figure 7) showed a significant difference between RS ON and RS OFF modes in the “physical limitations” domain. There were greater physical limitations with RS OFF compared with RS ON.

When asked at the end of the 5-month protocol which 2-month pacing period they preferred, 11 patients selected the RS ON arm, whereas only 3 selected the RS OFF arm. Six of those 11 were sufficiently satisfied that they deferred their ablation procedure. Four of the 6 remained well after 2 years with RS

### Table I. Baseline characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Chronic or paroxysmal AF</th>
<th>Drugs</th>
</tr>
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<tr>
<td>1</td>
<td>M</td>
<td>58</td>
<td>Chronic</td>
<td>Verapamil, digoxin, warfarin</td>
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<td>Paroxysomal</td>
<td>Diltiazem, aspirin</td>
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<tr>
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</table>

Mean heart rate (HR) and heart rate range at baseline, with DDDR plus RS ON and in OOO. There was a trend toward a greater heart rate range with OOO than with DDDR with RS ON ($P = .09$). RS ON pacing also resulted in a significant decrease in heart rate range compared with baseline ($P = .0003$).
ON. The remaining patients all proceeded to atrioventricular node–His bundle ablation.

Three patients developed congestive heart failure (CHF) during the study; all had a history of CHF. Two of the 3 episodes occurred during the RS ON phase. One patient (in the RS ON mode) developed frank CHF requiring hospitalization. This individual had a decrease in ejection fraction from 70% at baseline to less than 30% with the RS ON mode. It occurred early in the study, when the upper rate limit was set at 160 beats/min. This patient’s ejection fraction returned to normal after diuresis and cessation of pacing. (The upper rate limit was reduced to 120 beats/min for all subsequent patients.)

**Discussion**

This pilot study represents the first long-term evaluation of an intervention designed specifically to reduce the irregularity of the ventricular response in patients with AF. Ventricular irregularity has long been a well-recognized hallmark of AF, although the mechanism underlying the irregular and seemingly random ventricular response remains unclear. Concealed conduction within the atrioventricular node was first proposed in 1948 to explain the ventricular irregularity and remains the most popular explanation. Watanabe et al suggested that concealed conduction was related to decremental conduction rather than refactoriness. They postulated that the decreases in the upstroke velocity ($V_{max}$) of the atrioventricular node action potential secondary to decreases in calcium current could result in concealment within the N region of the atrioventricular node. However, Meijler et al argued that...
the basis for concealed conduction lies in the electrophysiological modulation of atrioventricular node propagation. Wittkampf et al. and Meijler and Wittkampf proposed that the ventricular response during atrial fibrillation is governed by junctional pacemaker automaticity rather than atrioventricular node conduction, although this hypothesis is the subject of considerable debate.

Management strategies for patients with AF have focused on attempts to restore and maintain sinus rhythm, or alternatively, to control the ventricular response to AF. There is no doubt that a rapid ventricular response contributes significantly to symptoms, but a significant minority of patients remains symptomatic despite an adequately controlled rate. Ventricular irregularity may contribute to symptoms as well as left ventricular dysfunction and the genesis of intracardiac thrombi. Daoud et al. reported that the cardiac output is lower with irregular ventricular pacing than with regular ventricular pacing at the same mean ventricular rate. This finding is supported by Clark et al., who demonstrated that RR interval irregularity, independent of rate, decreased cardiac output.

It is difficult to prove the relationship of symptoms and other adverse events to the irregularity of the ventricular response because it is difficult to isolate irregularity from the tachycardia, with the exception of the small proportion of AF patients who remain symptomatic despite a well-controlled ventricular response. Atrophicventricular node–blocking agents are usually effective in reducing heart rate but they do little to affect ventricular irregularity. Catheter atrioventricular node–His bundle ablation followed by permanent pacemaker implantation effectively deals with both problems. It is virtually impossible to determine what is most responsible for the observed improvement in ventricular function, functional capacity, and quality of life. More recently, catheter atrioventricular node modification has been advocated as an alternative to achieve control of the ventricular rate without the need for permanent pacing. This approach may be an alternative for those in whom usual pharmacologic measures do not control the ventricular response. However, it fails to address the issue of irregularity and in fact may actually increase irregularity of the ventricular response, as we have shown recently.

The observation that spontaneous premature ventricular contractions delayed or suppressed atrophicventricular node conduction of AF led to studies of the effects of various ventricular pacing techniques. Lau et al. showed that interpolated ventricular pacing beats introduced during AF at preset intervals effectively reduced the pulse rate with an apparent regularization of the rhythm. This was accompanied by increases in the systolic blood pressure with variable effects on the cardiac output. Jongste et al. examined fixed-rate ventricular pacing at progressively increasing pacing rates. As the pacing rate increased, an incrementally greater proportion of the long R-R intervals was eliminated simultaneously with a reduction in shorter cycle lengths. The net effect was a regularization of the R-R response with a minimal reduction in the mean rate. Jiang et al. used rate-adaptive pacing and demonstrated that pacing rates slightly above the mean intrinsic rate were necessary to suppress 95% of the intrinsic ventricular response to AF. At this pacing rate, shorter R-R intervals were inhibited but the effects was dependent on posture, and rate control was less effective during exercise owing to changes in the intrinsic rate.

Subsequently, more specialized pacing algorithms were developed. Wittkampf and Jongste developed the dynamic overdrive pacing algorithm in which the pacing cycle length was automatically incremented (by 10 ms) in response to every sensed intrinsic beat and decremented by 1 ms for every paced beat. Dynamic overdrive pacing effectively suppressed > 95% of intrinsic AF beats at a pacing cycle length slightly shorter than the mean AF R-R interval but longer than the shortest R-R interval. Greenhut et al. then described a ventricular rate stabilization (VRS) algorithm. R-R interval variability (normalized mean absolute difference over 8 consecutive R-R intervals) during AF is monitored continuously, and ventricular pacing intervenes if the variability exceeds a preprogrammed threshold value. This showed that a reduction in R-R interval variability could be achieved but the study design (acute effects only) precluded any measurement of symptom improvement.

The pacing algorithm in this study is unique in that it is not based on overdrive pacing. The pacing itself may lengthen and stabilize R-R intervals, but the narrow physiologic band and flywheel drop rate are designed to maintain the heart rate in a narrower range.

This study provides some insights into the relative contribution of ventricular irregularity to symptoms in patients with AF. The fact that 6 of 14 patients with drug-refractory symptoms deferred a previously planned atrioventricular node–His bundle ablation, opting instead to continue with the RS pacemaker, is an encouraging early result. Indeed, even after 2 years, 4 of those 6 remained well enough that they chose to continue without the ablation procedure.

There were, however, some concerns. The reduction in ejection fraction and fractional shortening with RS ON did not reach statistical significance, but a strong trend was found that may have become statistically significant if a greater number of patients had been enrolled. Two confounding factors may help to explain some of the difference seen between the RS ON and RS OFF study arms. First, nearly half of the patients were in sinus rhythm when these measurements were calculated, and comparisons of systolic function measures in AF with those during normal sinus rhythm create a potential for systematic error. Second, there...
may be an effect on systolic function measures as a result of altered septal motion during pacing. These possibilities notwithstanding, one of the patients in the RS ON study arm experienced a precipitous drop in ejection fraction coincident with a clinical episode of CHF requiring hospitalization. Although she had had ischemia-triggered CHF in the past, there was no evidence that ischemia had triggered this event. This, combined with the fact that the CHF resolved and ejection fraction returned to normal with cessation of pacing, suggests strongly a diagnosis of pacing-induced tachycardiomyopathy. It is well known that persistent elevations of heart rate during AF may lead to a tachycardia-induced reduction in systolic function.25 Even when no clinical episodes of CHF occur, AF may cause subtler, reversible left ventricular dysfunction.11 Pacing that results in a faster mean ventricular rate during AF may then be a major contributor to left ventricular function.

This particular patient and the 2 others who preferred the RS OFF arm of the study were all enrolled early in the study, when the upper rate limit in the algorithm was programmed to 160 beats/min. All 3 had less than optimal control of ventricular rates at baseline (mean ventricular rate > 100 beats/min at rest). After the patient with CHF was treated, we lowered the upper rate limit to 120 beats/min for all subsequent patients. No further instances of CHF were observed thereafter. We speculate that a combination of lowering the upper rate limit to 120 beats/min and selecting only symptomatic patients whose ventricular rates are already controlled (either pharmacologically or with an atrioventricular node modification procedure) contributed to increased safety of the algorithm.

Limitations

This was a small pilot study that examined the safety and feasibility of chronic rate-smoothed pacing for patients with both paroxysmal and chronic AF. For this reason, the efficacy of the RSA was not compared with other pacing modalities such as simple demand ventricular pacing. Such comparative trials are important to identify any benefit attributable to the algorithm alone and should be the basis of future studies. The small sample size is also too small to make any definitive statement regarding efficacy endpoints, such as ejection fraction and measures of functional capacity. Because of the large proportion of patients in the study with paroxysmal AF, some measurements were made during AF and others were made during sinus rhythm. This was not accounted for in the analysis.

Although all patients were on pharmacologic therapy in an attempt to control ventricular rate, maintain sinus rhythm, or both, some patients had inadequately controlled heart rates. It is not possible to exclude the possibility that medications may have contributed to some of the clinical results. However, all enrolled patients had a long history of unsatisfactory response to drugs, and it would be difficult to attribute much of the clinical response seen to drugs. Patients with ongoing symptoms despite adequate control of the ventricular response may derive more clinical benefit from RS ON, whereas patients with inadequate control at baseline may be more likely to develop problems related to pacemaker-related tachycardiomyopathy.

Conclusions

Long-term rate-smoothed pacing for patients with drug-refractory AF is feasible. Because rate-smoothed pacing in patients who have inadequately controlled ventricular responses may contribute to worsening heart failure, the pacing technique should perhaps be limited to patients who remain symptomatic despite adequate control of the ventricular rate. More studies will be required to determine the efficacy of this rate-stabilization technique for reducing morbidity and symptoms related to AF, but the early results from this pilot study are encouraging.

References

Clinical assessment of clonidine in the treatment of new-onset rapid atrial fibrillation: A prospective, randomized clinical trial

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Purpose The role of digoxin and verapamil in the control of ventricular response in rapid atrial fibrillation is well established. This study investigates how clonidine compares with these standard therapies in rate control for new-onset rapid atrial fibrillation. We set out to test the hypothesis that clonidine effectively reduces heart rate in patients with new-onset rapid atrial fibrillation.

Subjects and Methods Forty patients were seen in the emergency department with new-onset (<24 hours’ duration), stable, rapid atrial fibrillation. Eligible patients were randomized to receive either clonidine, digoxin, or verapamil. Changes in heart rate and blood pressure over 6 hours, as well as frequency of conversion to sinus rhythm were recorded and analyzed.

Results The mean reduction in heart rate over 6 hours was 44.4 beats/min (95% confidence interval [CI] 28.4-60.4 beats/min) in the clonidine group, 52.1 beats/min (95% CI 40.8-63.4 beats/min) in the digoxin group, and 41.8 beats/min (95% CI 22.5-61.0 beats/min) in the verapamil group. Analysis of variance of the heart rate changes in the 3 groups after 6 hours was not significant (P = .55). At 6 hours, 7 of 12 clonidine patients, 8 of 15 digoxin patients, and 7 of 13 verapamil patients remained in atrial fibrillation (P = .962 on c2).

Conclusion Clonidine controls ventricular rate in new-onset atrial fibrillation with an efficacy comparable to that of standard agents. (Am Heart J 2001;142:1406-8.)