Atrioventricular Node Modification in Patients With Chronic Atrial Fibrillation
Role of Morphology of RR Interval Variation

Stelios Rokas, MD; Styliani Gaitanidou, MD; Sofia Chatzidou, MD; Costas Pamboucas, MD; Dennis Achtipis, MD; Stamatios Stamatelopoulos, MD

Background—This study evaluates the role of RR interval distribution pattern as an outcome predictor of radiofrequency (RF) modification of atrioventricular (AV) node in chronic atrial fibrillation (AF) and attempts to elucidate the likely mechanism of rate control.

Methods and Results—Sixty-five patients with chronic AF underwent AV node modification. The RR interval distribution pattern was derived from 24-hour ECG recordings obtained before and after the procedure. The preablation pattern was bimodal (B) in 36 patients (55%) and unimodal (U) in 29 patients (45%). After the modification procedure, the B pattern shifted to U (78%) or became modified B (22%). The mean number of RF pulses delivered and the fluoroscopy time were n=8±5 and 24±11 minutes, respectively, in patients with B pattern versus n=18±7 and 45±17 minutes in patients with U pattern (P<0.001 for both). The location of successful ablation was posteroseptal and lower midseptal in 26 patients (81%) with B pattern versus 2 (13%) with U pattern (P<0.001). Mean and maximal ventricular rates and heart rate at peak exercise were reduced after the procedure in both groups (P<0.001 for all). Long-term success rate, AV block incidence, and pacemaker implantation rate were 89%, 0%, and 8%, respectively, in patients with B pattern versus 52% (P<0.001), 21% (P=0.006), and 48% (P<0.001) in patients with U pattern.

Conclusions—RF modification of the AV node is expected to be more effective, safe, and expeditious in patients with chronic AF and B RR interval distribution pattern. Posterior atrionodal input ablation may be the prevailing mechanism of rate control in these patients, whereas U-pattern patients may benefit from partial injury to the AV node. (Circulation. 2001;103:2942-2948.)

Key Words: catheter ablation □ atrioventricular node □ fibrillation □ intervals

Atrioventricular (AV) node modification has emerged as an effective means of rate control in symptomatic patients with chronic atrial fibrillation (AF) and rapid ventricular response despite pharmacological therapy.1-3 It has been suggested that ablation of the “slow pathway”4 or partial damage of the compact AV node5,6 might be the mechanisms that explain the benefit of this method. Because all patients in those studies had chronic AF, however, the underlying electrophysiological substrate of the AV node could not be evaluated by means of electrophysiological studies. In chronic AF, evidence is arising from RR interval analysis that a bimodal RR interval distribution pattern may indicate the presence of dual AV node physiology, whereas a unimodal pattern may be associated with orthodromic impulse propagation over the fast pathway alone.4,5 Therefore, we conducted a study to evaluate the possible role of the RR interval distribution pattern in the outcome of patients with chronic AF and rapid ventricular response who undergo radiofrequency (RF) modification of AV node conduction.

Methods
Symptomatic patients with chronic AF and uncontrolled ventricular rates who were referred for RF modification of AV node conduction were eligible to enter the study protocol provided that (1) all antiarrhythmic (AA) drugs, including amiodarone, has been proved ineffective in converting AF to sinus rhythm or in controlling ventricular rate; (2) electrical cardioversion had failed to restore sinus rhythm; and (3) the patients agreed to discontinue all the AA agents before the RF modification procedure for a period >5 half-lives. Amiodarone was discontinued ≥2 months before the patients entered the study. The following were criteria for exclusion from the study: (1) during the period of discontinuation of the AA treatment, the presence of (a) symptomatic bradyarrhythmia or pause >1.5 seconds, (b) arrhythmia-related symptoms during the 24-hour ambulatory ECG recording irrelevant to ventricular rate augmentation >100 bpm during the recording, or (c) severe symptoms at rest (eg, congestive heart failure) caused by tachyarrhythmia; (2) left ventricular function severely impaired (ejection fraction <0.40), angina pectoris, or recent myocardial infarction; and (3) abnormal thyroid function or severe systematic illness. In accordance with the Helsinki agreement, the study was subject to the local ethical committee, and all patients had given informed written consent.
Distribution Pattern of RR Intervals
The day before the RF modification procedure, a 24-hour ambulatory ECG recording was obtained from all patients under conditions of usual daily activities and while the patients were on no AA treatment. The data were recorded on tape. These analog data were stored in a computer, and the method of heart rate–stratified histogram was used for analysis of the distribution pattern of all 24-hour RR intervals during AF. The RR interval distribution pattern may be unimodal, bimodal, or multimodal. Bimodality is defined as the existence of 2 RR populations separated distinctly by a visually estimated intersection point, the value of which must be the same in ≥2 consecutive heart rate measurements. We have previously described the technique of analysis elsewhere.

RF Modification Protocol
All RF modification procedures were performed by the same operator, who was unaware of the patients’ RR interval distribution pattern. Induction of permanent AV block was not our intention in any case. Three quadripolar electrode catheters were introduced percutaneously and positioned in the right ventricular apex, His bundle region, and coronary sinus (CS). CS venography was performed with a multipurpose catheter to define the CS ostium. The sites of the His bundle catheter and the CS ostium were identified and recorded on cine film in the 30° right anterior oblique and 45° left anterior oblique projections before the delivery of RF energy. The ablation area from the His bundle region to the CS ostium was divided into 6 anatomic target regions (A 2 to P 1 ). Current generated by a 500-kHz RF energy source (Osypka 300S) was delivered between the distal 4-mm tip of a deflectable 7F catheter (EPT Steerocath-T, EP Technologies) and a left subscapular chest wall patch (7.25×1.5 in).

The same protocol of RF energy delivery was strictly followed in each patient, as follows: The ablation catheter was initially positioned in the most posterior region of the ablation area (P1), adjacent to the CS ostium. If the ablation attempts at this site were unsuccessful, the ablation catheter was gradually advanced anteriorly, toward sites P2, M1, M2, and A1. At each of those 5 sites, up to 5 RF pulses were delivered in a position slightly different from the previous one. If after the delivery of RF energy at a specific target region, transient reduction, either little or significant, of the ventricular rate occurred, 3 more RF pulses were delivered at this site before the catheter was moved to the next site. Power, impedance, and temperature were measured, displayed, and stored via an interface by use of a microprocessor. RF pulses were applied at a maximum of 50

<table>
<thead>
<tr>
<th>Results</th>
<th>Bimodal Pattern (n=36)</th>
<th>Unimodal Pattern (n=29)</th>
<th>All Patients (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term Success</td>
<td>34 (94)</td>
<td>17 (59)</td>
<td>51 (78)</td>
</tr>
<tr>
<td>Failure</td>
<td>2 (6)</td>
<td>7 (24)</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Inadvertent AV block</td>
<td>0 (0)</td>
<td>5 (17)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Intentional AV block</td>
<td>2 (6)</td>
<td>7 (24)</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Early events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>2 (6)</td>
<td>2 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Sudden death</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Syncope</td>
<td>0 (0)</td>
<td>1 (6)</td>
<td>NS</td>
</tr>
<tr>
<td>Long-term Success</td>
<td>32 (89)</td>
<td>15 (52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inadvertent AV block</td>
<td>0 (0)</td>
<td>6 (21)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Intentional AV block</td>
<td>3 (8)</td>
<td>8 (27)</td>
<td>0.019</td>
</tr>
<tr>
<td>Permanent pacemaker</td>
<td>3 (8)</td>
<td>14 (48)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are number (%) of patients.
W for 40 seconds to obtain a maximum distal tip temperature of 70°C. RF energy delivery was discontinued immediately in the case of impedance rise, catheter displacement, abrupt increase in RR interval, or occurrence of AV conduction block. The ablative procedure was considered successful when mean ventricular rate had been reduced by >20% and without exceeding the value of 130 bpm after administration of isoproterenol (2 μg/min). When this end point was not reached, the procedure was considered to have failed.

**Measurement of Ventricular Rate and Follow-Up**

Measurements of ventricular rate derived (1) from the whole 24-hour ECG recording in which the mean, maximal, and minimum heart rates were calculated or (2) from symptom-limited exercise treadmill testing at peak exercise. In all cases, these rates were measured in the absence of AA drug therapy both before and after the modification procedure.

After the procedure, the patients were admitted to the coronary care unit for 24 hours. Seven days after the procedure, a 24-hour ambulatory ECG recording was obtained under conditions of usual daily activities and was repeated after 3, 12, and 24 months during the follow-up period. An exercise stress test was carried out 3 months after the procedure. The follow-up period was not less than 8 months for any of the patients, and 60% of them were followed up for >2 years.

**Statistical Analysis**

Data are presented as mean±SD. Continuous and categorical variables were compared by Student’s t test and χ² test, respectively. Comparisons between the 2 groups, for various periods of follow-up, were made by 1-way ANOVA with Bonferroni transformation. Significance was set at *P*<0.05.

**Results**

During the period between June 1996 and November 1999, 65 of 133 patients with AF who underwent RF modification fulfilled the inclusion criteria for participation in this study. Forty patients were men and 25 were women, with a mean age of 63±8 years (range 40 to 75 years). The mean duration of symptoms was 4.1±2.9 years (range 3 months to 19 years). Before the ablation procedure, a mean of 3.7±1.6 AA drugs had been ineffective in converting AF to sinus rhythm or controlling ventricular rate. All patients had a left ventricular ejection fraction >0.50, except 13 patients whose left ventricular ejection fractions ranged from 0.40 to 0.49. The analysis of all 24-hour RR intervals showed that 36 patients (55%) had a bimodal pattern of RR interval distribution, and 29 patients (45%) presented a unimodal pattern. The baseline characteristics of the study population are summarized in Table 1.

**Ablation Results**

The ablation results are shown in Table 2. During the early follow-up period (within 3 months after the procedure), 2 patients from each group relapsed to rapid ventricular rates. Of those, 1 patient from each group responded adequately to a combination of AA medications (propranolol 40 mg BID and amiodarone 200 mg BID), whereas the other 2 patients (1 from each group) underwent AV junction ablation with subsequent pacemaker insertion. One patient with bimodal pattern died of sudden death on day 45 after the procedure. The autopsy findings were consistent with acute myocardial infarction. One patient with unimodal pattern experienced 2 episodes of near syncope 3 months after the procedure. The ECG revealed intermittent complete heart block.

In successful cases, the number of RF pulses ranged from 1 to 22 (mean 8.6±5.3) in patients with bimodal pattern and from 9 to 33 (mean 18.3±7.8) in patients with unimodal pattern (*P*<0.001), and the mean duration of fluoroscopy was 24.2±11.7 minutes (range 6 to 57 minutes) and 45±17.8 minutes (range 19 to 86 minutes), respectively (*P*<0.001). The location of successful ablation was posteroseptal and lower midseptal (P–Mₗ) in 26 patients (81%) with bimodal pattern versus 2 patients (13%) with unimodal pattern (*P*<0.001) and upper midseptal and anteroseptal (Mₘ–A₁) in 6 patients (19%) versus 13 patients (87%), respectively (*P*<0.001). The location of the target region where RF energy delivery resulted in high-degree AV block was midseptal in 3 and anteroseptal in another 3 patients.

**Ventricular Rate Control**

The mean and maximal ventricular rates derived from 24-hour ambulatory ECG recordings before the RF modification procedure and during the follow-up period in the 32 patients with bimodal pattern and in the 15 patients with unimodal pattern who had a successful outcome are shown in Figure 1. The baseline ventricular rate at peak exercise was 190±26 bpm in patients with bimodal pattern and 182±19 bpm in patients with unimodal pattern (*P*=NS). Three months after the procedure, the respective values were 150±13 and 142±12 bpm (*P*=0.058). The exercise duration was increased from 4.7±1.9 to 7.6±1.7 minutes in patients with bimodal pattern (*P*<0.001) and from 5.1±2.4 to 7.4±1.7 minutes in patients with unimodal pattern (*P*<0.001). All patients who underwent successful RF modification remained asymptomatic or minimally symptomatic, with no need for rate-limiting medications.
Patterns of Response to the Ablative Procedure

The distribution pattern of RR intervals was assessed at 7 days and at 3 months after the RF modification procedure in all patients who had a successful outcome. In 25 of the 32 patients (78%) with bimodal pattern, ablation resulted in elimination of the histogram lying to the left of the intersection point, which represents the RR population with short RR intervals. In other words, the bimodal pattern shifted to a unimodal one (Figure 2). In the remaining 7 patients (22%), ablation resulted in displacement of the intersection point to the right (Figure 3). In all patients with a unimodal preablation pattern, this pattern remained unimodal after the successful procedure. In the 2 patients with bimodal preablation pattern who relapsed to rapid ventricular rates after 12 and 35 days, a 24-hour ambulatory ECG recording was obtained immediately after the recurrence. It is remarkable that in both patients, the first 24-hour ECG recording obtained 7 days after the procedure (that is, before recurrence) exhibited a unimodal pattern, whereas the recording obtained after the recurrence displayed a bimodal pattern identical to the preablation pattern (Figure 4).

Discussion

Previous studies reported that adequate slowing of the ventricular rate can be achieved by posteroseptal RF ablation in \(~70\%\) of patients with chronic AF.\(^1\)\(^2\) The ablation results cannot be predicted, however, and \(~25\%\) of the patients receive a permanent pacemaker because of inadvertent AV block.\(^3\)\(^8\) The results of our study are comparable to those reported in the aforementioned studies. Indeed, in all 65 patients studied, the overall long-term success rate was 72%, and 26% of them received a permanent pacemaker. When the preablation RR interval distribution pattern is taken into consideration, however, the results of the AV node modification demonstrate several statistically significant differences. In patients presenting a bimodal preablation pattern, the short-term success rate of AV node modification reaches a value of 94%, with no occurrence of procedural AV block. Conversely, only half of the patients with a unimodal pattern had a successful outcome, whereas the other half received a permanent pacemaker because of inadvertent AV block or failure of the procedure. It is also remarkable that in patients presenting a bimodal pattern, successful AV node modification was achieved with smaller numbers of ablative attempts and
shorter fluoroscopy time, and the location of successful RF energy delivery was the posterior and midseptal region of the tricuspid annulus. By contrast, in patients presenting a unimodal pattern, almost twice as many RF pulses and double the fluoroscopy time were necessary, and the target area of successful RF energy delivery was more anterior. These findings suggest that AV node modification, when applied in patients with chronic AF and bimodal distribution pattern, is more likely to be achieved successfully and safely by posteroseptal and midseptal ablation, whereas in patients presenting a unimodal pattern, a more aggressive and strenuous procedure is needed for adequate rate control, with a high risk of AV block.

The present study demonstrated that in 69% of the patients with a bimodal preablation pattern, the population with a short RR interval was almost eliminated (transition to unimodal pattern) after a successful AV node modification. This finding might be consistent with elimination of the posterior AV nodal input. In 25% of the patients with bimodal preablation pattern who had a successful AV node modification, the postablation pattern remained bimodal, but the point of intersection of the 2 RR populations was displaced to the right. The resultant new population of short RR intervals consisted of cycle lengths “less short” than the preablation ones. Moreover, it is apparent that the preablation population of short RR intervals has been almost eliminated (Figure 3). This modified bimodal pattern may represent either a partial injury of the slow AV nodal input, a nonspecific damage of the compact AV node, or a combined modification of both posterior and anterior atrionodal inputs.

The findings of this study strengthen the notion that the arising morphology of RR interval histograms reflects the electrophysiological properties of a specific anatomic or functional substrate as well as the alterations that this substrate undergoes after the delivery of RF energy. This concept is further supported by the fact that in the 2 patients with relapse to rapid ventricular rates in whom a shift from bimodality to unimodality was noted after the successful RF modification, the bimodal pattern reappeared after the recurrence, with exactly the same characteristics as those of the preablation pattern (Figure 4). Therefore, it is reasonable to presume that the bimodality in the RR interval distribution pattern is associated with rapid...
Figure 4. Bimodal preablation RR interval histogram of patient who relapsed to rapid ventricular rates (top). After ablation procedure, a shift from bimodality to unimodality was noted, and population of short RR intervals was almost eliminated (middle). After recurrence of rapid ventricular response, population with short RR interval reappeared, and distribution pattern became bimodal (bottom).
ventricular response to AF and that the elimination of the population with short RR interval results in ventricular rate control.

The issue that arises is to identify the mechanism by which rate control was achieved in half of the patients in whom dual AV node physiology is lacking. Chen et al. attributed the postablation reduction of ventricular response to paroxysmal AF in patients without dual AV node physiology to the likely presence of a posterior atriodinal input with conduction properties almost similar to those of the anterior input, whereas Krahm et al. suggested that half of these patients might benefit by nonspecific injury to the compact AV node. In the latter case, the ablation procedure must be more aggressive and is associated with a higher risk of AV block.

Rate Control
Our data displayed a trend for preservation of the degree of maximal heart rate reduction throughout the follow-up period in patients with a unimodal pattern compared with those presenting a bimodal one. This consistency observed in the unimodal-pattern patients may be attributed to partial injury to the anterior atriodinal input, which is characterized by a low safety factor of conduction and a long refractory period. This notion is also supported by the fact that the extent of reduction in ventricular response during induced AF in patients with AV nodal reentrant tachycardia who underwent slow-pathway ablation depends on the functional properties of the anterior atriodinal input.

Clinical Implications
The resultant differences in parameters such as success rate, AV block incidence, number of RF pulses delivered, fluoroscopy time, and location of successful ablation site may reflect different patterns of response to AV node modification, depending on the morphology of RR interval variation. Therefore, patients with chronic AF and rapid ventricular response who present a bimodal preablation pattern of RR interval distribution may be more suitable candidates for RF modification of the AV node. By contrast, patients with a unimodal pattern may be rather inappropriate candidates and should be referred primarily for AV junction ablation and pacemaker implantation.

Limitations
Despite the detailed delineation of the AV junction and the division of the ablation area into 6 anatomic target regions, the accurate anatomic site of the compact portion of the AV node is not strictly confined in space. Therefore, in patients with bimal AF and rapid ventricular response who present a bimodal preablation pattern of RR interval distribution may be more suitable candidates for RF modification of the AV node. By contrast, patients with a unimodal pattern may be rather inappropriate candidates and should be referred primarily for AV junction ablation and pacemaker implantation.

Although we acknowledge the limitations of this study, we believe that the weight of our evidence indicates that RF modification of the AV node can be used safely and effectively in patients with chronic AF in whom the preablation RR interval distribution pattern is bimodal. In addition, our data suggest that in patients with bimodal pattern, the prevailing mechanism of rate control after AV node modification may be the posterior atriodinal input ablation, whereas patients presenting a unimodal pattern may benefit from partial injury to the AV node.

References
Atrioventricular Node Modification in Patients With Chronic Atrial Fibrillation: Role of Morphology of RR Interval Variation

Stelios Rokas, Styliani Gaitanidou, Sofia Chatzidou, Costas Pamboucas, Dennis Achtipis and Stamatios Stamatelopoulos

_Circulation_. 2001;103:2942-2948
doi: 10.1161/01.CIR.103.24.2942

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/103/24/2942

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/