Ventricular Rate Control by Selective Vagal Stimulation Is Superior to Rhythm Regularization by Atrioventricular Nodal Ablation and Pacing During Atrial Fibrillation

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Background—Selective atrioventricular nodal (AVN) vagal stimulation (AVN-VS) has emerged as a novel strategy for ventricular rate (VR) control in atrial fibrillation (AF). Although AVN-VS preserves the physiological ventricular activation sequence, the resulting rate is slow but irregular. In contrast, AVN ablation with pacemaker implantation produces retrograde activation (starting at the apex), with regular ventricular rhythm. We tested the hypothesis that, at comparable levels of VR slowing, AVN-VS provides hemodynamic benefits similar to those of ablation with pacemaker implantation.

Methods and Results—AVN-VS was delivered to the epicardial fat pad that projects parasympathetic nerve fibers to the AVN in 12 dogs during AF. A computer-controlled algorithm adjusted AVN-VS beat by beat to achieve a mean ventricular RR interval of 75%, 100%, 125%, or 150% of spontaneous sinus cycle length. The AVN was then ablated, and the right ventricular (RV) apex was paced either irregularly (i-RVP) using the RR intervals collected during AVN-VS or regularly (r-RVP) at the corresponding mean RR. The results indicated that all 3 strategies improved hemodynamics compared with AF. However, AVN-VS resulted in significantly better responses than either r-RVP or i-RVP. i-RVP resulted in worse hemodynamic responses than r-RVP. The differences among these modes became less significant when mean VR was slowed to 150% of sinus cycle length.

Conclusions—AVN-VS can produce graded slowing of the VR during AF without destroying the AVN. It was hemodynamically superior to AVN ablation with either r-RVP or i-RVP, indicating that the benefits of preserving the physiological antegrade ventricular activation sequence outweigh the detrimental effect of irregularity. (Circulation. 2002;106:1853-1858.)

Key Words: fibrillation ■ atrioventricular node ■ vagus nerve ■ ablation ■ hemodynamics

Despite recent advances in treatment of atrial fibrillation (AF), ventricular rate (VR) control remains the only realistic long-term solution in a majority of patients with AF.1,2 Clinically, several options are available to control VR, including drug therapy, atrioventricular nodal (AVN) modification, and AVN ablation with pacemaker implantation.2,3 However, drug therapy is not effective in some patients and not well tolerated in others because of side effects. AVN modification, because of its limited success rate, high recurrence, and higher probability of complete AVN block, is recommended only when AVN ablation with pacemaker implantation is intended.3 Currently, AVN ablation with pacemaker implantation is the last choice for patients with drug-resistant AF. This strategy destroys the AVN and results in permanent pacemaker dependency. At the same time, it has the advantage of eliminating tachycardia and heart rate irregularity associated with AF.4,5

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Recently, selective AVN vagal stimulation (AVN-VS) has emerged as a novel strategy for control of the VR during AF.6–8 Our previous studies have demonstrated that AVN-VS could be used to achieve desired predetermined VR slowing.7 Despite the persistence of an irregular VR, hemodynamics were remarkably improved by AVN-VS compared with rapid AF. This method has the advantage of “saving” the AVN and results in a more physiological antegrade activation of the ventricles, in contrast to AVN ablation with subsequent retrograde right ventricular (RV) pacing.9

VR slowing achieved by AVN-VS or by AVN ablation with pacing have advantages and drawbacks. Both irregular-

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ity of the heart rate (as in the case of VR slowing by AVN-VS) and an unphysiological retrograde electrical activation pattern of the ventricles (as in the case of AVN ablation with RV pacing) diminish cardiac function. However, it is not known which of these strategies have a greater advantage in terms of improving hemodynamics. Because hemodynamics is heart rate–dependent, it would be desirable to compare these strategies at several comparable levels of VR slowing during AF. Accordingly, in this study, we tested the hypothesis that at different comparable levels of VR slowing during AF, AVN-VS with a normal antegrade ventricular activation sequence is no more deleterious than AVN ablation with RV pacing. In addition, we also evaluated the detrimental effect of heart rate irregularity on hemodynamics at different VR levels by comparing regular RV pacing with irregular RV pacing.

Methods
This study was approved by the Institutional Animal Research Committee and is in compliance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health.

Surgical Preparation
The experiments were performed on 12 adult mongrel dogs (body weight 21 to 30 kg), instrumented as previously described. Briefly, dogs were premedicated with thiopental sodium (20 mg/kg IV), intubated, and ventilated with room air supplemented with oxygen and 1% to 2% isoflurane (Narkomed 2; North American Drager). Micromanometer catheters (Millar, Inc) were used to record aortic and left ventricular (LV) pressures. Custom-made pacing electrodes were sutured to the right atrium, the RV apex, and the epicardial fat pad that contains parasympathetic neural pathways selectively innervating the AVN. An aortic flow probe (A-series probes 16A or 20A) was placed around the ascending aorta and connected to a flowmeter (HT 207, Transonic System Inc). All signals were amplified, filtered, and displayed (GE Medical Systems, Prucka-Cardiolab EP System). In addition, they were recorded on magnetic tape (4000A Vetter Digital) for later computer analysis.

Delivery of Selective AVN-VS
As previously reported, AVN-VS was delivered to the inferior vena cava–left atrium fat pad by a computer-controlled feedback program to achieve different levels of VR slowing. The program was centered on an existing Microstar Laboratories command (PID1) that implemented a classic, proportional-integral-derivative, closed-loop process control.

AVN Ablation
Radiofrequency ablation of the AVN was performed with a standard 7F catheter that was positioned across the tricuspid valve annulus to record activation of the His bundle under fluoroscopy (Philips BV Pulsera). The temperature setting on the radiofrequency generator (Medtronic, Atakr) was 70°C. The end point was creation of complete AV block.

Echocardiographic Measurements
Epicardial echocardiography was performed with commercially available equipment (Sequoia model C512, Acuson) with a 3.5-MHz phased-array transducer. We calculated a single-plane LV ejection fraction (EF) from a 4-chamber view by Simpson’s method.

Study Protocol
The experiments consisted of 4 steps. In the first step, after surgical preparation and at least 30 minutes of stabilization, the sinus cycle length (SCL) was determined. Then AF was induced by rapid right atrial pacing (20 Hz, 2 ms) and baseline data—surface ECG, right atrial and ventricular electrogams, aortic pressure, LV pressure, and aortic flow—were collected. In the second step, while the AF was maintained, the feedback program was initiated to deliver the AVN-VS and to slow VR to 4 target levels: 75%, 100%, 125%, and 150% of the SCL. The RR intervals observed during each episode were saved for subsequent use. In the third step, after AVN ablation and while the AF was still maintained, the RV was paced at an irregular rate (i-RVP) using RR intervals collected during each of the 4 episodes in the second step. Finally, in the fourth step, a regular pacing was used (r-RVP), with the corresponding average RR interval for each episode.

The order of multiple episodes in each step was randomized, and at least 500 cardiac cycles were collected per episode.

Data Acquisition and Analysis
The tape-recorded data were played back offline and digitized at 1 kHz per channel (AxoScope, Axon Instruments). For each of the 3 steps of the protocol, 500 RR intervals, systolic and diastolic blood pressures, LV systolic and end-diastolic pressures (LVSP and LVEDP), and stroke volume (SV) were calculated beat by beat and averaged by a custom-written software. The dP/dT was derived from LV pressure, and cardiac output (CO) was calculated by multiplying the heart rate by the stroke volume (the CO determined in this manner represented the total LV outflow reduced by the coronary flow).

The time constant of pressure decay (τ) was determined by nonlinear regression: \( P(t) = (P_0 - P_s) e^{-t/\tau} + P_s \), where \( P_0 \) is the pressure decay asymptote, \( P_s \) is the pressure at \(-dP/dT\), \( t \) is time referenced to time of peak \(-dP/dT\), occurrence, and \( \tau \) is the time constant of relaxation.

Statistical Analysis
Data are presented as mean±SEM. Hemodynamic differences between 3 strategies (AVN-VS, r-RVP, and i-RVP) at 4 levels of heart rate were compared globally by ANOVA with contrasts that evaluate potential carryover effects introduced by using the same individual dogs for different strategies and levels of heart rate. If the difference among the strategies was not consistent over the levels of heart rate, comparisons of the strategies were then made at each level.

The hemodynamic difference during AF was compared with each strategy at 4 levels of heart rate by ANOVA.

Comparison among the 3 strategies was also made at each level of heart rate by ANOVA, and differences were determined by use of contrasts. Bonferroni correction for multiple comparisons was used to adjust the significance levels for the difference between strategies. Logarithmic transformation was used to normalize data before analysis where appropriate. The analysis was done with the statistical package SAS. Unless otherwise specified, all statistical tests were 2-sided and had a significance level of \( P=0.05 \).

Results
VR During AF and VR Levels of Slowing Achieved by AVN-VS
AF produced rapid and irregular ventricular responses that resulted in an average VR substantially faster than the spontaneous sinus rhythm. (The SCL was 495±20 ms. The average RR during AF was 291±38 ms, or 59% of the SCL, \( n=12 \).) In 3 of the 12 dogs, however, the average RR intervals during AF were longer than the target 75% SCL. In 1 dog, a target 125% SCL, and in 2 other dogs, a target 150% SCL were not achievable at the maximal available intensity of AVN-VS. Therefore, there were 9, 12, 11, and 10 dogs in the groups, with slowing of the VR to targets of 75%, 100%, 125%, and 150% SCL, respectively. The achieved VR levels were very close to the target values (achieved 78%, 101%, 123%, and 148% SCL, respectively).
Hemodynamic Responses During AF, AVN-VS, r-RVP, and i-RVP

Figure 1 shows representative electrical and hemodynamic traces during AF (A), VR slowing at 100% SCL achieved by AVN-VS (B), i-RVP delivered using the same RR intervals as collected in the previous step (C), and r-RVP using the average RR interval value (D). AF resulted in a rapid irregular VR, and characteristically, many beats occurring with short coupling intervals were not followed by aortic flow because of insufficient LV pressure (A, asterisks). Such beats were previously called "aborted beats," and they constituted up to 40% of the total number of electrical depolarizations. AVN-VS decreased the VR and dramatically reduced the number of aborted beats (B, asterisks). Note also that VR slowing with AVN-VS preserves the normal antegrade ventricular activation sequence, evidenced by a narrow QRS on the surface ECG in C and D. ECG indicates standard surface ECG lead II; RA, right atrial electrogram; RV, RV electrogram; AoP, aortic blood pressure; LVP, left ventricular pressure; and AoF, aortic flow.

Hemodynamic Comparison of AF, AVN-VS, r-RVP, and i-RVP at 4 Different VR Levels

The composite hemodynamic data during AF, AVN-VS, r-RVP, and i-RVP are shown in Figure 2. Differences in hemodynamic responses between different strategies were compared separately at each of the 4 VR levels. A significance level of $P<0.05$ is indicated with the symbol $\alpha$ for the comparison AVN-VS versus r-RVP, $\beta$ for AVN-VS versus i-RVP, and $\gamma$ for r-RVP versus i-RVP.

At the 75% SCL level, AVN-VS produced better CO, SV, systolic blood pressure, diastolic blood pressure, and $+\frac{dP}{dt}$ than r-RVP and i-RVP. In addition, it resulted in better LVSP, LVEDP, and $-\frac{dP}{dt}$ than r-RVP. At the 100% SCL level, AVN-VS performance was significantly superior to both r-RVP and i-RVP for all parameters (for LVSP with r-RVP and EF with i-RVP, the tendency did not reach the statistical threshold of $P=0.05$).

With further slowing of VR, the hemodynamically superior position of the AVN-VS mode remained, although the differences among the 3 strategies became less pronounced. At the 125% SCL level, AVN-VS produced better outcomes in 4 parameters than r-RVP and in 6 parameters than i-RVP. Finally, at the 150% SCL level, AVN-VS was better than r-RVP only in 2 parameters and better than i-RVP in 4 parameters.
Interestingly, the regularization of the VR did not result in marked hemodynamic improvement. Although r-RVP in general resulted in better measured values than i-RVP, statistically significant differences were documented for only 2 parameters at 75% SCL (≥dp/dT) and 100% SCL (LVEDP and −dp/dT) and for 1 parameter at 125% SCL (τ). There was no difference between r-RVP and i-RVP at the 150% SCL level. The gradual decrease of differences among the 3 strategies with slowing of the VR suggested that the relative role of the ventricular activation sequence and irregularity on hemodynamics was heart rate dependent.

An overall global comparison is illustrated in Figure 3. Each experimental strategy is illustrated with its symbol as in Figure 2, and the symbols are placed from top to bottom in 4 rows in diminishing order of a strategy’s hemodynamic performance. Individual ANOVA that compared AF (⊙) with AVN- VS (□), r-RVP, (△) and i-RVP (●) indicated that all 3 latter strategies produced significant (P<0.05) improvement versus AF in SV, systolic blood pressure, LVSP, LVEDP, +dp/dT, and −dp/dT (Figure 3, B, C, and E–H). Both AVN- VS and r-RVP improved CO and τ (A, I). AVN- VS also improved diastolic blood pressure (D).

When the 3 strategies were compared with each other by use of ANOVA that evaluates carryover effects across 4 levels of heart rate, AVN- VS yielded better hemodynamic responses for CO, SV, systolic blood pressure, diastolic blood pressure, LVSP, LVEDP, +dp/dT, −dp/dT, τ, and EF versus both r-RVP and i-RVP (Figure 3, A–J). Compared with i-RVP, r-RVP was associated with better improvements in diastolic blood pressure, LVEDP, +dp/dT, −dp/dT, τ, and EF (D, F–J).

Discussion

Major Findings

This study demonstrates that VR slowing by both AVN- VS and AVN ablation with pacing improves hemodynamics during AF. The fact that VR control by AVN- VS resulted in better hemodynamic responses than by AVN ablation with RV pacing suggests that the benefits of keeping the normal physiological antegrade ventricular activation sequence outweigh the detrimental effect of irregularity associated with AVN- VS. The relative roles of irregularity and ventricular activation sequence on hemodynamics are VR dependent and diminish when VR is progressively slowed.

Rate Control Versus Rhythm Regularity in AF

It has long been argued which strategy, rate control or rhythm regularization, is preferable for treatment of AF. Clinically, rate control depends on drugs known to depress the AVN propagation (such as β-blockers, calcium channel blockers, and digoxin). The ultimate goal of the rhythm regularization is to restore the normal sinus function by medications and/or cardioversion. Two recent clinical trials, AFFIRM and RACE, concluded that rate control is at least as good as rhythm regularization for patients with persistent AF. Similar results were previously reported in the PIAF study. These studies did not evaluate the relative role of the rate irregularity. Moreover, it remains unknown how important the value of the mean VR is. Nevertheless, the above-mentioned trials established that pursuing an optimal slowing of the VR while preserving the AVN and thus the normal anterograde sequence of ventricular activation is a viable clinical strategy.

A number of smaller clinical studies compared the hemodynamic outcomes of medication-slowed VR with AVN ablation and regular (retrograde) ventricular pacing. Although some authors felt that AVN ablation produced better results, another reported that rhythm regularization did not confer any superiority. It is generally accepted that the hemodynamic response of a regularly paced ventricle is better than that of an irregularly paced ventricle, but no comparison is available with irregular but anterograde slower rates during AF.

Our study addressed the above-mentioned shortcomings and was designed to evaluate several predetermined levels of slowing of the VR while preserving the normal anterograde sequence of activation. This was achieved by the use of selective AVN- VS that was computer-controlled on a beat-by-beat basis. Moreover, we were able to compare the hemodynamic outcome of this strategy with retrograde ventricular pacing at precisely the same levels of irregular rate or regular rhythm.

AVN- VS as a Novel Approach for VR Control During AF

Currently, the only option for VR control in drug-refractory patients is AVN ablation with implantation of a pacemaker. Although AVN modification remains an alternative, it is usually recommended only when ablation is intended. AVN ablation with RV pacing has been shown to be beneficial in improving symptoms, quality of life, and exercise duration in patients with AF. However, because of lifelong pacemaker dependency, alternative approaches are desired for these drug-refractory AF patients.

The selective AVN- VS takes advantage of the rich supply of vagal nerves in the AVN, which exert negative dromotropic effects. There are several approaches to implement this strategy. The epicardial fat pad approach is the most direct. The endocardial approach, because of its instability or requirement of...
higher energy, 8,24–26 appears less suitable for long-term usage at the present time.

We have demonstrated in our previous studies that AVN-VS through the epicardial fat pad approach is highly effective in slowing the VR during AF. 6,7 By titration of stimulation intensity, we could achieve graded VR slowing, which allowed us to obtain the best hemodynamic response. We found that slowing the VR to the spontaneous sinus rate level has the best overall hemodynamic benefit. 7 Although further slowing improved the average SV, LVSP, and EF (Figure 2), the CO declined because of the substantial reduction of the number of beats per minute when VR was slowed to 150% SCL.

AVN-VS Versus AVN Ablation

RV apical pacing may cause abnormal contraction patterns and a negative inotropic effect that compromise cardiac efficiency. 27–29 Sustained RV pacing has been associated with structural and histological changes in the myocardium that may cause deterioration of ventricular function. 15,30–32 Several reports confirmed the adverse effects of RV pacing on cardiac function in humans. 13,14,33 Despite these adverse effects of RV pacing, several studies 4,5,21,23 have demonstrated that AVN ablation with pacing has a positive impact on LV function and quality of life in patients with chronic AF. His-bundle pacing, which preserves normal ventricular depolarization, has been attempted as an alternative cardiac pacing approach. 24 However, because of technical difficulties, its application is limited. 34 VR slowing by AVN-VS preserves the normal ventricular activation pattern. The results of this study clearly demonstrated that this strategy, although associated with an irregular rate, has better hemodynamic response than AVN ablation with RV pacing. This study also demonstrated that the detrimental effects of irregularity and abnormal ventricular activation sequence are heart rate dependent and that their role would diminish with progressive VR slowing. This is an important finding, because it stresses again the dominant role of rate control as a leading mechanism responsible for the improved hemodynamics in AF achieved by either AVN-VS or AVN ablation. 35

Implications of the Reported Findings and Study Limitations

This and previous studies 6,7 have demonstrated that AVN-VS can provide adequate VR control during AF in dogs. Because humans have similar vagal innervation, and the dromotropic effect of vagal nerve stimulation on AVN has already been demonstrated clinically, 26 we believe that this novel strategy might be applicable in some patients, eg, postoperative patients with AF.

In view of the increased evidence that rate control may be as good as rhythm regularization for patients with persistent AF, 20 this study evaluated AVN-VS as a novel approach for rate control that might carry additional hemodynamic benefits compared with AVN ablation.

Certain limitations should be considered in our experiments. First, although the order of data collection was randomized, the data sets with AVN-VS were always collected before ablation. This limitation could not be overcome because of the destructive nature of the ablation. Second, because these studies were performed in anesthetized dogs, further experiments are needed to elucidate the chronic effects in conscious dogs at rest and during exercise. Third, a comparison of the AVN-VS with biventricular pacing during AF may permit better elucidation of superior strategy. Finally, although AVN-VS showed hemodynamic superiority, we could not evaluate potential discomfort symptoms (such as palpitation, dyspnea, etc) despite adequate rate control. This issue could only be addressed in patients.

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