Chronic Atrioventricular Nodal Vagal Stimulation: First Evidence for Long-Term Ventricular Rate Control in Canine Atrial Fibrillation Model

Youhua Zhang, Hirotsugu Yamada, Steve Bibevski, Shaowei Zhuang, Kent A. Mowrey, Don W. Wallick, Seil Oh and Todor N. Mazgalev

Circulation 2005;112;2904-2911; originally published online Oct 31, 2005;
DOI: 10.1161/CIRCULATIONAHA.105.568832
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Chronic Atrioventricular Nodal Vagal Stimulation

First Evidence for Long-Term Ventricular Rate Control in Canine Atrial Fibrillation Model

Youhua Zhang, MD, PhD; Hirotsugu Yamada, MD, PhD; Steve Bibevski, MD, PhD; Shaowei Zhuang, MD; Kent A. Mowrey, MS; Don W. Wallick, PhD; Seil Oh, MD, PhD; Todor N. Mazgalev, PhD

Background—We have previously demonstrated that selective atrioventricular nodal (AVN) vagal stimulation (AVN-VS) can be used to control ventricular rate during atrial fibrillation (AF) in acute experiments. However, it is not known whether this approach could provide a long-term treatment in conscious animals. Thus, this study reports the first observations on the long-term efficacy and safety of this novel approach to control ventricular rate during AF in chronically instrumented dogs.

Methods and Results—In 18 dogs, custom-made bipolar patch electrodes were sutured to the epicardial AVN fat pad for delivery of selective AVN-VS by a subcutaneously implanted nerve stimulator (pulse width 100 μs or 1 ms, frequency 20 or 160 Hz, amplitude 6 to 10 V). Fast-rate right atrial pacing (600 bpm) was used to induce and maintain AF. ECG, blood pressure, and body temperature were monitored telemetrically. One week after the induction of AF, AVN-VS was delivered and maintained for at least 5 weeks. It was found that AVN-VS had a consistent effect on ventricular rate slowing (on average 45±13 bpm) over the entire period of observation. Echocardiography showed improvement of cardiac indices with ventricular rate slowing. AVN-VS was well tolerated by the animals, causing no signs of distress or discomfort.

Conclusions—Beneficial long-term ventricular rate slowing during AF can be achieved by implantation of a nerve stimulator attached to the epicardial AVN fat pad. This novel concept is an attractive alternative to other methods of rate control and may be applicable in a selected group of patients. **(*Circulation*. 2005;112:2904-2911.)**

Key Words: atrioventricular node ■ fibrillation ■ heart rate ■ hemodynamics ■ vagus nerve

Atrial fibrillation (AF) is recognized as the most common clinically significant cardiac arrhythmia. Current data estimated that 2.3 million Americans have AF.[1,2] Because the prevalence of AF increases with age[1,2] and because of the aging population, the number of AF patients is estimated to increase 2.5-fold during the next 50 years.[1]

Currently, there are 2 broad strategic treatment options for AF: rhythm control and rate control. Although rhythm control (restoring and maintaining the sinus rate) is thought to be ideal, it cannot be achieved or maintained in a large number of patients, rendering rate control (controlling ventricular rate while AF continues) the only realistic long-term solution in a majority of patients.[3,4] Recent clinical trials (AFFIRM and RACE)[5,6] demonstrated that rate control is at least as good as rhythm control for most patients with AF. Thus, rate control can be considered a "primary approach" in treating these AF patients.[7,8]

The strategy of rate control during AF essentially deals with efforts to utilize and adjust the filtering properties of the atrioventricular node (AVN)[9] because the AVN is the only normal structure responsible for the conduction of atrial impulses to the ventricles. Drug therapy (calcium channel antagonists, β-blockers, and digitalis) is the most common approach in rate control. However, drug therapy is not effective in some patients and may not be well tolerated in others because of side effects. AVN modification can be used to control the ventricular rate. Because of the limited success rate and high probability of complete AV block, it is currently recommended only when AVN ablation with pacemaker implantation is intended.[10] The latter option results in a lifelong pacemaker dependency. In addition, there are hemodynamic drawbacks because of the retrograde ventricular contraction.[11,12] Recently, lesions encircling rather than destroying the AVN were shown to result in acceptable junctional escape rhythm.[13,14] However, this technique needs further refinements and verification.

Clinical Perspective p 2911

Received April 13, 2005; de novo received June 14, 2005; revision received August 18, 2005; accepted August 26, 2005.

From the Department of Cardiovascular Medicine, The Cleveland Clinic Foundation (Y.Z., H.Y., S.Z., K.A.M., D.W.W., S.O., T.N.M.), and Department of Physiology and Biophysics, Case Western Reserve University (S.B.), Cleveland, Ohio.

Correspondence to Todor N. Mazgalev, PhD, Research Institute FF1-02, Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195. E-mail mazgalt@ccf.org

Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.105.568832**

Recently, a novel strategy, selective AVN vagal stimulation (AVN-VS), has emerged for rate control during AF.[12,15–18] We have previously demonstrated that AVN-VS could be used to achieve desired predetermined ventricular rate slowing with improved hemodynamics in acute experiments.[16] Moreover, ventricular rate slowing by AVN-VS provided better hemodynamic benefit than AVN ablation and right ventricular pacing.[12] However, it is unknown whether AVN-VS could be used as a long-term therapy during AF. Thus, the purpose of this study was to determine the long-term effects of VS in slowing ventricular rate and the safety and tolerability of this novel therapeutic strategy in conscious animals during AF.

Methods

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

Animal Model: Surgical Preparation and Device Implantation

A total of 18 adult mongrel dogs (body weight, 21 to 35 kg) underwent device implantation. Each dog received an atrial pacemaker for induction and maintenance of AF, a vagal nerve stimulator, and a telemetric device (TL11-M2-D70-PCT, Data Science International DSI) for monitoring ECG, blood pressure, and temperature.

The surgical procedures for implantation of these devices are briefly described. All dogs were premedicated with thiopental sodium (20 mg/kg IV), intubated, and ventilated with room air supplemented with oxygen by a respirator (NARKOMED 2, North American DRAGER). Anesthesia was then maintained with 1% to 2% isoflurane throughout the experiment. Normal saline at 100 to 200 mL/h was infused to replace spontaneous fluid losses. Standard surface ECG leads (I, II, III) were monitored continuously throughout the procedure. Body temperature was monitored with a rectal probe (TM-2400, Electromedics, Inc), and an electric heating pad under the animal and operating room lamps were used to maintain body temperature of 37°C.

Under sterile surgical procedures, dogs underwent a right lateral thoracotomy at the fourth intercostal space. With ribs and lungs retracted, the pericardium was opened. A custom-made bipolar patch electrode (St Jude Medical) was sutured on the AVN fat pad, located at the junction of the inferior vena cava and the left atrium.[15] This electrode was connected to a nerve stimulator.

We used 2 types of nerve stimulators: ITREL II 7424 nerve stimulator (Medtronic Inc) or a modified Photon ICD (St Jude Medical). Both devices could deliver a continuous mode of stimulation (train of stimuli with duration of 100 μs, at 20 Hz). The modified Photon ICD could also be programmed to deliver a synchronized mode of stimulation: Each sensed QRS signal triggers a burst consisting of 20 impulses, 1 ms in duration, and 6 ms apart (corresponding to ≈160 Hz).[16] The Photon ICD was used in synchronized mode in 5 dogs, in which an additional sensing electrode was sutured on the apex of the right ventricle to detect the triggering signal. In these dogs the 2 modes of delivery of AVN-VS could be compared.

A custom-made bipolar patch electrode (St Jude Medical) was sutured to the right atrial appendage in all dogs and connected to a modified high-rate atrial pacemaker (600 bpm; Identity XL DR, St Jude Medical). Both the atrial pacemaker and the nerve stimulator were buried subcutaneously at the back area. At the end, the pericardium and the chest were closed in layers. A drain chest tube was used, and negative pressure in the pleural cavity was reestablished.

We also implanted a telemetric device (TL11-M2-D70-PCT) subcutaneously at the left flank area, with the tip of a pressure line inserted into the abdominal aorta through the left femoral artery. Two ECG wires were buried subcutaneously for ECG transmission. The device also transmitted body temperature via a sensor in the case.

All incisions were closed, and the dogs were carefully monitored during their recovery. Standard postoperative care was performed daily until the incisions were healed (≈2 weeks).

Study Protocol and Conscious Monitoring

After recovery, AF was induced and maintained for the entire duration of the study by the atrial pacemaker, which delivered high-rate pacing at 600 bpm (1-ms impulses, 2 to 3 V). One week later, while the AF was maintained, nerve stimulation was initiated and delivered for at least 5 weeks (in 2 dogs the AVN-VS was maintained for 6 months). We titrated AVN-VS voltage output, attempting to slow the average ventricular rate toward the sinus rate level observed before AF induction (121±13 bpm). The adjustments were done typically within the first few days. When sinus rate target was not achievable, the output of the device was set to the maximum output (10 V) available in the ITREL II and the Photon ICD nerve stimulators.

We observed the dogs daily but collected ECG and blood pressure data every other day between 10 AM and noon. During monitoring, the dogs were kept unrestrained in a moderate-sized cage (or lying on a couch during echocardiography). A typical episode of data collection consisted of the following steps. First, we recorded ECG and blood pressure signals with the ongoing VS. Then the VS was turned off, and after a 10-minute stabilization period another set of data was collected to determine the intrinsic ventricular rate during AF. After this brief interruption, VS was reinitiated. In the first 6 animals, we also collected data immediately after VS reinitiation and verified that the heart rate returned to the level at the start of the observations. The duration of each recording step permitted collection of at least 500 beats for subsequent analysis. The reported electrophysiological data are averages from 3 daily observations in a given week.

In 5 dogs implanted with the Photon ICD, we compared the effectiveness of 2 modes for delivery of the nerve stimulation: continuous and synchronized.[12,15,16] In these cases, data were collected with consecutive delivery of continuous and synchronized modes of AVN-VS at 10-V output. For the rest of the time, continuous mode was maintained.

Conscious Echocardiographic Measurements

Left ventricular function was assessed weekly by transthoracic echocardiography.[19,20] Left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were determined by 2-dimensional guided M-mode echocardiography (SystemFive, General Electric-Vingmed). Left ventricular ejection fraction (LVEF) was calculated with the use of the Teichholz equation.[21] Left ventricular cavity dimensions and LVEF were calculated from an average of 7 to 15 heart cycles during AF.

Daily Animal Status Monitoring

Since there are no generally accepted objective criteria for assessing the degree of pain/discomfort in animals, we followed accepted recommendations based on the recognition of a departure from the normal behavior and appearance of the animals.[22] Any noticeable behavioral changes, including activity, appetite, and/or any signs of pain and distress in the animals, would be recorded on the animals' log chart by our technician and the Biological Resource Unit staff personnel.

Statistical Analysis

Data are presented as mean±SD. The ventricular rate changes at different time courses during AF (without VS) were evaluated by single-factor repeated measurements of ANOVA followed by the Tukey honestly significant difference (HSD) test. The ventricular rate and hemodynamic parameters with and without AVN-VS for each week were compared by paired t test. The analysis was performed with the use of statistical software (STATISTICA version 5.1, StatSoft Inc). All statistical tests were 2-sided, and a probability value <0.05 was required for statistical significance.

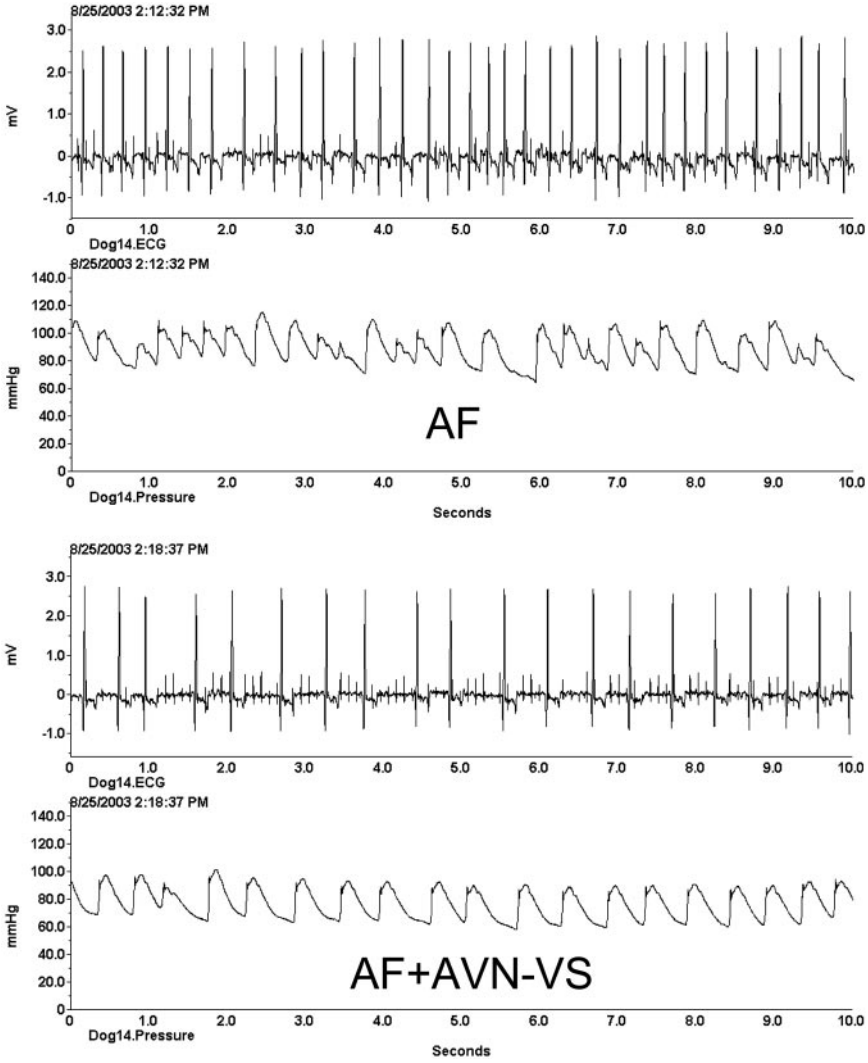

Figure 1. Telemetric ECG and blood pressure tracings collected by DSI device from a dog during delivery of continuous mode AVN-VS. The top panel shows data during AF alone, when AVN-VS was temporarily turned off. The bottom panel shows data during continuous mode AVN-VS. See text for details.

Results

Of the 18 dogs, successful experiments were performed on 15 (body weight, 27±2 kg; range, 23 to 31 kg). One dog died suddenly 6 days after AF induction before initiation of AVN-VS. The other 2 dogs had lead/device problems requiring premature termination of the study. A total of 15 dogs completed the study protocol with at least 5-week AVN-VS, and in the first 2 dogs the AVN-VS period was extended to 6 months. In all dogs, the long-term AVN-VS was maintained with the use of the continuous mode of VS, whereas the synchronous mode was used during the tests. The intensities of AVN-VS were 9.4±1.3 V. In 3 dogs, VS was titrated (6.0 to 8.0 V), and the averaged ventricular rate was maintained within 10% of the sinus rate. In all other dogs, the target was not reached, and the VS output was set to 10 V.

AVN-VS Effects on Ventricular Rate During AF

Figure 1 shows ECG and blood pressure tracings recorded by a DSI telemetric device at the end of 5 weeks of AVN-VS in 1 dog. The top panel shows ECG and blood pressure tracings taken when the VS was temporarily turned off, and the bottom panel shows tracings taken when continuous mode AVN-VS was on (output at 7.0 V). Clearly, VS decreased ventricular rate from 205 bpm (top panel) to 122 bpm (bottom panel). Note that the slower rate was associated with more stable blood pressure readings.

Figure 2 shows another example when AVN-VS was delivered during a synchronized mode test. In this case, ventricular rate was decreased from 246 bpm (top panel) to 148 bpm (bottom panel) by AVN-VS at 10.0 V. Note the AVN-VS artifacts at the end of each QRS when VS was on.

The composite data for the ventricular rate in all 15 dogs are shown in Figure 3. Several important observations are as follows: (1) The average sinus rate before AF induction was 121±13 bpm (filled circle) and increased to 270±33 bpm immediately after AF was initiated by high-rate right atrial pacing (week −1). (2) The intrinsic ventricular rate gradually decreased to a level of 251±50 bpm 1 week after AF induction, just before initiation of AVN-VS (week 0, filled triangle). (3) When AVN-VS was initiated, the ventricular rate decreased sharply to 180±37 bpm (week 0, open circle). (4) In the subsequent 5 weeks, AVN-VS treatment had a consistent effect in slowing the ventricular rate. This is evident from the comparison of data obtained in the presence, and during the temporary cessation, of the nerve stimulator. Thus, the average rates were (in bpm) 182 versus 217 (week 1), 172 versus 218 (week 2), 165 versus 209 (week 3), 157 versus 195 (week 4), and 153 versus

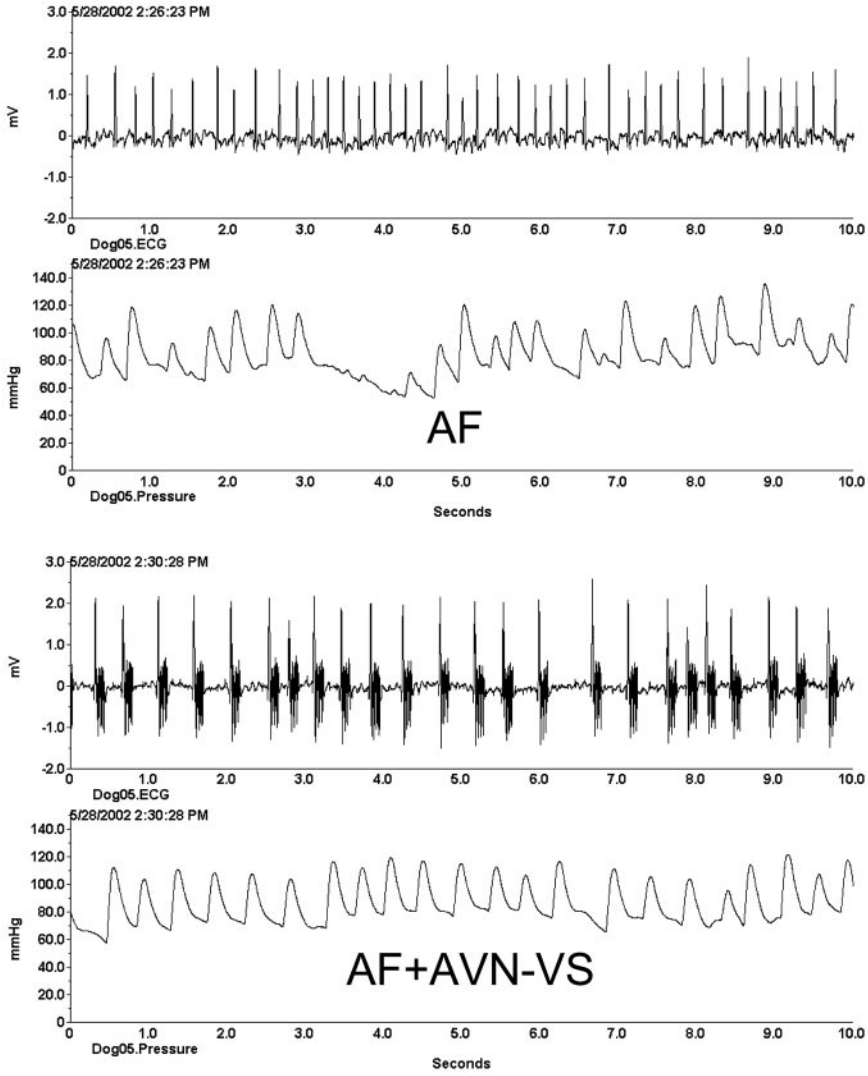

Figure 2. Telemetric ECG and blood pressure tracings collected by DSI device from a dog during delivery of synchronized mode AVN-VS. Data without (top) and with AVN-VS (bottom) are shown. Note the AVN-VS artifacts at the end of each QRS complex.

192 (week 5) (Figure 3; compare open symbols with AVN-VS versus filled symbols without AVN-VS; paired *t* test, $P<0.01$ for each week).

We kept 2 of the dogs for 6 months under the same experimental conditions and confirmed the presence of significant vagal effect throughout the observation period. For example, the average ventricular rate in these 2 dogs stayed in the range of 150 to 135 bpm.

Of interest, the data illustrated in Figure 3 revealed that the intrinsic ventricular rate (ie, the rate observed when AVN-VS was temporarily turned off) had a tendency to slow down as the study progressed. As seen in Figure 3, the intrinsic ventricular rate (without AVN-VS) decreased from 270±33 bpm when AF was initiated (week −1) to 192±50 bpm at the end of the fifth week of AVN-VS treatment (ANOVA with HSD test, $P<0.001$). Although at any point the intrinsic ventricular rate (without AVN-VS, filled symbols) was always faster than that observed with VS (open symbols), the 2 processes were "parallel" and resulted in an average VS-induced slowing of 45±13 bpm.

AVN-VS Effects on Blood Pressure During AF

As shown in Figures 1 and 2, more stable blood pressure was associated with the slower ventricular rate achieved by AVN-VS. Figure 4 summarizes the averaged blood pressure responses in all dogs. AF decreased both the systolic and diastolic pressures compared with those during sinus rate (filled circles at sinus rate and filled triangles at week −1; paired *t* test, $P<0.001$). The values for systolic blood pressure during the AVN-VS treatment period (open circles) remained higher than the values observed at initiation of AF (97±21 mm Hg, week −1). However, intermittent removal of AVN-VS (solid triangles versus open circles) indicated that the direct effect of AVN-VS on the averaged SBP during AF had statistical significance only during the initial 2 weeks ($P<0.05$). Similarly, AVN-VS had no direct effect on the averaged diastolic blood pressure during AF (bottom panel).

AVN-VS Hemodynamic Effects Derived From Echocardiography

Echocardiographic averaged data of LVEF, LVEDV, and LVESV are shown in Figure 5. As expected, AF significantly decreased LVEDV and LVEF and increased LVESV compared with values observed during sinus rhythm (closed circles versus closed triangles; $P<0.05$). In weeks 0 to 5, AVN-VS did not affect LVESV (bottom panel) but had a

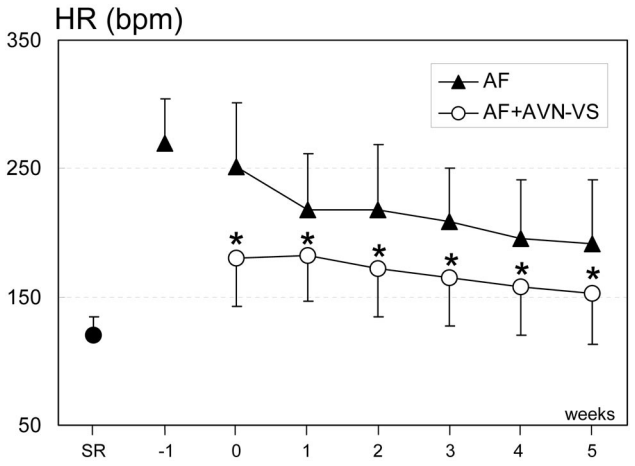

Figure 3. Ventricular rate at selected test times during the study. Averaged values from 15 dogs are shown: during sinus rate before AF induction (SR), immediately after AF was induced (week −1), at the start of AVN-VS (week 0), and at the end of each subsequent week (weeks 1 to 5). *Statistical difference ($P<0.05$) between data without (filled triangles) and with (open circles) AVN-VS in a given week. See text for details.

direct effect on LVEDV (middle panel, except week 1) and significantly improved LVEF (top panel) ($P<0.05$ as marked for each week).

Continuous Mode Versus Synchronized Mode of AVN-VS

In 5 dogs implanted with Photon ICD, we compared the effects of AVN-VS using the continuous versus synchronized mode. In these 5 dogs, the intrinsic ventricular rate during AF without VS was 216±50 bpm. When programmed to the same output of 10 V, the continuous AVN-VS mode (train of stimuli with duration of 100 μs, at 20 Hz) decreased ventricular rate to 174±42 bpm, while in the synchronized mode (bursts consisting of 20 impulses, 1 ms in duration, and delivered after each QRS), ventricular rate was decreased to 177±43 bpm. Thus, the achieved rates were not different (paired t test, $P>0.05$).

Safety and Tolerability of AVN-VS

The procedure was well tolerated by all animals. There were no signs of distress or discomfort associated with AVN-VS. All studied dogs with VS remained healthy, and their body weight, temperature, and vital signs were normal.

Discussion

Major Findings

This study demonstrated for the first time that long-term ventricular rate slowing during AF could be achieved by implantation of a "nerve pacemaker" attached to the epicardial AVN fat pad. Rate control by AVN-VS during AF was associated with hemodynamic improvement. Furthermore, the epicardial approach of AVN-VS to control ventricular rate during AF was a well-tolerated modality in this animal model and did not produce any noticeable side effects.

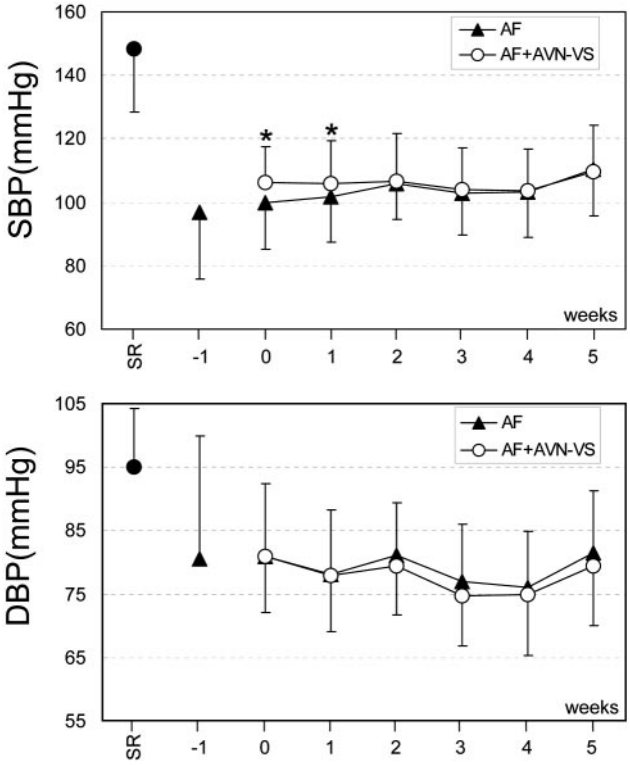

Figure 4. Systolic (SBP) and diastolic blood pressure (DBP) changes at selected test times during the study. The format, symbols, and probability values are as described in Figure 3. See text for details.

AVN-VS as a Novel Strategy for Rate Control During AF

Current clinical trials have established that rate control is 1 of 2 primary approaches in treating AF patients.[7,8] The strategy of rate control during AF essentially deals with efforts to utilize and adjust the filtering properties of the AVN.[9] It is well known that the AVN area is richly supplied with vagal terminals, which project mostly from a discrete epicardial ganglion ("fat pad"). The AVN fat pad is located at the junction between the inferior vena cava and the left atrium, at the crux of the heart.[23–26] When electric stimulation is applied to the AVN fat pad in the dog heart, the spontaneous sinus cycle length remains mostly unchanged, but the AVN conduction is substantially delayed.[15] We have previously demonstrated in acute experiments in animals that with the use of feedback-controlled delivery of the therapy, different predetermined levels of ventricular rate slowing could be achieved and maintained, resulting in significant hemodynamic improvement.[16] Moreover, it has been demonstrated that ventricular rate slowing by selective AVN-VS was hemodynamically superior to AVN ablation followed by regular right ventricular pacing.[12]

However, all the aforementioned studies were short-term acute experiments. Previous observations in vitro[27] have suggested that persistent VS might result in gradual reduction of cellular hyperpolarization that constitutes the basic mechanism of vagally induced control of the sinus and atrioventricular nodes.[28,29] Such "fading effect," however, is most likely a consequence of the limited pool of choline in vitro rather than of

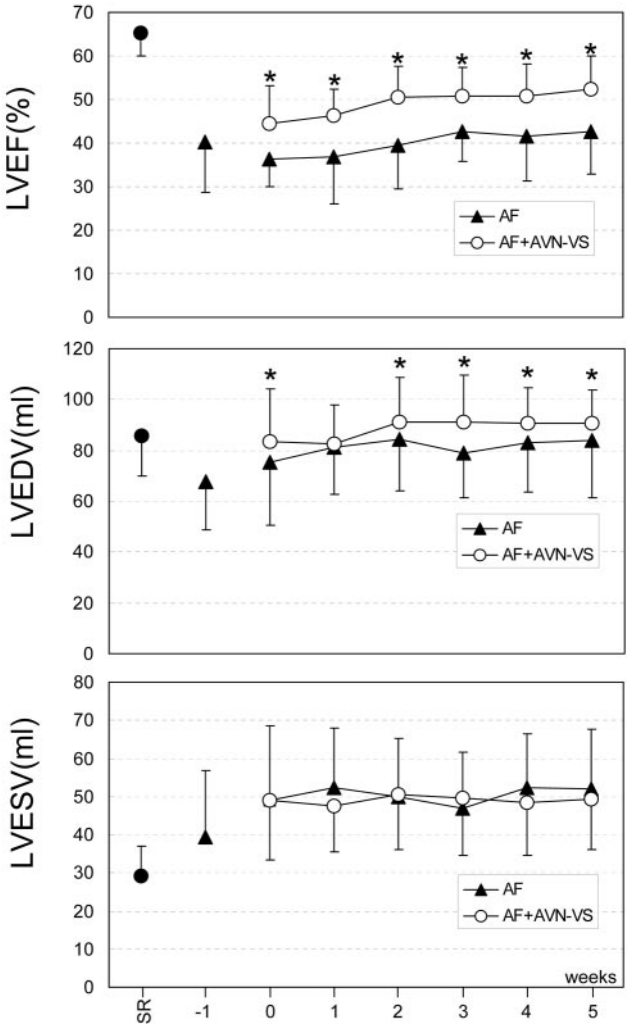

Figure 5. Echocardiographic measurements of LVEF, LVEDV, and LVESV taken at the same times as indicated in Figure 3. All symbols and marked statistical differences are as in Figure 3. See text for details.

desensitization of the muscarinic receptors,[30] ie, the uptake in the synaptic cleft is a slow process, and this is the main source of choline in vitro.[31] Indeed, direct acetylcholine injection was shown to maintain the cholinergic effect over a prolonged period of time.[32] One should expect that in vivo, where there is normally an unlimited pool of choline provided by the plasma,[33] the synthesis of acetylcholine during repetitive VS should be unhampered.[17] Nevertheless, it remained imperative to determine whether AVN-VS could provide long-term therapeutic effects and whether it is safe and tolerated by conscious animals.

To our knowledge, this is the first study to explore the feasibility of employing AVN-VS for long-term control of ventricular rate in AF. Our results clearly demonstrated that the epicardial AVN fat pad stimulation could be used in chronically instrumented animals, producing sustained long-term effects in controlling ventricular rate and improving hemodynamic status. In addition, this novel approach was not associated with any noticeable side effects.

The present dog study may have important clinical implications. Since a similar fat pad in humans has been identified,[34] AVN-VS could be applied to control ventricular rate in some AF patients. Future advancement of technology (as with epicardial ablation[35]) may permit avoidance of open chest surgery and may provide a means for transcutaneous lead implantation for epicardial nerve stimulation.

AVN Remodeling During AF and Chronic AVN-VS

It appeared that chronic application of AVN-VS was accompanied by progressive slowing of the intrinsic ventricular rate, ie, the steady state rate during AF when the vagal stimulator was temporarily turned off (Figure 3). The direct effect of VS remained almost unchanged (45±13 bpm) and disappeared promptly with termination of the stimulation as a result of fast acetylcholine hydrolysis.[28]

Although the exact mechanism(s) responsible for the intrinsic ventricular rate slowing is not known, it is likely related to the filtering function of the AVN during AF and/or to the AF pattern itself. The atrial activation pattern could change during a prolonged high atrial rate because of atrial remodeling[36–38] and affect conduction through the AVN.[39] Whether this proposed mechanism is also dependent on the presence of chronic VS that might affect the atrium remains speculative.

Although the atrial component is a significant functional and structural determinant of AVN conduction,[40] it is reasonable to speculate that AVN itself might also undergo some remodeling during AF. For example, it is known that AF induces significant remodeling in the sinus node function.[41,42] We have previously demonstrated in rabbits that chronic AF increased basic AVN conduction times and refractory periods.[43] Such AVN electrophysiological remodeling would be favorable for reducing the intrinsic ventricular rate during chronic AF. Again, the potential role of persistent VS in the process of AVN remodeling remains unknown.

Finally, there is evidence that electric stimulation of the atria and sympathetic ganglia induces nerve sprouting.[44,45] It is possible that long-term ganglionic AVN-VS might also induce nerve sprouting and changes in the autonomic balance, thus affecting AVN conduction. Unfortunately, this study was not designed to differentiate and elucidate such possible mechanisms.

VS: Synchronized Versus Continuous Mode of Delivery

Previously we had explored 2 modes of VS in acute studies: continuous and synchronized.[12,15,16] The appeal of the latter is in its perceived safety because it is delivered during the ventricular refractory period and the arrhythmic consequences of ventricular capturing are minimized. There are energy considerations as well. As with any electric stimulation, the impulses used for AVN-VS must have amplitude above a certain threshold (in our experiments it was typically 2.5 to 3.5 V), and the vagal effects are determined by the overall intensity. Thus, at a given amplitude, the effect of the VS would be proportional to the duration and frequency of the impulses. Therefore, the synchronized mode allows the "bundling" of substantial energy in a short burst containing relatively long (1 ms) and high-frequency (160 Hz) impulses that are delivered discretely after the QRS complex. In contrast, the energy delivered during the continuous mode of VS at the same amplitude is homogeneously distributed in time and delivered by a sequence of brief (100 μs) impulses

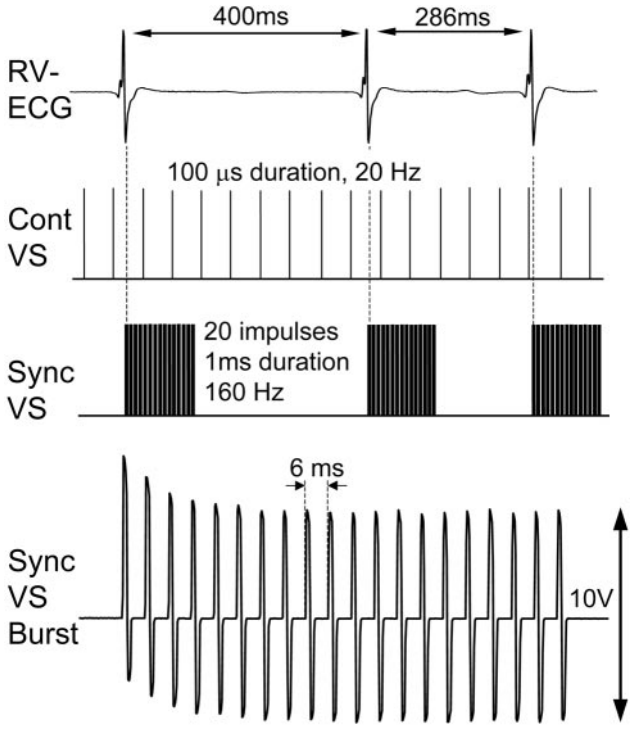

Figure 6. Schematic illustration of the delivery of AVN-VS in continuous (Cont VS) vs synchronized (Sync VS) mode. Top tracing, Right ventricular (RV) ECG signal. Second tracing, Continuous train of impulses with duration of 100 μs, 20 Hz. Third tracing, Each AVN-VS burst is synchronized with the QRS and consists of 20 impulses with duration 1 ms, 160 Hz. Bottom tracing, The real burst delivered by Photon ICD during bench testing in synchronized mode. See text for details.

at 20 Hz. As illustrated in Figure 6 (only 3 ventricular beats are shown in the top tracing, corresponding to an average rate of 175 bpm), during continuous AVN-VS (second tracing), the nerve pacemaker would deliver 14 impulses. If we assume amplitude of 10 V and lead impedance of 1 kΩ, the energy for this segment is 0.14×10^{-3} J. In the synchronized mode (third tracing), the nerve stimulator would deliver only 2 bursts but with a total energy of 4×10^{-3} J.

On the basis of the aforementioned considerations, we were expecting that the synchronized mode of delivery of the AVN-VS would produce much stronger vagal effects. However, this study showed that the 2 modes (at the same programmed amplitude of 10 V) produced similar effects in slowing the ventricular rate. This unexpected outcome was partially due to design limitations of the Photon ICD in this mode (Figure 6). Since it is not a dedicated nerve stimulator, its capacitor-charging output resulted in a biphasic waveform (Figure 6, bottom tracing, actual device output). Thus, even though the device was programmed to deliver 20 impulses at 10 V, it actually delivered positive and negative spikes at roughly half the expected amplitude. This diminished the effectiveness of neurostimulation since the same energy was delivered by impulses that were closer to the threshold of nerve excitation (typically 2.5 to 3.5 V). Future studies with improved dedicated neural stimulators should permit fuller evaluation and optimization of the mode of delivery of the VS.

Study Limitations

AVN-VS had consistent long-term effects, but the ventricular rate slowing was less dramatic than in our previous acute studies.[12,16] Even though direct comparison is not warranted, a thick fibrous socket that formed around the patch vagal electrode in the chronic experiments might have reduced the efficacy of current delivery, even though the measured impedance of the electrode remained unchanged (1017$\pm$306 Ω at implantation versus 922$\pm$258 Ω at the end of the experiments). Efforts that seek to reduce fibrosis, such as steroid-eluting electrodes, may enhance the efficacy of VS. In addition, while we have developed algorithms for a feedback-controlled delivery of VS,[16] such a sophisticated feature is not yet available in chronic implantable nerve stimulators. Future devices would be able to deliver individualized therapy by maintaining predetermined levels of ventricular rate slowing. Similarly, they would permit more detailed evaluation of the VS therapy in the presence of increased sympathetic tone (eg, controlled exercise). Finally, although no side effects were observed in these dogs, because of the nature of animal studies, the clinical tolerability of this approach needs future investigations.

Acknowledgments

This study was supported in part by a National Institutes of Health grant (NHLBI RO1-HL-60833, Dr Mazgalev). Dr Zhang was supported by an American Heart Association (Ohio Valley Affiliate) Grant (0120236B) during this study. The authors also acknowledge expert technical assistance from William Kowalewski and the device and leads support provided by Drs Rahul Mehra (Medtronic, Inc) and Gene A. Bornzin, John W. Poore, and Michael Yang (St Jude Medical).

References

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285:2370–2375.
2. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation: analysis and implications. *Arch Intern Med*. 1995;155:469–473.
3. Prystowsky EN, Benson DW Jr, Fuster V, Hart RG, Kay GN, Myerburg RJ, Naccarelli GV, Wyse DG. Management of patients with atrial fibrillation: a statement for healthcare professionals: from the Subcommittee on Electrocardiography and Electrophysiology, American Heart Association. *Circulation*. 1996;93:1262–1277.
4. Jung F, DiMarco JP. Treatment strategies for atrial fibrillation. *Am J Med*. 1998;104:272–286.
5. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825–1833.
6. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG, Crijns HJ. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347:1834–1840.
7. Cain ME. Atrial fibrillation: rhythm or rate control. *N Engl J Med*. 2002; 347:1822–1823.
8. Falk RH. Management of atrial fibrillation: radical reform or modest modification? *N Engl J Med*. 2002;347:1883–1884.
9. Zhang Y, Mazgalev TN. Ventricular rate control during atrial fibrillation and AV node modifications: past, present, and future. *Pacing Clin Electrophysiol*. 2004;27:382–393.
10. Scheinman MM, Morady F. Nonpharmacological approaches to atrial fibrillation. *Circulation*. 2001;103:2120–2125.
11. Tse HF, Lau CP. Long-term effect of right ventricular pacing on myocardial perfusion and function. *J Am Coll Cardiol*. 1997;29:744–749.
12. Zhuang S, Zhang Y, Mowrey KA, Li J, Tabata T, Wallick DW, Popovic ZB, Grimm RA, Natale A, Mazgalev TN. Ventricular rate control by selective

vagal stimulation is superior to rhythm regularization by atrioventricular nodal ablation and pacing during atrial fibrillation. *Circulation*. 2002;106:1853–1858.
13. Antz M, Scherlag BJ, Otomo K, Pitha J, Tondo C, Patterson E, Jackman WM, Lazzara R. Evidence for multiple atrio-AV nodal inputs in the normal dog heart. *J Cardiovasc Electrophysiol*. 1998;9:395–408.
14. Strohmer B, Hwang C, Peter CT, Chen PS. Selective atrionodal input ablation for induction of proximal complete heart block with stable junctional escape rhythm in patients with uncontrolled atrial fibrillation. *J Interv Card Electrophysiol*. 2003;8:49–57.
15. Wallick DW, Zhang Y, Tabata T, Zhuang S, Mowrey KA, Watanabe J, Greenberg NL, Grimm RA, Mazgalev TN. Selective AV nodal vagal stimulation improves hemodynamics during acute atrial fibrillation in dogs. *Am J Physiol*. 2001;281:H1490–H1497.
16. Zhang Y, Mowrey KA, Zhuang S, Wallick DW, Popovic ZB, Mazgalev TN. Optimal ventricular rate slowing during atrial fibrillation by feedback AV nodal-selective vagal stimulation. *Am J Physiol*. 2002;282:H1102–H1110.
17. Schauerte P, Scherlag BJ, Scherlag MA, Goli S, Jackman WM, Lazzara R. Ventricular rate control during atrial fibrillation by cardiac parasympathetic nerve stimulation: a transvenous approach. *J Am Coll Cardiol*. 1999;34:2043–2050.
18. Schauerte P, Mischke K, Plisiene J, Waldmann M, Zarse M, Stellbrink C, Schimpf T, Knackstedt C, Sinha A, Hanrath P. Catheter stimulation of cardiac parasympathetic nerves in humans: a novel approach to the cardiac autonomic nervous system. *Circulation*. 2001;104:2430–2435.
19. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation*. 1978;58:1072–1083.
20. Gardin JM, Adams DB, Douglas PS, Feigenbaum H, Forst DH, Fraser AG, Grayburn PA, Katz AS, Keller AM, Kerber RE, Khandheria BK, Klein AL, Lang RM, Pierard LA, Quinones MA, Schnittger I. Recommendations for a standardized report for adult transthoracic echocardiography: a report from the American Society of Echocardiography's Nomenclature and Standards Committee and Task Force for a Standardized Echocardiography Report. *J Am Soc Echocardiogr*. 2002;15:275–290.
21. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. *Am J Cardiol*. 1976;37:7–11.
22. Committee on Pain and Distress in Laboratory Animals, Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council. *Recognition and Assessment of Pain, Stress, and Distress: In Recognition and Alleviation of Pain and Distress in Laboratory Animals*. Washington, DC: National Academy Press; 1992:32–52.
23. Lazzara R, Scherlag BJ, Robinson MJ, Samet P. Selective in situ parasympathetic control of the canine sinoatrial and atrioventricular nodes. *Circ Res*. 1973;32:393–401.
24. Ardell JL, Randall WC. Selective vagal innervation of sinoatrial and atrioventricular nodes in canine heart. *Am J Physiol*. 1986;251:H764–H773.
25. Furukawa Y, Narita M, Takei M, Kobayashi O, Haniuda M, Chiba S. Differential intracardiac sympathetic and parasympathetic innervation to the SA and AV nodes in anesthetized dog hearts. *Jpn J Pharmacol*. 1991;55:381–390.
26. Randall WC, Ardell JL, Calderwood D, Miloslavljevic M, Goyal SC. Parasympathetic ganglia innervating the canine atrioventricular nodal region. *J Auton Nerv Syst*. 1986;16:311–323.
27. Salata JJ, Jalife J. "Fade" of hyperpolarizing responses to vagal stimulation at the sinoatrial and atrioventricular nodes of the rabbit heart. *Circ Res*. 1985;56:718–727.
28. Mazgalev T, Dreifus LS, Michelson EL, Pelleg A. Vagally induced hyperpolarization in atrioventricular node. *Am J Physiol*. 1986;251:H631–H643.
29. Slenter VA, Salata JJ, Jalife J. Vagal control of pacemaker periodicity and intranodal conduction in the rabbit sinoatrial node. *Circ Res*. 1984;54:436–446.
30. Jalife J, Hamilton AJ, Moe GK. Desensitization of the cholinergic receptor at the sinoatrial cell of the kitten. *Am J Physiol*. 1980;238:H439–H448.
31. Blusztajn JK, Wurtman RJ. Choline and cholinergic neurons. *Science*. 1983;221:614–620.
32. Mazgalev TN, Garrigue S, Mowrey KA, Yamanouchi Y, Tchou PJ. Autonomic modification of the atrioventricular node during atrial fibrillation: role in the slowing of ventricular rate. *Circulation*. 1999;99:2806–2814.
33. Tucek S. Problems in the organization and control of acetylcholine synthesis in brain neurons. *Prog Biophys Mol Biol*. 1984;44:1–46.
34. Quan KJ, Lee JH, van Hare GF, Biblo LA, Mackall JA, Carlson MD. Identification and characterization of atrioventricular parasympathetic innervation in humans. *J Cardiovasc Electrophysiol*. 2002;13:735–739.
35. Lam C, Schweikert R, Kanagaratnam L, Natale A. Radiofrequency ablation of a right atrial appendage-ventricular accessory pathway by transcutaneous epicardial instrumentation. *J Cardiovasc Electrophysiol*. 2000;11:1170–1173.
36. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. *Circulation*. 1995;92:1954–1968.
37. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing: structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. *Circulation*. 1995;91:1588–1595.
38. Van Wagoner DR. Electrophysiological remodeling in human atrial fibrillation. *Pacing Clin Electrophysiol*. 2003;26:1572–1575.
39. Garrigue S, Tchou PJ, Mazgalev TN. Role of the differential bombardment of atrial inputs to the atrioventricular node as a factor influencing ventricular rate during high atrial rate. *Cardiovasc Res*. 1999;44:344–355.
40. Mazgalev TN, Ho SY, Anderson RH. Anatomic-electrophysiological correlations concerning the pathways for atrioventricular conduction. *Circulation*. 2001;103:2660–2667.
41. Elvan A, Wylie K, Zipes DP. Pacing-induced chronic atrial fibrillation impairs sinus node function in dogs: electrophysiological remodeling. *Circulation*. 1996;94:2953–2960.
42. Hadian D, Zipes DP, Olgin JE, Miller JM. Short-term rapid atrial pacing produces electrical remodeling of sinus node function in humans. *J Cardiovasc Electrophysiol*. 2002;13:584–586.
43. Zhang Y, Mowrey KA, Bharati S, Van Wagoner DR, Mazgalev TN. Atrioventricular nodal remodeling induced by chronic atrial fibrillation in rabbits. *Pacing Clin Electrophysiol*. 2003;26:984. Abstract.
44. Swissa M, Zhou S, Gonzalez-Gomez I, Chang CM, Lai AC, Cates AW, Fishbein MC, Karagueuzian HS, Chen PS, Chen LS. Long-term subthreshold electrical stimulation of the left stellate ganglion and a canine model of sudden cardiac death. *J Am Coll Cardiol*. 2004;43:858–864.
45. Hamabe A, Chang CM, Zhou S, Chou CC, Yi J, Miyauchi Y, Okuyama Y, Fishbein MC, Karagueuzian HS, Chen LS, Chen PS. Induction of atrial fibrillation and nerve sprouting by prolonged left atrial pacing in dogs. *Pacing Clin Electrophysiol*. 2003;26:2247–2252.

CLINICAL PERSPECTIVE

Symptoms of atrial fibrillation (AF) are commonly due to a rapid ventricular response. Achieving control of the ventricular rate is important for control of symptoms and to prevent tachycardia-induced ventricular dysfunction. Rate control often requires a combination of medications that depress AV nodal conduction, including β-adrenergic blockers, calcium channel blockers, and digoxin. When these fail or are not tolerated, AV junction ablation with permanent pacemaker implantation is sometimes required, despite concern that ventricular pacing has the potential to adversely affect ventricular function. We have explored a novel nondestructive, nonpharmacological strategy for ventricular rate control during AF. Specifically, we investigated the feasibility of using chronic, selective vagal stimulation for controlling ventricular rate during AF in dogs. This new therapy was well tolerated by the animals, achieved significant slowing of ventricular rate over prolonged periods of time, and produced the desirable hemodynamic consequences of slowing the rate in AF. This study provides the basis for the development of novel neural stimulators for future clinical evaluation of this therapy.