Increase of Ventricular Interval During Atrial Fibrillation by Atrioventricular Node Vagal Stimulation

Chronic Clinical Atrioventricular-Nodal Stimulation Download Study

Stefano Bianchi, MD; Pietro Rossi, MD, PhD; Patrick Schauerte, MD, PhD; Arif Elvan, MD, PhD; Carina Blomström-Lundqvist, MD, PhD; Lilian Kornet, PhD; Pim Gal, MD; David Mörtzell, MD; Griet Wouters, MSc; Christopher Gemein, MD

Background—Patients with a high ventricular rate during atrial fibrillation (AF) are at increased risk of receiving inappropriate implantable cardioverter defibrillator shocks. The objective was to demonstrate the feasibility of high frequency atrioventricular-nodal stimulation (AVNS) to reduce the ventricular rate during AF to prevent inappropriate implantable cardioverter defibrillator shocks.

Methods and Results—Patients with a new atrial lead placement as part of a cardiac resynchronization therapy and defibrillator implant and a history of paroxysmal or persistent AF were eligible. If proper atrial lead position was confirmed, AVNS software was uploaded to the cardiac resynchronization therapy device, tested, and optimized. AVNS was delivered via a right atrial pacing lead positioned in the posterior right atrium. Software allowed initiation of high frequency bursts triggered on rapidly conducted AF. Importantly, the efficacy was evaluated during spontaneous AF episodes between 1 and 6 months after implant. Forty-four patients were enrolled in 4 centers. Successful atrial lead placement occurred in 74%. Median implant time of the AVNS lead was 37 minutes. In 26 (81%) patients, manual AVNS tests increased the ventricular interval by >25%. Between 1 and 6 months, automatic AVNS activations occurred in 4 patients with rapidly conducted AF, and in 3 patients, AVNS slowed the ventricular rate out of the implantable cardioverter defibrillator shock zone. No adverse events were associated with the AVNS software.

Conclusions—The present study demonstrated the feasibility of implementation of AVNS in a cardiac resynchronization therapy and defibrillator system. AVNS increased ventricular interval >25% in 81% of patients. AVNS did not influence the safety profile of the cardiac resynchronization therapy and defibrillator system.

Clinical Trial Registration—ClinicalTrials.gov; Unique Identifier: NCT01095952.

Key Words: atrial fibrillation • shock • vagal stimulation
WHAT IS KNOWN

- Atrioventricular nodal-stimulation (AVNS) is effective in reducing ventricular rate chronically in animals.
- AVNS is effective in reducing ventricular rate acutely in humans.
- AVNS can be done using a standard atrial pacing lead.
- Lead characteristics remain stable over months when a lead is positioned where AVNS can be accomplished.

WHAT THE STUDY ADDS

- AVNS can be performed automatically in a chronic setting using a standard active fixation atrial lead and AVNS software uploaded to a cardiac resynchronization therapy–implantable cardioverter defibrillator.
- AVNS probably reduces inappropriate shocks.
- The effectiveness of acute AVNS is quantified.

by the Medical Ethics Committees of participating hospitals and the Competent Authorities of the relevant countries. All adverse events, technical observations, and deaths were reviewed by an independent Adverse Event Advisory Committee.

In-and Exclusion Criteria

Patients with a documented history of paroxysmal or persistent AF were eligible for this study if they had an indication for the following:

- Cardiac resynchronization therapy and defibrillator (CRT-D) implant
- Upgrade to CRT-D from a single-chamber device
- Upgrade or revision to CRT-D with an atrial lead positioned septally at the AVNS site or a dislodged atrial lead

Exclusion criteria were permanent AF; patients who were not on anticoagulant therapy; advanced atrioventricular block; patients who had previously undergone valvular surgery, which potentially resulted in damage of the atrioventricular-node or the parasympathetic nerve(s); age <18 years; patients who had previously undergone atrioventricular or parasympathetic nerve(s); and patients who had previously undergone valvular surgery, which potentially resulted in damage of the atrioventricular-node or the parasympathetic nerve(s); age <18 years; pregnancy; and participation in other studies, which could potentially conflict with this study.

AVNS Software Design

An investigational AVNS algorithm (AVNSₐ) was developed to deliver AVNS (ie, selective high frequency stimulation of parasympathetic nerves to the atrioventricular node) in a burst pattern during the ventricular refractory period (50 Hz, pulses 8, pulse width 1.5 ms, burst duration 160 ms) for 30 seconds via the posteroseptal right atrium.9–14 After right ventricular lead implantation, a standard atrial screw in lead (Medtronic type 5076 [2] and 4076 [29] or St Jude’s 2088TC [1]) was directed and screwed into the postero-septal region of the coronary sinus ostium. The septum is recognized as a feasible and safe site for chronic pacing to reduce paroxysmal AF recurrences, AF burden, and progression to permanent AF, with the rationale of reducing the duration of atrial activation.15,16 After right ventricular lead implantation, a standard atrial screw in lead (Medtronic type 5076 [2] and 4076 [29] or St Jude’s 2088TC [1]) was directed and screwed into the postero-septal region of the coronary sinus ostium. The septum is recognized as a feasible and safe site for chronic pacing to reduce paroxysmal AF recurrences, AF burden, and progression to permanent AF, with the rationale of reducing the duration of atrial activation.15,16

The atrial lead was considered implanted successfully during sinus rhythm if significant atrioventricular conduction slowing (defined as a ≥25% increase of PR interval) could be induced using an external pulse generator by delivering high frequency burst stimulation (pulse amplitude 8 V, pulse duration 1.5 ms, frequency 50 Hz, 8 pulses synchronized on P-wave to prevent AT/AF induction) and P-wave sensing was at least 0.5 mV.

The atrial lead was considered implanted successfully during sinus rhythm if significant atrioventricular conduction slowing (defined as a ≥25% increase of PR interval) could be induced using an external pulse generator by delivering 10 seconds of continuous high frequency stimulation (pulse amplitude 8 V, pulse duration 1.5 ms, frequency 50 Hz). Patients in whom the atrial lead could not be successfully positioned were withdrawn from the study.

At the end of the surgical procedure, the AVNS software was uploaded to the CRT-D device through the telemetric system commonly used to program the device and tested. In patients with sinus rhythm, AF was induced by burst pacing. Pulse width was set at 1.5 ms and burst duration at 160 ms (to remain in ventricular refractory period). The threshold for a 25% increase in ventricular activation during AF was tested, with the voltage output titrated from 8, 6, 4 to 2 V. For the in-hospital tests, ventricular intervals obtained from continuous ECG recordings 30 seconds before the start of the AVNSₐ test were compared with those recorded 30 seconds after the start of the AVNSₐ test. The AVNSₐ was switched off at the end of the procedure.

Follow-Up

Patients were required to be followed for 6 months, during which 1, 3, and 6 months visits were scheduled to obtain recordings of automatic AVNSₐ and arrhythmia, adverse events, medication, standard pacing tests, and safety tests. The AVNSₐ was activated at the 1 month visit and deactivated at the 6 month visit, when the software function was removed from the device via the telemetric programmer. The AVNSₐ was programmed at 8 V unless this gave symptoms during the in-hospital tests than the voltage was set at 6 V for the follow-up period.

Statistics

Sample Size

The primary objective was to assess the relative increase in ventricular interval during AT/AF by AVNSₐ programmed to maximal output during in-hospital tests. The primary end-point was the proportion of patients that achieved a ventricular interval increase of at least 25%. Assuming 70% of those with a successful atrial lead placement would fulfill this end-point, a confidence interval of 95%, and a precision (i.e., half of if a single short VV interval (<360 ms) was detected after this point, or if the programmed duration of AVNS therapy of 30 seconds had passed. Ventricular tachycardia (VT) and ventricular fibrillation (VF) limits were set to 360 and 300 ms, respectively.

Atrial Lead Implant Procedure

Atrioventricular nodal conduction is modulated by the parasympathetic nervous system through nerve fibers residing in an epicardial plexus located in the posterior right atrium. These nerve fibers extend through the interatrial septum at the coronary sinus ostium or the posterior right atrium.9–14 After right ventricular lead implantation, a standard atrial screw in lead (Medtronic type 5076 [2] and 4076 [29] or St Jude’s 2088TC [1]) was directed and screwed into the postero-septal region of the coronary sinus ostium. The septum is recognized as a feasible and safe site for chronic pacing to reduce paroxysmal AF recurrences, AF burden, and progression to permanent AF, with the rationale of reducing the duration of atrial activation.15

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the desired confidence interval width) of 15%, it was estimated that at least 37 patients would be needed to reach the primary end-point.

Considering early experiences in selective His bundle pacing without appropriate implant tools, an implant success rate of 67% was reported. We assumed that a similar result would be acceptable as first implant experiences in the AVNS study. It was estimated that ≥55 patients needed to be enrolled to obtain the required 37 patients for the primary end-point. Slower than expected enrollments as a result of reimbursement difficulties resulted in an evaluation of the initial sample size calculations during the study. The proportion of patients meeting the primary end-point was found to be higher than expected. Therefore, a new sample size calculation was performed, assuming 78% of those with a successful lead placed would fulfill the end-point and using a confidence interval of 95% and a precision (ie, half of the desired confidence interval width) of 15%. The 32 successfully implanted patients appeared to be acceptable to meet the precision requirement of the primary objective.

Secondary objectives were to evaluate (1) the performance of AVNS, in shock reduction during the follow-up period, (2) safety of AVNS, and (3) to assess symptoms related to interventions of AVNS, both during acute tests and follow-up.

Statistical Analyses

The statistical analysis for this feasibility study was based on a per-protocol approach to assess the effect in those patients who were able to receive the therapy. Continuous variables were expressed as mean with standard deviation in case of normal distribution or median with interquartile ranges of the 25th and 75th percentile (IQR) when variables were not normally distributed. Chi-square tests were used to compare categorical data. Continuous data were compared with a paired t test or repeated measures analysis of variance for ≥2 group comparisons. P values <0.05 were considered statistically significant. All statistical analyses were performed using SAS software version 9.3 (SAS Institute).

Results

Patient Population

Forty-four patients were enrolled between January 2011 and June 2013. Baseline characteristics are displayed in Table 1. In 1 patient, the atrial lead placement was not attempted. Thirty-seven patients had a new device implantation, 5 underwent an upgrade to CRT-D with a new atrial lead placement, and 1 patient already had a septally positioned right atrial lead. Atrial lead placement was successful in 32 (74%) patients. In 6 cases, a site with a negative dromotropic effect could not be found, and in 3 cases, the ventricular R wave influenced accurate atrial sensing. In one case, the atrial lead dislodged and could not be replaced because of a VT storm, and in one case, the atrial pacing threshold was too high. Median implant time of the atrial lead was 37 minutes (IQR, 17–84), with a median number of (re)positioning of 3 (IQR, 1–7).

Directly after the implant procedure, the median atrial pacing threshold determined at 1 ms was 0.9 V (IQR 1–2), and median P wave amplitude was 1.6 mV (IQR 1–3), median Far Field R wave was 0 mV (IQR 0–1), and median pacing impedance was 494 Ω (IQR 456–627).

AVNS, Test Directly After Implant

Directly after the implant procedure, AVNS, efficacy tests were performed manually in 11 patients, who were already in AF, and in 21 patients in whom AF was induced by burst pacing. A typical example of the effects of AVNS, on the ventricular interval during AF is illustrated in Figure 1.

<table>
<thead>
<tr>
<th>Table 1. Patient Demographics</th>
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<tbody>
<tr>
<td>Patient Characteristics</td>
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<tr>
<td>-------------------------------</td>
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<tr>
<td>Gender (N, %)</td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<tr>
<td>Age, y</td>
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<td>Height, cm</td>
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<td>Weight, kg</td>
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<tr>
<td>BMI, kg/m²</td>
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<td>LVEF, %</td>
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<tr>
<td>Valvular regurgitation, mitral</td>
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<tr>
<td>NYHA</td>
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<td>Class I</td>
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<tr>
<td>Class II</td>
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<tr>
<td>Class III</td>
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<tr>
<td>Class IV</td>
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<tr>
<td>Not available</td>
</tr>
<tr>
<td>Primary heart failure</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
</tr>
<tr>
<td>Idiopathic dilated</td>
</tr>
<tr>
<td>Hypertensive</td>
</tr>
<tr>
<td>Valvular</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Symptoms experienced in the last year</td>
</tr>
<tr>
<td>Chest pain</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Dyspnea</td>
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<tr>
<td>Edema</td>
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<tr>
<td>Exercise</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Palpitations</td>
</tr>
<tr>
<td>Orthopena</td>
</tr>
<tr>
<td>Cardiovascular history</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association.

Manual AVNS was always effective (>150 ms increase in median VV interval at 5 VV intervals after it started) and was therefore never terminated because of inefficacy. In 26 patients (81%), AVNS performed at 8 V increased the ventricular interval by ≥25%. Baseline ventricular interval was 670±220 ms, which was significantly increased during AVNS at 8 V to 930±310 ms (P<0.001), corresponding to an average increase...
in ventricular interval of 40%±29%. In 12 patients, AVNS was tested at 2 V, 4 V, and 8 V, with a significant dose-dependent difference in terms of ventricular interval increase (% increase at 8 V, 57±34; 4 V, 31±21; and 2 V, 27±20; \(P<0.001\)).

No patients experienced palpitations, shortness of breath, dizziness, or phrenic nerve stimulation during the AVNS test at maximal output. Five out of 32 patients reported chest, arm, or jaw discomfort during the AVNS test, but only at 8 V output.

**Follow-Up**

Automatic AVNS activations occurred in 4 patients because of AT/AF with a ventricular interval <360 ms. In 5 AVNS activations in 3 patients, AVNS was associated with an increase in ventricular interval out of the ventricular tachycardia/ventricular fibrillation (VT/VF) zone, as displayed in Figure 2. These patients did not receive an inappropriate ICD shock during the AF episode. The patient in whom automatic AVNS at 8 V was not effective had an increase of VV interval of 7% during the in-hospital test at 8 V and did not receive an inappropriate ICD shock during the AF episode.

Ten patients developed 30 VF episodes, which were terminated by an ICD shock in 22 cases. AVNS was activated in one of these episodes because the VF episode coincided with an AT/AF episode (Figure 3). After 5 ventricular beats, the AVNS was automatically deactivated and did not delay the treatment with an appropriate ICD shock.

There were no differences found in the atrial pacing threshold (\(P=0.89\)), P-wave amplitude (when in sinus rhythm; \(P=0.54\)), far-field R-wave amplitude (\(P=0.63\)), and pacing impedance (\(P=0.24\)) at 1, 3, or 6 months when compared with implant. During follow-up, we did not observe ventricular capture because of AVNS. Seven patients were lost to follow-up.

**Safety**

All safety issues related to the atrial lead placement or its procedure are displayed in Table 2. Of note, there were no adverse events related to the AVNS software.

In 2 patients, an atrial lead dislodgement was diagnosed 1 and 24 days after implant, respectively. These leads were repositioned in the right atrial appendage. In the same patients, 2 left ventricular lead dislodgements were reported.
In this feasibility study, high frequency stimulation of the right inferior ganglionated plexus with AVNS was successfully implemented using a conventional CRT-D system in 32 patients. Directly after the implant procedure, AVNS increased ventricular intervals by >25% in 81% of these patients. AVNS did not influence the safety profile of the CRT-D implant and was not associated with adverse events. AVNS activations during follow-up increased the ventricular interval during AF.

AVNS may be an important tool in reducing inappropriate shocks in patients with paroxysmal AF and an ICD.

**Shock Prevention**
Significant improvements have been made to reduce inappropriate shocks in the last few years, ranging from 21% during a 3 year German registry to 3% to 6% in 1.4 years in a recent study. Furthermore, a reduction of ICD shocks was achieved by using higher VT/VF detection thresholds, longer

**Discussion**
In this feasibility study, high frequency stimulation of the right inferior ganglionated plexus with AVNS was successfully implemented using a conventional CRT-D system in 32 patients. Directly after the implant procedure, AVNS increased ventricular intervals by >25% in 81% of these patients. AVNS did not influence the safety profile of the CRT-D implant and was not associated with adverse events. AVNS activations during follow-up increased the ventricular interval during AF.

**Figure 3.** This figure displays activation of AVNS during a VT/VF episode, which occurred during follow-up. The top is the atrial electrogram, the middle is the ventricular electrogram, and the bottom electrogram is the interpretation channel of the cardiac resynchronization therapy and defibrillator (CRT-D). In the first part of the electrogram, before the first arrow, the patient is in atrial fibrillation (AF) with an irregular ventricular interval. At the first arrow, the ventricular interval is <360 ms, activating AVNS after 7 ventricular beats (red arrow). After 5 ventricular intervals, the ventricular rate is not reduced, and AVNS is automatically ceased (purple arrow). After 21 ventricular intervals, the implantable cardioverter defibrillator (ICD) correctly identifies the VT/VF episode, starts charging (blue arrow), and appropriately applies the ICD shock (green arrow), terminating the ventricular tachyarrhythmia (gray arrow). Note that the AVNS software does not influence the time to the appropriate ICD shock. AVNS indicates atrioventricular-node stimulation; CE, electric charging starts; CD shock, cardio defibrillation by a shock; FD, fibrillation detection; and VT/VF, ventricular tachycardia/ventricular fibrillation.

**Table 2.** SAEs Related to the Procedure and System (AEAC Classification)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term (MedDra)</th>
<th>Number of Events</th>
<th>Events/Enrolled Subjects [%] (N=44)</th>
<th>Relatedness</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration</td>
<td>Device connection issue</td>
<td>1</td>
<td>2.3%</td>
<td>RA lead, implant procedure</td>
</tr>
<tr>
<td>site conditions</td>
<td>Device dislocation</td>
<td>4</td>
<td>9.1%</td>
<td>LV lead, RA lead implant procedure</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Tachyarrhythmia</td>
<td>1</td>
<td>2.3%</td>
<td>Device (external pulse generator)</td>
</tr>
<tr>
<td>Infections</td>
<td>Implant site infection</td>
<td>1</td>
<td>2.3%</td>
<td>RA lead, RV lead, LV lead, implant procedure</td>
</tr>
</tbody>
</table>

AEAC indicates Adverse Event Advisory Committee; LV, left ventricle; RA, right atrium; RV, right ventricle; and SAEs, serious adverse events.
VT/VF detection durations, use of supra ventricular tachycardia discriminators, and use of antitachycardiac pacing.\(^6\) By using data from previous studies\(^{36-38}\) combining wavelet, T-wave discrimination, lead noise discrimination, lead integrity alert, and improved recognition of rhythm termination during charging, it seems to be possible to reduce the occurrence of inappropriate shocks within 1 year to 1.8\%.\(^6\) The majority (55\%) of the inappropriate shocks were because of rapidly conducted AT/AF.\(^6\) The present study shows that AVNS is effective in increasing the ventricular interval during paroxysmal AF and may possibly reduce the inappropriate shock rate even more.

**Safety**

Implantation of the atrial lead was unsuccessful in 11 patients. Potentially, the angle of the atrial lead was too steep in relation to the myocardial wall compromising lead implant time and success rate. Furthermore, implant time of the atrial lead seems to be increased compared with normal atrial lead placement. A supportive sheath with an improved curve and stiffness can be designed, allowing easier navigation of the atrial lead and increasing implant success rate, while reducing procedure time. In addition, atrial lead dislodgement rate in the present study (6\%) seems to be in line with the 5\% dislodgement rate reported in a previous study on septally positioned atrial leads\(^9\) compared with a 2\% dislodgement rate for atrial leads positioned in the right atrial appendage.\(^40,41\) Of note, atrial lead impedance, pacing threshold, impedance, and far-field R-wave oversensing were within normal ranges and remained stable during follow-up.

The AVNS software was not associated with adverse events, neither during the implant procedure nor during the follow-up period. During the implant procedure, the ICD system was tested extensively to exclude ventricular capture because this may induce VT/VF episodes because of rapid pacing. We did not observe any VT/VF episodes related to AVNS. Importantly, AVNS does not prolong time to ICD shock in case of VT/VF, as is demonstrated in Figure 3. However, future studies with larger patient populations are necessary to provide sufficient statistical power for the safety aspects of AVNS.

**Future Studies**

AVNS\(_u\) may be useful to prevent inappropriate shocks in patients with rapidly conducted paroxysmal AT/AF, as illustrated by the 3 patients, who did not receive an inappropriate ICD shock because of the application of AVNS. However, with a larger population size are necessary to provide more extensive clinical evidence. It should be noted though that chronic AF patients will be more readily treated by atrio-ventricular node ablation. Furthermore, lead placement and the AVNS software appeared to be safe in this feasibility study, but more studies are necessary to confirm these observations, potentially using leads with adapted stiffness, curvature, screws, and implant tools.

**Conclusions**

The present study demonstrated the feasibility of implementation of AVNS in a CRT-D system. During the implant procedure, AVNS increased ventricular interval >25% in 81% of patients. AVNS did not influence the safety profile of the CRT-D system. AVNS may be an important tool in reducing inappropriate ICD shocks in patients with a short ventricular interval during AF.

**Acknowledgments**

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**Disclosures**

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