A n implantable cardioverter defibrillator (ICD) has become an important treatment modality in patients at risk of sudden cardiac death.1 However, patients with an ICD are also at risk of receiving inappropriate shocks, possibly affecting mortality,2,3 quality of life,4,5 and overall ICD longevity. About half of the inappropriate ICD shocks have been found to be caused by atrial tachycardia (AT) and atrial fibrillation (AF).3,6–8

Slowing the atrioventricular node conduction, that is, high frequency atrioventricular nodal vagal stimulation (AVNS) can be achieved by selective stimulation of the parasympathetic nerve fibers arising from the inferior ganglionated plexus to the atrioventricular node using an endocardial atrial pacing lead. AVNS has recently emerged as a nonpharmacological treatment to reduce the ventricular rate during AF.9–31

In this multicenter study, we tested the hypothesis that automated intermittent selective stimulation of parasympathetic nerves fibers, innervating the atrioventricular-node, increases the ventricular interval during rapidly conducted AF and may prevent inappropriate ICD shocks. This feasibility study reports on the implant procedure data and safety aspects of the AVNS software.

Methods

In this multicenter study, 44 patients were included. The study took place at 4 sites, that is, in Aachen, Germany; Rome, Italy; Uppsala, Sweden; and Zwolle, the Netherlands. The protocol was approved

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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 nerves; patients who had previously undergone atrioventricular or AF ablative procedures, which potentially resulted in damage of the atrioventricular node or the parasympathetic nerves; age <18 years; pregnancy; and participation in other studies, which could potentially conflict with this study.

AVNS Software Design

An investigational AVNS algorithm (AVNSia) 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 posteroseptally positioned atrial lead. AVNS software could be uploaded to the Medtronic ConsultaTM biventricular ICDs only. High frequency stimulation was performed during the refractory period of the ventricles to prevent induction of ventricular arrhythmias in case of atrial lead dislodgement and movement of this lead into the right ventricle. AVNSia was designed to initiate when AT/AF is detected in combination with manual activation during the in-hospital tests or in combination with detection of 7 subsequent rapid ventricular intervals (<360 ms) during the follow-up period. AVNSia was terminated if the therapy was ineffective (defined as <150 ms reduction in median VV (ventricular) interval check at 5 ventricular intervals after AVNS was started), or 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 posterosuperior 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 posteroseptal 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.15–18 Each atrial lead was repositioned. If the patient was in sinus rhythm during the implantation procedure, the following was verified: (1) atrial lead impedance <1500 Ohm, (2) pacing threshold <2 V at 0.5 ms, and (3) far-field R-wave oversensing was not leading to atrial oversensing.

The atrial lead was considered implanted successfully during sinus rhythm if significant atrioventricular conduction slowing (defined as a ≥225% 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 the implantation procedure, the following was verified: (1) atrial lead impedance <1500 Ohm, (2) pacing threshold <2 V at 0.5 ms, and (3) far-field R-wave oversensing was not leading to atrial oversensing.

The atrial lead was considered implanted successfully during sinus rhythm if significant atrioventricular conduction slowing (defined as a ≥225% increase of mean VV interval, could be induced using an external pulse generator by delivering 10 seconds of continuous high frequency burst 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 loaded 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 VV interval during AF was tested, with the voltage output titrated from 8, 6, 4 to 2 V. For the in-hospital tests, VV intervals obtained from continuous ECG recordings 30 seconds before the start of the AVNSia test were compared with those recorded 30 seconds after the start of the AVNSia test. The AVNSia 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 AVNS and arrhythmia, adverse events, medication, standard pacing tests, and safety tests. The AVNSia 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 AVNSia 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 VV interval during AT/AF by AVNSia programmed to maximal output during in-hospital tests. The primary end-point was the proportion of patients that achieved a VV 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
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 35 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 during acute tests and follow-up.

Statistical Analyses
The statistical analysis for this feasibility study was based on a 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 for 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>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Characteristics</td>
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<tr>
<td>Gender (N, %)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Height, cm</td>
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<tr>
<td>Weight, kg</td>
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<tr>
<td>BMI, kg/m²</td>
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<tr>
<td>LVEF, %</td>
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<tr>
<td>Valvular regurgitation, mitral</td>
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<td></td>
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<td></td>
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<tr>
<td>NYHA</td>
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<tr>
<td>Class I</td>
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<tr>
<td>Class II</td>
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<tr>
<td>Class III</td>
</tr>
<tr>
<td>Class IV</td>
</tr>
<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>
</tr>
<tr>
<td>Edema</td>
</tr>
<tr>
<td>Exercise</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Palpitations</td>
</tr>
<tr>
<td>Orthopnea</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 ia test at maximal output. Five out of 32 patients reported chest, arm, or jaw discomfort during the AVNS ia 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 ia. 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 ia 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.

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**Figure 1.** Typical example of the effect of atrioventricular-nodal stimulation (AVNS) during in-hospital test on ventricular rate during atrial fibrillation (AF). The atrial electrogram displays an episode of AF. Note the rapid and irregular ventricular rate at the left part of the tracing. At the black triangles, AVNS is activated. Note that immediately after the QRS complex, AVNS (8 V, 8 pulses, 1.5 ms, synchronized on QRS) is applied, and the ventricular rate instantly becomes slower and even necessitates ventricular pacing.

**Figure 2.** This graph shows the effect of atrioventricular-nodal stimulation (AVNS) on ventricular rate during atrial fibrillation (AF) in a typical patient during follow-up. On the left part of the graph, irregular ventricular intervals are depicted. In the middle of the graph, ventricular rate during AF accelerates, reaching the ventricular tachycardia/ventricular fibrillation (VT/VF) zone of the implantable cardioverter defibrillator (ICD). At a VT/VF count of 7 (red line in the middle of the graph), AVNS elicits an increase in VV intervals to ≈600 ms, which is in between the sensor rate of 120 beats per minute (ventricular interval of 500 ms) and the lower rate of 80 beats per minute (ventricular interval of 750 ms) because of rate adaptive pacing. At the second red line, the AVNS therapy is terminated after the programmed duration of 30 seconds. After this period, the patient remained in atrial tachycardia/atrial fibrillation (AT/AF), and it took 10 days until the ventricular interval reached the VT/VF zone again.
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. 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.2,3,7,34 Furthermore, a reduction of ICD shocks was achieved by using higher VT/VF detection thresholds, longer

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.35 By using data from previous studies, 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 compared with a 2% dislodgement rate for atrial leads positioned in the right atrial appendage.6 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 subscripts 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, studies 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 atrioventricular 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.

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Disclosures
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