Simplified Method for Vagal Effect Evaluation in Cardiac Ablation and Electrophysiological Procedures

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ABSTRACT

OBJECTIVES The aim of this study is to show a simplified reversible approach to investigate and confirm vagal denervation at any time during the ablation procedure without autonomic residual effect.

BACKGROUND Parasympathetic denervation has been increasingly applied in ablation procedures such as in vagal-related atrial fibrillation and cardioneuroablation. This method proposes an easy way to study the vagal effect and to confirm its elimination following parasympathetic denervation through vagal stimulation (VS) by an electrophysiological catheter placed in the internal jugular vein.

METHODS A prospective controlled study including 64 patients without significant cardiopathy (48 male [75.0%], age 46.4 ± 16.4 years) who had a well-defined RF ablation indication for symptomatic arrhythmias, comprising a “denervation group” (DG), with indication for ablation with parasympathetic denervation (vagal-related atrial fibrillation or severe cardioinhibitory syncope) and a “control group” (CG), with ablation indication without parasympathetic denervation (accessory pathway or ventricular arrhythmia). By using a neurostimulator, both groups underwent non-simultaneous bilateral VS (8 to 12 s, frequency: 30 Hz, pulse width: 50 μs, amplitude: 0.5 to 1 V/kg up to 70 V) through the internal jugular vein pre- and post-ablation.

RESULTS Significant cardioinhibition was achieved pre-ablation in all cases (pause of 11.5 ± 1.9 s in DG vs. 11.4 ± 2.1 s in CG; p = 0.79). Eight patients (12.5%) presented catheter progression difficulty in 1 jugular vein (2 right, 6 left); however, the contralateral VS was adequate for cardioinhibition. After ablation, the cardioinhibition was reproduced only in CG (pause of 11.2 ± 2.2 s) as in DG it was entirely eliminated. There was no significant difference between pre- and post-ablation cardioinhibition in CG (p = 0.84). There was no complication (follow-up 8.8 ± 5 months).

CONCLUSIONS The vagal stimulation was feasible, easy, and reliable, and showed no complications. It may be repeated during the procedure to control the denervation degree without residual effect. It could be a suitable tool for vagal denervation confirmation or autonomic tests during electrophysiological studies. Ablation without parasympathetic denervation did not change the vagal response.

Parasympathetic denervation has been applied in several ablation procedures, such as in vagal-related atrial fibrillation (VRAF) ablation (1,2,3) or for treating functional bradyarrhythmias (cardioneuroablation [CNA]) (4). The success of this approach depends on a correct definition of the target areas and on a sure evaluation of the denervation. In that way, several methods may be considered, such as the high-frequency endocardial stimulation (5,6) and atropine response abolition (7). High-frequency endocardial stimulation aims to stimulate neural fibers in the atrial wall (8). Even though it may be well applied...
Simplified Vagal Stimulation for Electrophysiological Procedures

**ABBR EVIAT I O N S AND ACRONYMS**

- AF = atrial fibrillation
- AV = atrioventricular
- CNA = cardioneuroablation
- GP = ganglionated cardiac plexuses, cardiac paraganglia
- IVC = inferior vena cava
- RF = radiofrequency
- SVC = superior vena cava
- VRAF = vagal-related atrial fibrillation (during sleep, at rest, after meals, and in the physical exercise recovery)
- VS = vagal stimulation

**METHODS**

**STUDY DESIGN.** This prospective controlled study comprised 2 groups: the “denervation group” (DG) underwent ablations targeting vagal tone reduction, and the “control group” (CG) submitted to conventional ablations without aiming vagal tone modification. Both were submitted to a similar routine of catheter RF ablation. VS were identically performed before and after ablations to compare the results in both groups. The control group was included to verify whether the autonomic changes obtained at the end of the intervention resulted from a real denervation or if they were a nonspecific ablation outcome.

**PATIENTS.** Recruitment of patients began on July 6, 2013, and ended on December 17, 2014. A total of 64 patients without significant structural heart disease (48 male [75.0%], age 46.4 ± 16.4 years) with symptomatic arrhythmias and a well-defined indication for RF ablation were included. Written informed consent was obtained from all patients before the procedure. They were distributed into the DG, having indication for ablation with autonomic intervention (vagal denervation for treating AF clinically related to vagal tone or severe cardioinhibitory syncope), and the CG, with ablation indication without autonomic intervention (accessory pathways or benign ventricular ectopic beats and/or idiopathic ventricular tachycardia). General features of the patients are depicted in Table 1. In the DG, there were 47 patients with severe cardioinhibitory syncope or AF clinically associated with high vagal tone who underwent vagal denervation (vagal denervation aimed and performed), following methodology previously published (4,9). The CG included 17 patients who underwent conventional ablation of accessory pathways, symptomatic benign premature beats, or idiopathic nonsustained ventricular tachycardia (vagal denervation not aimed and not performed).

Inclusion criteria for the DG were:
1. Absence of significant structural cardiopathy;
2. Severe cardioinhibitory syncope or VRAF (AF clinically related to increased vagal tone: during sleep, at rest after meals, and in the physical exercise recovery);
3. Severe cardioinhibition confirmed by head-up tilt test or Holter monitoring with symptom reproduction or AF recording related to high vagal tone;
4. Pacemaker indication at least by 1 clinician as a consequence of clinical treatment refractoriness in case of neurocardiogenic syncope;
5. Refractoriness to at least 2 antiarrhythmic drugs in case of AF;
6. Positive response to atropine test (0.04 mg/kg intravenous atropine up to a maximal dose of 2 mg, causing the heart rate to double or to reach >100 beats/min for at least 15 min); and
7. Absence of a metabolic or systemic disease that could be the syncope or AF origin.

Inclusion criteria for the CG were:
1. Absence of significant structural cardiopathy;
2. Frequent symptomatic ventricular ectopic beats and/or nonsustained monomorphic ventricular tachycardia with indication for catheter RF ablation, or symptoms or risk related to an accessory pathway with guideline ablation indication; and
3. Absence of a coronary, inflammatory, metabolic, or systemic disease that could be the arrhythmia origin.

**MATERIALS.** Materials included irrigated RF ablation catheter Biosense Webster (Johnson & Johnson, Diamond Bar, California), Duo-decapolar catheter for coronary sinus (St. Jude Medical, Minnetonka, Minnesota), transseptal puncture system (St. Jude Medical), Inquiry AFocus II circular decapolar catheter (St. Jude Medical, Irvine, California), customized neurostimulator (Pachón & Pachón, Sao Paulo, Brazil) and other support systems including: Velocity electroanatomic system (St. Jude Medical, St. Paul, Minnesota), Atakr II RF Generator (Medtronic, Minneapolis, Minnesota), BIS spectral system (Philips, Böblingen, Germany), Anesthesia (Drager workstation, Lubeck, Germany) intraesophageal echocardiography (Philips, Bothell, Washington), intraesophageal multipolar thermometer (Circa Scientific, Englewood, Colorado), and GE OEC 9900 radiological workstation (GE, Salt Lake City, Utah).
**Vagal stimulator.** The vagal stimulator used in this study presents the following features: DC stimulation with square wave pulses of 50 μs in duration, frequency of 30 Hz, and amplitude from 10 to 70 V, adjusted according to patient features (Figure 1A). An extremely short pulse duration with current limitations was employed for preventing tissue lesions. In addition, a timer function allowed the application of pulse trains with pre-defined timing, usually between 8 and 12 s.

**Vagal stimulation.** The stimulation was obtained by an endovascular electrical field created in the internal jugular vein from the distal and the third pole of the ablation catheter, temporarily used as a stimulation catheter detached from the RF generator (Figure 1B).

There was no contact with the vagus nerve. As the distance between the vagus and the catheter in the internal jugular vein may vary, the catheter used an energy of 0.5 to 1 V/kg limited to 70 V, with 30 Hz and a remarkably short pulse width of 50 μs.

**PROCEDURES.** Technical details of the several ablation procedures, such as AF ablation, vagal denervation, accessory pathway ablation, or ventricular ectopic beats or ventricular tachycardia ablation, will not be addressed in this study as they are comprehensively considered in the bibliographic references and are not the aim of the present paper. All cases were treated with intravenous anesthesia with propofol under endotracheal intubation and BIS index control.

<table>
<thead>
<tr>
<th>TABLE 1 Baseline Demographic and Clinical Data of Patients</th>
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<tbody>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td><strong>Denervation group (ablation with vagal ablation)</strong></td>
</tr>
<tr>
<td>Ablation indication</td>
</tr>
<tr>
<td><strong>Control group (ablation without vagal ablation)</strong></td>
</tr>
<tr>
<td>Ablation indication</td>
</tr>
<tr>
<td>Follow-up for VS, months</td>
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</table>

Values are n, n (%), or mean ± SD.

VEB = ventricular ectopic beat; VRAF = vagal-related atrial fibrillation; VS = vagal stimulation; VT = ventricular tachycardia.
Bilateral VS were identically performed before and after ablation in both groups, and the results were recorded for comparison. All stimulations were carried out with BIS index from 40 to 50 to avoid significant autonomic depression, to have similar autonomic tone in all evaluations, and to ensure comfort and safety for patients.

**VAGAL STIMULATION.** In the supine position, the irrigated ablation catheter was detached from the RF generator and was progressed into the internal right jugular vein up to the level of the upper wisdom tooth (Figures 1 and 2). The neurostimulator was temporarily connected between the distal and the third pole of the RF catheter. From this point, with the catheter slightly turned to the medial direction, short stimulations and minor adjustments were performed to search for the position of maximum response on the basis of the sudden cardioinhibition (sinus arrest or bradycardia and/or atrioventricular [AV] block) induction (Figure 2B). Afterward, the same type of VS was performed in the left internal jugular vein. The best response points were marked with fluoroscopy where 8 to 12 s of stimulation was performed and were recorded on each side. Identical VS were made post-ablation.

**Denervation group.** These patients underwent an isolated vagal denervation (4) or vagal denervation with complete AF ablation (9), according to the methodology previously described and published, aiming for vagal response elimination or reduction. The AF ablation was performed with 3 sequential steps: 1) conventional pulmonary vein isolation; 2) AF nest ablation; and 3) residual tachycardia (12) ablation when induced at the end of the procedure. The AF nests were defined as areas of the atrial wall having fibrillar myocardium with segmented spectrum in the frequency domain or fractionated potentials in time domain by filtering the signal from 300 to 500 Hz.

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**FIGURE 2 Vagal Stimulation Approach**

(A) Fluoroscopy of the position of the radiofrequency catheter progressed into the right and left internal jugular veins to get appropriate proximity to the jugular foramen for vagal stimulation (VS). Any new VS during the procedure was performed repeating the identical radiological position. (B and C) Example of repetitive VS near the right jugular foramen pre- and post-atropine. The right VS caused immediate sinus node arrest. After atropine, the vagal response was completely abolished.
A duodecapolar catheter was placed in the coronary sinus, and the left atrium was accessed by transseptal puncture. The 3-dimensional left and right atrial anatomy was acquired by the Velocity system in a procedure very similar to a conventional AF ablation. Intravenous heparin was used to keep the activated coagulation time from 300 to 400 s.

The ablations were essentially applied to the pulmonary vein insertion, the AF nests, and over the areas overlapping the ganglionated cardiac plexuses (GPs):

1. Area of the superior right pulmonary vein GP through the left atrium (from the insertion of the right superior pulmonary vein to the interatrial septum up to the puncture area);
2. Antrum of the pulmonary veins with complete pulmonary vein isolation in the AF group;
3. Coronary sinus roof through the left atrium aiming at additional denervation of the inferior vena cava (IVC) GP;
4. Area of the superior vena cava (SVC) GP (medial lower part of SVC) reached by the right atrium;
5. Area of the IVC-GP by the right atrium (medial upper portion of the IVC up to the coronary sinus ostium); and
6. AF nests located in the left and right surface of the interatrial septum and in the cristae terminalis.

New VS were performed at the same place as the pre-ablation ones. In case it was observed at any degree of vagal response, ablation was revised and resumed, seeking for AF nests that casually were not treated in the first phase. Again, VS were performed until complete elimination of the vagal response.

To finish, having confirmed the absence of vagal response, these patients underwent an additional atropine test (infusion of 0.04 mg/kg up to 2 mg) observing the cardiac rate by 15 min.

Control group. These patients underwent a conventional ventricular ablation for treating an accessory pathway or for ablating very frequent ventricular ectopic beats and/or idiopathic ventricular tachycardia. The transseptal approach was not necessary, and the ablations were restricted to the ventricular wall. Three catheters were used: 1 for coronary sinus mapping, 1 for ventricular pacing, and other for ablation (irrigated RF catheter, Johnson & Johnson). Similarly to the DG, before and after ablations, VS was performed for 10 s with recordings and evaluations of the responses.

Statistical analysis. Quantitative data are shown as the mean ± SD. Normality was evaluated by the Kolmogorov-Smirnov test. Paired or nonpaired samples 2-tailed Student t tests were applied to establish comparisons between continuous data before and after ablation. Statistical analysis was performed using SPSS Statistics version 19 software (IBM, Armonk, New York). All 2-tailed p values <0.05 were considered statistically significant.

Results

Most cases had easy bilateral access to the internal jugular vein. VS was easily obtained at several points from the jugular foramen to the level of the posterior arch of the third rib; however, stimulations at lower levels caused significant and undesirable stimulation of the brachial plexus, which can be prevented by using the upper approach near the jugular foramen. In all but 2 patients, the bilateral VS was obtained. It was possible to place the catheter and to stimulate each side very quickly, in 2 to 5 min. All but 1 patient developed asystole. Only 1 patient developed transitory total AV block. In this case, the response to right VS was poor, but the left VS produced a consistent transitory total AV block allowing evaluation of the vagal denervation. In another case, there was an anatomical barrier to reach a good left VS. All patients were closely monitored, and there was no case of symptoms or signs related to neurostimulation or vascular injury in a median follow-up of 8.8 ± 5 months. The ablation extension was determined by the complete elimination of the vagal response to VS. The results from the DG and CG are presented in Table 2.

Both groups presented a massive vagal response before ablation that completely disappeared in the DG following ablation (Figures 3 and 4). However, in the CG, this vagal response persisted practically without modification (pauses comparison pre- and post-ablation: p = 0.79) (Figures 5 and 6). The pre-ablation response was not significantly different between groups (p = 0.84). A total of 14 patients in the DG (29.8%) presented some degree of vagal response post-ablation that was completely corrected by resuming the ablation of the targeted areas to ablate additional AF nests in the same session. In all patients with cardioinhibitory syncope, the atropine test was normal pre-ablation (inclusion criterion) and became negative post-ablation in all cases (the heart rate changed no more than 1 beat/min).

In patients with Wolff-Parkinson-White syndrome, atrial pacing was performed during VS post-ablation to prove the accessory pathway elimination. The result was the same as obtained with the adenosine test: the pre-excitation was eliminated in all patients but 1, who was successfully treated in the same session with additional ablation. There were no complications.
DISCUSSION

A simple method of VS during electrophysiological procedures is very timely and appropriate due to the worldwide increase in autonomic cardiac interventions (10,11,17,18). In the first cardioneuroablation study (4), intravenous atropine was employed to determine whether the vagal denervation was complete. Additional ablation had to be performed in case of response. However, the long autonomic atropine effect (average half-life of 4.1 h) made any further evaluation difficult. For this reason, a simplified VS that can be repeated at any time during stepwise ablations causing no persistent autonomic modification seems to be attractive.

Because of the steerability for vein catheterization, the RF catheter was elected for VS by detaching it from the RF generator, although any other electrophysiology catheter could also be used for this purpose depending on the convenience of the operator.

As the sympathetic fibers usually regenerate in a few months, the term “parasympathetic denervation” could be correct only for the late phase. In the acute phase, there are both a parasympathetic and a sympathetic denervation (autonomic denervation); however, by using the VS in this study, we were able to test only the vagal (parasympathetic) denervation. The sympathetic one was not accessed.

The feasibility and the immediate effect of this stimulation could be quickly observed before and after the electrophysiological procedures. Nevertheless, it is essential to assess whether the electrophysiological manipulation would cause some residual undesirable influence on the VS response. Therefore, our study

**TABLE 2** Results Pre- and Post-Ablation

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients</th>
<th>Age (yrs)</th>
<th>Diagnostic</th>
<th>Vagal Response Pre (n)</th>
<th>Pause Pre</th>
<th>Procedure</th>
<th>Vagal Response Post</th>
<th>Pause Post</th>
<th>Drug Test</th>
</tr>
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<tbody>
<tr>
<td>VVS</td>
<td>7 (5 M)</td>
<td>35.7 ± 13.0</td>
<td>SCIS</td>
<td>Asy or AVB</td>
<td>12.4 ± 2.2</td>
<td>CNA</td>
<td>None</td>
<td>0</td>
<td>Atropine no response</td>
</tr>
<tr>
<td>VRAF</td>
<td>40 (32 M)</td>
<td>52.9 ± 14.2</td>
<td>VRAF</td>
<td>Asy or AVB/AF (10)*</td>
<td>11.3 ± 1.8</td>
<td>AF Abl + CNA</td>
<td>None/No AF</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
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<tr>
<td>AP</td>
<td>13 (10 M)</td>
<td>32.0 ± 14.0</td>
<td>7 WPW</td>
<td>Asy or AVB/AF (2)*</td>
<td>11.5 ± 2.3</td>
<td>AP Abl</td>
<td>Asy or AVB</td>
<td>11.3 ± 2.1</td>
<td>Adenosine TCAB</td>
</tr>
<tr>
<td>VA</td>
<td>4 (1 M)</td>
<td>47.5 ± 13.4</td>
<td>VEB/NSVT/IVT</td>
<td>Asy or AVB/VEB/NSVT (3)!</td>
<td>11.3 ± 2.0</td>
<td>Abl VEB/VT</td>
<td>Asy or AVB</td>
<td>11.3 ± 2.1</td>
<td>—</td>
</tr>
</tbody>
</table>

*10 patients in the VRAF group and 2 in the AP group presented with spontaneous AF after asystole. + in the VA group; 2 patients presented with VEB and 1 presented with NSVT following the VS. Comparison of pre-ablation pauses of denervation group vs. control group: \( p = 0.79 \); comparison of pauses pre- and post-ablation in control group: \( p = 0.84 \).

Abl = ablation; AF = atrial fibrillation; AP = accessory pathway; Asy = asystole; AVB = atrioventricular block; CAP = concealed accessory pathway; CNA = cardioneuroablation; IVT = idiopathic ventricular tachycardia; M = male; NSVT = nonsustained ventricular tachycardia; SCIS = severe cardioinhibitory syncope; TCAB = transitory complete atrioventricular block; VA = ventricular arrhythmia; VRAF = vagal related atrial fibrillation; VVS = vasovagal syncope; WPW = Wolff-Parkinson-White; — = not necessary; other abbreviations as in Table 1.

**FIGURE 3** An Example of a Patient From the Denervation Group Presenting With Severe Cardioinhibitory Syncope

The upper strip shows 9.8 s of vagal stimulation (VS) causing a pause (asystole) of 12.8 s pre-ablation. Following the vagal denervation, the VS is repeated in the same place causing no pause (lower strip), demonstrating a clear vagal denervation. During the stimulation, the rhythm remains normal without any change in the heart rate and in the atrioventricular conduction. The complete absence of vagal response in these cases is considered the primary endpoint for this procedure. RA = right atrial channel.
included a DG on the basis of CNA, whose primary objective was vagal denervation, and a CG in which extensive electrophysiological manipulation would be performed, but without aiming at vagal denervation. The results showed that VS was easily obtained, was repeated during and at the end of the procedures, and was quite useful for evaluating electrophysiological parameters. The stimulation was reliable as it was not changed by anesthesia and electrophysiology handling, showing specificity for vagal denervation. In addition, VS was found to be harmless, having no residual effect during a mean follow-up of 8.8 ± 5.0 months, and it was also an inexpensive alternative with a high potential for employment in diagnostic, therapeutic, and investigational electrophysiology.

VS is also a fundamental resource in the possibility of attaining a significant, persistent, or permanent vagal denervation through catheter ablation. This may be of interest as it can potentially allow for treatment of functional bradyarrhythmias without pacemaker implantation (10). The long-term outcomes of this therapy are showing remarkable results, reinforcing its potential therapeutic value (11). Nevertheless, its success depends on the correct demarcation of the sites that allow for extensive and long-lasting parasympathetic denervation. In this sense, it is essential to eliminate the cell body of the post-ganglionic parasympathetic neuron, widely spread in the atrial walls (AF nests) and cardiac GP (19,20). Indeed, the atrial conventional ablation, mainly the AF ablation, eliminates cell bodies of parasympathetic postganglionic efferent neurons and the neuronal fibers of the sympathetic efferent and sensory afferent. Several studies have shown that the fibers regenerate if the cell body is preserved (21,22). Thus, although there is sympathetic and sensory reinnervation, an extensive and permanent parasympathetic denervation can be observed due to elimination of the parasympathetic postganglionic cell body neurons located in the atrial walls (AF nests) and even in the GP. That is the main purpose of this technique. However, the success depends on absolute confirmation of wide vagal denervation that can be progressively tested during the ablation by the method proposed here (Figures 3 and 4).

Another potential convenience of direct vagal denervation is in the treatment of the VRAF (1,2,4). In these cases, validation of the vagal denervation during ablation seems to be a significant hint. Additionally, in this group, the spontaneous appearance of AF following the asystole caused by the VS is very interesting, linking the AF trigger to the vagal tone modification (Figure 4). Also, we have observed that the appearance of AF can be greatly increased by VS during isoproterenol infusion. However, that was not the aim of the current study.

Besides the spontaneous induction of AF, another potential usage of VS was to detect the presence of a second accessory pathway during Wolff-Parkinson-White syndrome ablation (mainly useful in cases with contraindication to adenosine) (Figure 6). Both, right and left VS cause immediate sinus depression; however, for accessory pathway searching, the left VS is likely more appropriate as it usually causes functional AV block due to AV nodal inhibition. In this

**Figure 4** An Example of a Patient in the Denervation Group Presenting With AF Typically Related to Increase of the Vagal Tone

![Diagram](https://via.placeholder.com/150)

The upper strip shows a VS during 9 s that causes an immediate pause, leading to an asystole of 10.2 s that was followed by a spontaneous induction of atrial fibrillation (AF). The RA shows the sinus rhythm on the left, the sinus pause in the middle, and the AF on the right. This patient was treated with conventional AF ablation plus vagal denervation to abolish the vagal induction of the arrhythmia. At the end of the procedures, the VS was repeated for 11.5 s, and no pause and no AF were observed. There was a complete absence of the vagal response, reaching an important immediate endpoint of the treatment. Abbreviations as in Figure 3.
sense, the endovascular stimulation of the left pulmonary artery is another source of AV block induction with less effect over the sinus node.

In addition, VS may be helpful for supraventricular tachycardia reversion, VRAF reproduction, and even restarting missed ventricular ectopic beats, helping the pace-mapping and testing the ablation result.

All of these potential benefits justify an easy, low-cost, reliable, and transient VS, particularly if its effect vanishes in a few seconds, as does the VS proposed in this study.

Although not the aim of the present paper, as the vagal denervation is the “study model” in this research, it is timely to comment about the mapping of vagal innervation. Beyond the pulmonary vein antrum, the targets for ablation were defined by mapping the neuro-myocardial interface and anatomically overlapped regions of cardiac GP. The former was carried out on the basis of the identification of AF nests according to the methodology of the CNA (4,11). As confirmed by other studies, the AF nests are present even in the absence of AF and represent areas of higher innervation density related to the neuro-myocardial interface (16). Thus, their elimination results in vagal denervation, previously shown in the initial study by the abolishment of the atropine response. Mapping was complemented with RF application in anatomic regions related to the main cardiac GP. Beyond the AF nest mapping, functional studies have confirmed that there are 3 main parasympathetic GP located in

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FIGURE 5 An Example of the Control Group

This patient had very symptomatic ventricular ectopic beats that were successfully treated by RF ablation in the right ventricle. Before ablation, 8 s of VS caused a pause of 13.4 s. Following the ablation, a new VS of 8 s produced another pause of 15.3 s. This assay shows the reproducibility of this VS method and also shows that there is no change in vagal function in cases without autonomic ablation. Abbreviations as in Figure 3.

FIGURE 6 Patient From the Control Group With Ablation Not Aiming for Vagal Denervation

This patient was included to test the vagal stimulation (VS) pre- and post-Wolff-Parkinson-White syndrome ablation. In this case, the ablation had no intention of autonomic denervation. In the upper strip, VS was applied during 10 s. Just at the beginning, there is immediate sinus pause (A), followed by a short period of atrial pacing (black arrows) during VS (B). At this moment, despite the nodal block, the patient presents conduction over the accessory pathway, as it is not depressed by the vagal action. The previous short QRS (unapparent Wolff-Parkinson-White syndrome) became aberrant, revealing the presence of the anomalous conduction. The middle strip shows a new VS at the end of the ablation, and subsequently the accessory pathway elimination. There is a long asystole (12.8 s) beginning in C, showing that the conventional ablation without denervation preserves the vagal function. In D, there was a short period of atrial pacing (black arrows) showing functional transitory complete atrioventricular block, caused by the vagal action and absence of the abnormal conduction. In the lower strip is shown a short atrioventricular block (E) induced by adenosine, proving the lack of abnormal conduction. This effect is similar to the atrial pacing during VS. The latter can be useful in cases with adenosine contraindication. P = blocked P-wave due to the vagal effect.
epicardial fat pads (23). Most of the vagal innervation of the sinus node originates from the SVC-GP and superior right pulmonary vein GP, whereas most vagal innervation of the AV node originates from the IVC-GP. Thus, it is possible to get a wide vagal denervation by anatomically ablating the atrial endocardium overlapping the GP areas (23).

**STUDY LIMITATIONS.** In this study, we used the most intense vagal response, regardless of the side; however, more detailed researches of vagal response from each side will be highly desirable. Nonsimultaneous bilateral VS was the rule in CNA; however, it was not performed in all cases of VRAF and in the patient with anatomical barrier.

Another important issue would be the study of the laterality of the VS that was not foreseen in this initial paper; nevertheless, by using the present stimulation parameters, the VS caused a massive depression of both the sinus node (asystole) and of the AV node (complete AV block), independent of the stimulated side. This suggests that there is probably a great blend of fibers from both vagus nerves innervating most of the GPs at the end. The absolute requirement of bilateral VS cannot be elucidated with the present study. Because both sinus and AV node denervation are equally desired, a solution could be to stimulate one side 2 times: first without and second with atrial pacing. If both asystole and total AV block are demonstrated, the contralateral vagal stimulation would not be necessary. This protocol was not used in this initial investigation, as the focus was only the VS feasibility.

This study did not include the long-term follow-up of denervation, accessory pathways, or ventricular arrhythmia ablation because the aim was to show the immediate vagal effect under VS, its complete disappearance after acute vagal denervation, and its maintenance without change on ablations without denervation.

**CONCLUSIONS**

The VS method proposed in the current study was feasible, easy, reversible in a few seconds, harmless, reliable, inexpensive, and showed no complications. It seems to be a potential tool for the immediate confirmation of vagal denervation, for evaluating the progression of the parasympathetic denervation during ablation, and for autonomic tests during any electrophysiological study. The vagal denervation methodology used in this controlled investigation showed complete elimination of the vagal response. Ablation without denervation did not affect the vagal response, indicating that this parameter is consistent and does not change with general anesthesia and electrophysiological handling.

**REFERENCES**


**PERSPECTIVES**

**COMPETENCY IN MEDICAL KNOWLEDGE:** The possibility of having a simplified technique to check the vagal action repeatedly without residual effects during electrophysiology studies is very attractive. After the publication of the long-term cardioneuroablation results, there has been growing interest in vagal denervation techniques that has led to the development of randomized trials to test this new therapeutic approach. A major application is the treatment of the cardioinhibitory vasovagal syncope by ablation without pacemaker implantation. However, the future of this therapy relies on an accurate validation of denervation during and immediately at the end of the procedure. In this setting, VS is essential to rationalize, validate, and optimize the results of this new therapeutic option and could constitute an indispensable tool in this type of study.

**TRANSLATIONAL OUTLOOK:** VS is also critical to confirm the denervation in other applications, such as in cardioneuroablation for the treatment of sinus node dysfunction, functional bradycardia syndrome, functional AV block, and vagal atrial fibrillation. By mimicking a kind of electronic adenosine, the VS may have several potential diagnostic applications in electrophysiology studies, such as identification of unapparent anterograde or retrograde accessory pathways (by AV nodal block induction), reversion of cholinergic-dependent tachycardias, reproduction of vagal AF, and assessment of the vagal depression degree of the sinus node and the AV conduction in autonomic studies. Last, this kind of VS may have potential additional uses for studying efferent and afferent vagal effects by evoked responses in the heart and in the central nervous system, respectively.


KEY WORDS ablation, atrial fibrillation, neurocardiogenic, syncope, vagal stimulation, vasovagal