Catheter Stimulation of Cardiac Parasympathetic Nerves in Humans
A Novel Approach to the Cardiac Autonomic Nervous System

Patrick Schauerte, MD; Karl Mischke, MD; Jurgita Plisiene, MD; Matthias Waldmann, MD; Markus Zarse, MD; Christoph Stellbrink, MD; Thomas Schimpf, MD; Christian Knackstedt, MD; Anil Sinha, MD; Peter Hanrath, MD

Background—Cardiac parasympathetic nerves run alongside the superior vena cava (SVC) and accumulate particularly epicardially adjacent to the orifice of the coronary sinus (CS). In animals, these nerves can be electrically stimulated inside the SVC or CS, which results in negative chronotropic/dromotropic effects and negative inotropic effects in the atria but not the ventricles. Parasympathetic nerve stimulation (PS) with 20 Hz in the CS, however, also excites the atria, thereby inducing atrial fibrillation. The present study overcomes this limitation by applying high-frequency nerve stimuli within the atrial refractory period. Using this technique, we investigated for the first time whether neurophysiological effects similar to those in animals can be obtained in humans.

Methods and Results—In 25 patients, parasympathetic nerves were stimulated via a multipolar electrode catheter placed in the SVC (stimulation with 20 Hz; n = 14) or CS (pulsed 200-Hz stimuli; n = 11). A significant sinus rate decrease and prolongation of the antegrade Wenckebach period was achieved during PS in the SVC. During PS in the CS, a graded-response prolongation of the antegrade Wenckebach interval was observed with increasing PS voltage until third-degree AV block occurred in 8 of 11 patients. The negative chronotropic/dromotropic effects started and terminated immediately after the onset and termination of PS, respectively. Atropine abolished these effects (n = 11).

Conclusions—Human parasympathetic efferent nerve stimulation induces reversible negative chronotropic and dromotropic effects. PS may serve as an adjunctive tool for the diagnosis/treatment of supraventricular tachycardias and may be beneficial for ventricular rate slowing during tachycardic atrial fibrillation in patients with congestive heart failure. (Circulation. 2001;104:2430-2435.)

Key Words: nervous system, autonomic electrical stimulation arrhythmia vagus nerve

Animal experiments have revealed several intravascular sites that contain parasympathetic nerves that innervate the sinus node, atioventricular (AV) node, and atria and can be stimulated electrically. Furthermore, catheter ablation of parasympathetic efferent nerves that innervate the atria abolishes vagally mediated atrial fibrillation (AF). In animals, epicardial parasympathetic cardiac nerve stimulation (PS) slows the ventricular rate during supraventricular tachycardia, thereby increasing ventricular stroke volume and mean arterial blood pressure. Stimulation of human parasympathetic efferent nerves that lie along the surface of the superior vena cava (SVC) or in the posteroinferior right atrium induces negative chronotropic and dromotropic effects. Intracardiac parasympathetic nerve stimulation, however, inevitably stimulates adjacent atrial myocardial tissue, thereby inducing and maintaining AF.

Transvenous PS is desirable because such a technique could be used to slow the ventricular rate during tachycardic AF in patients with ventricular dysfunction while avoiding the negative ventricular inotropic side effects of most of the currently clinically applied drugs with negative dromotropic or chronotropic effects. Beyond that, transvenous PS might be beneficial during electrophysiological studies when transient negative dromotropic effects are desired for the diagnosis and treatment of tachycardias.

The purpose of our study was 3-fold: First, to identify locations within the human SVC at which parasympathetic cardiac nerves can be stimulated with electrode catheters and to describe the electrophysiological effects of PS at these SVC sites; second, to develop a technique for PS within the ostium of the coronary sinus (CS) that produces consistent results while avoiding concomitant atrial tissue stimulation; and finally, to evaluate the presence and characteristics of pain elicited during PS in the SVC and CS in conscious patients.

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From the Technical University RWTH Aachen, Department of Cardiology, Aachen, Germany, and the University of Kaunas, Department of Cardiology, Kaunas, Lithuania (J.P.).
Correspondence to Patrick Schauerte, MD, Technical University of Aachen, Department of Cardiology, Pauwelstrasse 30, 52074 Aachen, Germany. E-mail psch@pcserver.mk1.rwth-aachen.de
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Methods

The study was performed at the Technical University RWTH Aachen, Germany. After informed consent had been obtained, neural stimulation was attempted during electrophysiological studies in 25 patients (12 male, 13 female, age 58 ± 14 years). The baseline rhythm was sinus rhythm in 22 patients and AF in 2 patients. Tetrapolar electrode catheters (Torq, Medtronic Inc) were placed into the high right atrium and into the right ventricular apex for pacing and sensing, respectively. In addition, an octapolar electrode catheter (Cordis Corp) was positioned at the His bundle.

Parasympathetic Stimulation in the SVC

Parasympathetic cardiac nerves that innervate the sinus node, AV node, and atria run toward the heart alongside the SVC.1,3,5,9,11 For stimulation of these nerves along the SVC, deflectable multipolar electrode catheters (Cordis Corp) were introduced through the vena femoralis. Under fluoroscopy, the catheter was advanced into the SVC and directed toward the medial wall of the vessel above its junction with the right atrium (Figure 1). Sleeves of atrial myocardial tissue extend far into the SVC.12 Because nerve stimulation with high-frequency electrical stimuli would have excited atrial myocardial tissue within the SVC, stimulation at a cycle length of 500 ms and 50 V (impulse duration 2 ms) was attempted to rule out atrial myocardial capture in the SVC. If no atrial capture occurred, neural stimulation with a frequency of 20 Hz (rectangular pulses, impulse duration 2 ms, Grass stimulator S-88, Astro-Med Inc, Grass Instruments) was initiated during sinus rhythm. During PS attempts, the PS voltage was increased stepwise from 10 to 30 V in 10-V steps. PS at each voltage level was continued for 10 seconds if the patient complained about significant discomfort or if sinus arrest or third-degree AV block occurred. At each stimulation voltage, 5 A-A intervals with and without PS were averaged and compared. In addition, the atrial and ventricular refractory periods were determined during PS at 30 V with the extrastimulus technique. To evaluate AV conduction during PS, the antegrade Wenckebach period was determined. In 6 patients, PS at 30 V was repeated after muscarinergic blockade with 1 mg atropine IV.

Statistical Analysis

All data are expressed as mean ± 1 SD. Repeated-measures ANOVA was used to test whether the nerve stimulus strength affected the sinus cycle length or antegrade Wenckebach cycle length. For individual comparison of the sinus cycle length or antegrade Wenckebach cycle length at different stimulation voltages (10 to 30 V in 5-V steps), paired t-tests were used. A value of P < 0.05 was considered significant.

PS in the CS

Most parasympathetic nerves that innervate the AV node accumulate epicardially between the ostium of the CS, the entrance of the inferior vena cava into the right atrium, and the low right atrium. This inferior vena cava–inferior atrial ganglionated plexus contains axons that preferentially innervate the AV node but contains some fibers that innervate adjacent atrial myocardial tissue.2,7,13–16 In animals, these nerves can be electrically stimulated with specifically shaped basket catheters, resulting in significant negative dromotropic effects.1,2,4 The drawback of such an approach, however, was that continuous transvascular high-frequency electrical stimulation of the inferior vena cava–inferior atrial ganglionated plexus intended for nerve stimulation inevitably excited atrial myocardial tissue, thereby inducing and maintaining AF. In the present study, we used a stimulation algorithm that allowed for selective PS in the proximal CS without simultaneous myocardial tissue stimulation. This was achieved by delivering high-frequency electrical stimuli (200 Hz) within the atrial refractory period. For this purpose, the atria were paced from the proximal CS, and the high-frequency nerve stimulation trains (train duration 50 ms) were coupled to the pacing stimulus at a delay of 20 ms.

After the introduction of a deflectable decapolar electrode catheter (Cordis Corp) through the vena femoralis, the tip of the catheter was situated in the CS ostium (Figure 2). Subsequently, probatory nerve stimulation was performed over each of the 5 bipolar pairs of the decapolar electrode catheter, starting with the most proximal electrode pair. To quantify a negative dromotropic effect during PS, the antegrade Wenckebach period was determined during PS at different stimulation voltages (10 to 30 V in 5-V steps). In 5 patients, PS at 30 V was repeated after muscarinergic blockade with 1 mg atropine IV.

Figure 1. Anteroposterior view of stimulation catheter (*) in SVC. Octapolar electrode catheter was directed toward medial wall of SVC. At this site, a slowing of sinus rate and prolongation of AV conduction was observed during PS from distal electrode pair of catheter; RVA indicates right ventricular apex.

Figure 2. A 30° left anterior oblique view of decapolar electrode catheter in CS. Transvascular PS from proximal electrode pair (PS site) resulted in high-degree AV block as long as PS was ongoing. RVA indicates right ventricular apex; HRA, high right atrium.
ebach cycle length with the baseline values, a paired Student’s t test was applied. Probability values $<0.05$ were considered significant.

**Results**

**PS in the SVC (n=14)**

In each patient, an effective PS site in the SVC could be identified. An example of PS in the SVC is shown in Figure 3. The negative chronotropic effect depended significantly on the applied stimulation voltage ($P<0.01$, ANOVA, Figure 4). PS in the SVC also led to a significant prolongation of AV nodal conduction: the antegrade Wenckebach period increased from $349\pm78$ ms without PS to $396\pm94$ ms with PS ($P<0.01$; n=9). In 1 patient with chronic AF, a significant ventricular rate slowing was observed during PS. In addition to these effects on the sinus and AV node, a slight but insignificant shortening of the right atrial refractory period ($230\pm32$ ms without PS versus $207\pm29$ ms with PS; $P=0.2$; n=6), whereas the right ventricular refractory period remained unchanged ($248\pm8$ ms without PS versus $253\pm10$ ms with PS; $P=0.3$; n=5). After administration of atropine, the negative dromotropic and chronotropic effects during PS were abolished (n=6).

**PS in the CS (n=11)**

In every patient, an effective nerve stimulation site within the proximal CS was found. PS in the CS did not induce ventricular tachycardia or ventricular fibrillation. In addition, nerve stimulation in the atrial refractory period prevented the induction of AF. PS substantially prolonged AV conduction, as shown by a graded response increase of the antegrade Wenckebach period during increasing nerve stimulation voltages. At higher PS voltages, third-degree AV block occurred in 8 of 11 patients. Figure 5 illustrates an example of third-degree AV block during PS. The negative dromotropic effect was prevented after the injection of atropine (n=5). In one patient with chronic AF, PS in the CS with increasing stimulation voltage resulted in a decrease of AV conduction until third-degree AV block occurred (Figure 6). The negative dromotropic effect depended significantly on the delivered PS voltage, as depicted in Figure 7 ($P<0.01$, ANOVA). As opposed to PS in the SVC, chest discomfort was significantly less during stimulation in the CS but also correlated with the magnitude of the nerve stimulation voltage. The discomfort was felt very locally and was reported to be located just behind the lower end of the sternum. In some patients, however, significant negative dromotropic effects could be obtained without sensations of discomfort. In most instances, the pain quality was described as a deep burning. As with the SVC, chest discomfort during PS was not abolished by the injection of atropine. Of interest, pain during PS did not occur
at ineffective CS sites at which negative dromotropic effects could not be achieved during PS.

**Discussion**

The present study introduces a novel method to increase the parasympathetic tone to the heart by transvascular electrical stimulation of parasympathetic nerves in patients. Thus far, we have identified 2 intravascular sites in patients at which these nerves can be consistently stimulated: high-frequency stimulation in the SVC excites parasympathetic nerves that innervate the sinus node, AV node, and the atria, whereas electrical stimulation in the proximal CS elicits a graded negative dromotropic response.

Because of high voltage (20 V) of high-frequency stimulation trains, huge electrical artifacts are also visible in surface ECG (arrows). After fifth PS train, third-degree AV block with a ventricular escape beat occurred. Immediately after PS was terminated (after last arrow), 1:1 AV conduction resumed. Last negative P wave after cessation of PS (*) is still a paced beat from CS, which is conducted with a prolonged P-R interval. After this beat, atrial pacing was discontinued and sinus rhythm resumed, as can be seen from now upright P waves in lead II (Y). B, Magnification of onset of PS as marked by box in A. First beat is a stimulated beat from proximal CS (A indicates atrial signal; H, His-bundle deflection; and V, ventricular signal). Starting with second paced beat, a high-frequency (200-Hz) stimulation train (arrow) lasting 50 ms is coupled to pacing stimulus (S) with a delay of 20 ms, which allows delivery of high-frequency stimuli within local atrial refractory period. In His-bundle recording, an increasing prolongation of A-H interval can be seen with increasing numbers of nerve stimulation trains until supra-His third-degree AV block occurs after fifth nerve-stimulation train.

The negative dromotropic effects elicited during activation of CS parasympathetic nerves were significantly greater than those elicited by activation of nerves accompanying the SVC. The higher PS efficacy in the CS is underlined by the lower stimulation voltages, despite the intermittent stimulation mode (coupled to the P wave) and a less effective stimulation frequency of 200 Hz in the CS compared with 20 Hz in the SVC. The reason for a higher PS efficacy in the CS may be 3-fold: First, many right- and left-sided parasympathetic nerves that innervate the AV node converge in fat located adjacent to the ostium of the CS. By contrast, predominantly right-sided vagal nerve fibers run along the SVC. It is well known that electrical stimulation of the right vagal nerve has a greater effect on the sinus node than on the AV node, whereas the opposite holds true for the left vagal nerve, although a considerable overlap of the innervation exists.

**Figure 5.** Third-degree AV block during PS in proximal CS. A, Surface ECG leads II and V4. HIS indicates His-bundle electrogram; RVA, right ventricular apex electrogram. Atria were paced from same electrode pair within ostium of CS over which nerve stimuli were delivered (note negative P waves in surface ECG lead II, *). Arrows indicate short nerve stimulation trains (50-ms train duration) of high-frequency stimuli (200 Hz), which were coupled to pacing stimuli with a delay of 20 ms to ensure nerve stimulation within local atrial myocardial refractory period. Because of high voltage (20 V) of high-frequency stimulation trains, huge electrical artifacts are also visible in surface ECG (arrows). After fifth PS train, third-degree AV block with a ventricular escape beat occurred. Immediately after PS was terminated (after last arrow), 1:1 AV conduction resumed. Last negative P wave after cessation of PS (*) is still a paced beat from CS, which is conducted with a prolonged P-R interval. After this beat, atrial pacing was discontinued and sinus rhythm resumed, as can be seen from now upright P waves in lead II (Y). B, Magnification of onset of PS as marked by box in A. First beat is a stimulated beat from proximal CS (A indicates atrial signal; H, His-bundle deflection; and V, ventricular signal). Starting with second paced beat, a high-frequency (200-Hz) stimulation train (arrow) lasting 50 ms is coupled to pacing stimulus (S) with a delay of 20 ms, which allows delivery of high-frequency stimuli within local atrial refractory period. In His-bundle recording, an increasing prolongation of A-H interval can be seen with increasing numbers of nerve stimulation trains until supra-His third-degree AV block occurs after fifth nerve-stimulation train.

**Figure 6.** PS during AF. Surface ECG leads II and V4. CS indicates CS electrogram; RVOT, right ventricular outflow tract electrogram. A, Without PS, shortest R-R interval during AF was 300 ms. Arrows indicate PS trains delivered over CS catheter (CS 7 to 8, not shown because of stimulation artifacts). PS consisted of brief trains (50-ms duration) of high-frequency (200-Hz) stimuli (arrows). Shortly after onset of PS, third-degree AV block with 2 ventricular escape beats (Y) occurred. After cessation of PS, rapid AV conduction resumed. B, After 1 mg of atropine, PS effect completely dissipated.

**Figure 7.** Influence of nerve stimulation voltage on antegrade Wenckebach (AWB) cycle length during PS in CS: with increasing stimulation voltage, a graded increase of AWB cycle length was observed (P<0.01; ANOVA). *P<0.01 vs baseline.
similar overlap of parasympathetic innervation has been reported for the right and left atria. Second, the parallel and close alignment of the CS catheter along the wall of the CS may have resulted in a more stable electrode contact than in the SVC. Third, the discomfort during PS was significantly higher in the SVC than in the CS, which prevented a further increase of the PS voltage in the SVC.

Similar effects are induced in animal models when equivalent structures in the SVC or CS are stimulated, because of the pentobarbital anesthesia applied in animals, however, we were not able to evaluate possible pain perception during PS. The observations made in this study show that PS in patients elicits symptoms. The sensations of discomfort during PS in the present study were most likely due to concomitant afferent autonomic nerve stimulation; chest discomfort increased with increasing nerve stimulation voltage, as did the negative dromotropic or chronotropic effects. In addition, the discomfort occurred predominantly at stimulation sites at which negative dromotropic or chronotropic effects were achieved, which argues against an unspecific excitation of nociceptors within the wall of the SVC or CS.

The reason for the reduced pain perception during CS stimulation compared with stimulation in the SVC, however, is not clear. Theoretically, a lower density or recruitment of afferent axons adjacent to the ostium of the CS as opposed to the SVC may underlie the lower pain perception during PS in the CS. Afferent cardiac nerve fibers travel within sympathetic and parasympathetic cardiac nerves and are part of the intrinsic cardiac nervous system. Such afferent cardiac nerve projections have been characterized thoroughly by Armour et al., Ardell et al., and others. Knowledge about the distribution and quantity of afferent nerve fibers, specifically afferent axons arising from nociceptors located at either stimulation site identified in the present study, however, is sparse and certainly deserves further investigation.

Clinical Implications
In light of the results of the present study, it seems justified to investigate the effect of transvascular PS in critically ill patients who suffer from atrial tachycardia or AF with rapid AV conduction. Especially in patients with a reduced left ventricular function and/or arterial hypotension, the ventricular rate often cannot be controlled adequately with drugs that exert negative dromotropic effects (such as β-receptor blockers or calcium channel antagonists) because of the negative inotropic side effects and the vasodilating properties of these drugs. Transvascular PS might offer the opportunity to reduce the ventricular rate in these patients without significantly affecting left ventricular contractile force. Because the majority of these critically ill patients are anesthetized, discomfort during PS should not limit the application of PS at least in the CS.

A different scenario in which PS may become very helpful is during electrophysiological studies. Intermittent blockade of the AV node by PS during narrow QRS tachycardias may facilitate the differentiation of atrial tachycardias from AV reentrant tachycardias or may ease mapping procedures of AV (Wolff-Parkinson-White) accessory pathways with little or intermittent antegrade conduction over the accessory pathway.

Limitations
Theoretically, bradycardia during PS might have been a reaction to the occurrence of discomfort. The fact that in some patients, significant negative dromotropic effects were observed during PS in the CS without discomfort, however, is evidence for a direct efferent neuronal effect rather than a reflex bradycardia due to pain perception.

A rather high stimulation voltage of up to 30 V was delivered to achieve third-degree AV block, possibly resulting in high current densities through the stimulated part of the heart or vessel. In the present study, we did not measure the current and electrode-tissue impedance during PS. We excluded any repolarization abnormalities after PS by recording 12-lead surface ECGs at the end of the study. In addition, no patient reported complaints during follow-up that might have been attributed to PS.

Pain perception in the present study was not systematically evaluated by, for example, a pain scale. Based on the patients’ descriptions, we found that for a constant nerve-stimulation frequency, there was an increase of discomfort that paralleled the increase of stimulation voltage rather than an all-or-nothing pain response to nerve stimulation. Whether this was due to an increase of the number of recruited axons with increasing stimulation voltage or to a more intense stimulation of a given number of nerve fibers cannot be answered by this study. In addition, our results do not allow us to draw conclusions concerning pain perception versus stimulation voltage delivered. Thus, we were unable to determine whether there is a linear or nonlinear increase in the degree of pain with increasing stimulation voltage. Despite these limitations, pain perception during human PS is noteworthy by itself, because it provides clinical evidence that afferent nerve fibers course in the human inferior vena cava–inferior atrial ganglionic plexus and along the outer surface of the SVC.

Finally, we did not extend PS beyond a duration of 10 seconds. Therefore, we did not evaluate whether efferent neuronal effects faded after prolonged PS in this study. We have, however, demonstrated in dogs that parasympathetic efferent nerves can be effectively stimulated over a period of ≥22 hours.

Conclusions
Parasympathetic nerves that innervate the sinus and AV nodes can be stimulated in humans by transvenous catheter stimulation techniques. Stimulation of such nerves results in readily reversible negative chronotropic or dromotropic effects. PS may serve as an adjunctive tool for the diagnosis or treatment of supraventricular tachycardias during electrophysiological studies when transient negative dromotropic effects are desired. In addition, PS may be beneficial in slowing the ventricular rate during tachycardic AF or supraventricular tachycardias in patients with ventricular dysfunction, because PS avoids the negative inotropic ventricular side effects of most of the currently clinically applied drugs with negative dromotropic or chronotropic effects.
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