Augmentation of Left Ventricular Contractility by Cardiac Sympathetic Neural Stimulation

Christian Meyer, MD*; Obaida R. Rana, MD*; Erol Saygili, MD; Christopher Gemein, MD; Michael Becker, MD; Kay W. Nolte, MD; Joachim Weis, MD; Thomas Schimpf, MD; Christian Knackstedt, MD; Karl Mischke, MD; Rainer Hoffmann, MD; Malte Kelm, MD; Dainius Pauza, PhD; Patrick Schauerte, MD

Background—Electric stimulation of mediastinal sympathetic cardiac nerves increases cardiac contractility but is not selective for the left ventricle because it elicits sinus tachycardia and enhanced atrioventricular conduction. The aim of this study was to identify sympathetic neural structures inside the heart that selectively control left ventricular inotropy and can be accessed by transvenous catheter stimulation.

Methods and Results—In 20 sheep, high-frequency stimulation (200 Hz) during the myocardial refractory period with electrode catheters inside the coronary sinus evoked a systolic left ventricular pressure increase from 97 ± 20 to 138 ± 32 mm Hg (P < 0.001) without changes in sinus rate or PR time. Likewise, the rate of systolic pressure development (1143 ± 334 versus 1725 ± 632 mm Hg/s; P = 0.004) and rate of diastolic relaxation (531 ± 128 versus 888 ± 331 mm Hg/s; P = 0.001) increased. The slope of the end-systolic pressure-volume relationship increased (2.3 ± 0.8 versus 3.1 ± 0.6 mm Hg/mL; P = 0.04), as did cardiac output (3.5 ± 0.8 versus 4.4 ± 0.8 L/min; P < 0.001). Systemic vascular resistance and right ventricular pressure remained unchanged. There was a sigmoid dose-response curve. Ultrasound analysis revealed an increase in circumferential and radial strain in all left ventricular segments that was significant for the posterior, lateral, and anterior segments. Pressure effects were maintained for at least 4 hours of continued high-frequency stimulation and abolished by β1-receptor blockade. Histology showed distinct adrenergic nerve bundles at the high-frequency stimulation site.

Conclusions—Cardiac nerve fibers that innervate the left ventricle are amenable to transvenous electric catheter stimulation. This may permit direct interference with and modulation of the sympathetic tone of the left ventricle. (Circulation. 2010;121:1286-1294.)

Key Words: contractility | coronary disease | nervous system, sympathetic | heart failure

During worsening of congestive heart failure (HF), an intrinsic counterregulatory increase of humoral and neural sympathetic tone tries to compensate for the loss of ventricular contractility. This sympathetic hyperactivity might contribute to even more deterioration of coronary artery disease and HF. Antiadrenergic pharmacological therapy has been shown to decrease mortality in both coronary artery disease and HF but cannot be applied to all patients because of systemic side effects like arterial hypotension and bradycardia. On the other hand, in the end stage of acute HF, catecholamine treatment is often needed to override β-receptor downregulation and acutely augment left ventricular (LV) contractility. In contrast to pharmacological attempts to modulate inotropy, identification of cardiac neural elements that selectively innervate the contractility of the LV may allow selective modulation of the sympathetic tone of the LV. Previously, we were able to show how the neuronal adrenergic tone to the heart can be increased by catheter stimulation of cardiac efferent sympathetic nerves within neural sleeves adjacent to both subclavian arteries. Although this approach was cardioselective without changes in systemic vascular resistance, it was not structure selective inside the heart because concomitant sinus tachycardia and enhanced atrioventricular conduction were observed. Here, we describe a transvenous catheter approach to reliably identify and stimulate intracardiac sympathetic neural elements that selectively innervate the LV.

Clinical Perspective on p 1294

Methods

Animal Preparation

In 20 sheep (weight, 50 to 70 kg), anesthesia was induced with 400 mg azaperone intramuscularly and maintained by sodium pentobarbital (5 to 20 mg · kg⁻¹ · h⁻¹). Heparin was administered to maintain
activated clotting times >250 seconds. A hexapolar electrode catheter (Cordis Corp, Baldwin Park, Cali) was inserted into the right atrium and right ventricle via both jugular veins. All tracings were amplified and digitally recorded (Axiom Sensis XP, Siemens, Erlangen, Germany). All animals received humane care in compliance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the Guide for Care and Use of Laboratory Animals prepared by the National Academy of Sciences and published by the National Institutes of Health.

Sym pathetic Nerve Stimulation
Sym pathetic nerves originating from the central nervous system are interconnected with postganglionic nerves via the cervicohoracic ganglia. From these ganglia, most sympathetic fibers course toward the heart alongside the great vessels. Previous anatomic studies have shown that sympathetic fibers also cross the coronary sinus (CS). To identify these fibers, a deflectable 8-mm-tip multielectrode catheter (Cordis Corp) was introduced inside the CS via the left jugular vein and connected to an external stimulator (Grass-S-88 stimulator, Astro-Med Inc, West Warwick, RI). To avoid inadvertent electric stimulation of the atria or ventricles, high-frequency stimulation (HFS) trains within the myocardial refractory periods (train duration, 50 ms; frequency, 200 Hz; 37.5 V; 2-ms pulse duration) were coupled to the pacing stimulus during atrial (n = 20) or ventricular (n = 8) pacing at a delay of 20 ms. While the catheter was gently rotated, advanced, or withdrawn inside the CS, the effenter sympathetic response was identified by an ≥20-mm Hg increase in systolic arterial pressure during pacing at 120 bpm.

A decapolar electrode catheter with 2-mm electrode spacing was positioned inside the CS across the takeoff of the left marginal vein (LMV). At the effective sympathetic nerve stimulation (SNS) site, the stimulation catheter was moved slightly to distal or proximal along the decapolar catheter to estimate the length alongside this catheter at which an SNS effect could be maintained. In 8 sheep, SNS was performed after β-receptor blockade (propranolol 0.2 mg/kg IV, n = 4; esmolol 1 mg/kg IV, n = 4). In 4 sheep, SNS at 37.5 V was continuously delivered for 4 hours. In 2 additional animals, aortic and CS norepinephrine concentrations were determined before and after 20 minutes of SNS. This was done 30 minutes after the SNS site had been identified inside the CS to allow normalization of norepinephrine levels. Transcardiac norepinephrine gradients were defined as CS minus aortic norepinephrine concentrations. For blood sample drawings, a pigtail catheter was positioned inside the ascending aorta while an Amplatz catheter was introduced inside the proximal CS (Medtronic, Minneapolis, Minn). Each blood sample (5 mL) was immediately centrifuged and kept frozen (−70°C). High-performance liquid chromatography was used to measure plasma norepinephrine levels.

Hemodynamics
A pigtail catheter was introduced into the LV (n = 20) to record LV pressure and rate of LV systolic pressure increase (end diastole to peak systole) and decrease (aortic valve closure to beginning of diastole). In 5 sheep, a pigtail catheter was positioned inside the right ventricle for pressure recording. To determine LV contractility independently of preload or afterload, pressure-volume loops were recorded via a pressure-volume catheter (CD Leycom, Zoetermeer, the Netherlands) that was advanced into the LV (n = 4) via the femoral artery. Pressure-volume signals were digitized at a sample frequency of 250 Hz. LV volume was calibrated with thermodilution and hypertonic saline dilution as described previously. Under stable hemodynamic conditions, LV pressure and volume were recorded during a 15-second balloon occlusion of the inferior vena cava. To calculate cardiac output (thermodilution method), total systemic vascular resistance, and pulmonary vascular resistance, a Swan-Ganz catheter (Becton Dickinson, Sandy, Utah) was introduced into the pulmonary artery (n = 5).

Regional LV Function
Indices of regional systolic LV function were derived from echocardiographic images (Vivid ii, GE Healthcare, Milwaukee, WIs) of the LV (n = 6). Three parasternal short-axis views (basal, midventricular, and apical) were acquired with 2-dimensional tissue harmonic imaging. Regional wall motion scoring was performed following American Society of Echocardiography guidelines; the LV was divided according to a 16-segment model. Additionally, circumferential strain and radial strain as reliable parameters of regional LV function were analyzed. The focus was adjusted to the center of the LV cavity. In the parasternal short axis, radial strain relates to deformation of the myocardial wall from the endocardium to epicardium, whereas circumferential strain relates to deformation along the curvature of the LV. Analysis was performed offline with dedicated software (EchoPAC BT05.2, GE Vingmed, Horton, Norway). The system calculates mean strain values for whole predefined LV segments as changes in length of myocardium related to the baseline size at the beginning of the QRS complex. These changes are given in term of percentage. All values are given as peak systolic data. Two echocardiographers blinded to the stimulation mod analyzed the data.

Cardiac Electrophysiology
Because SNS stimuli were delivered inside the atrial refractory period during atrial pacing at 120 bpm, the effect of SNS on sinus rate could be investigated only by indirect means. For this purpose, the sinus node recovery time (SNRT) was determined as sinus rhythm return cycle immediately after atrial pacing at 120 bpm for 30 seconds with and without additional SNS. The corrected SNRT (SNRTc) was the difference between the SNRT and the atrial cycle length just before each pacing episode. The SNRTc was repeated 3 times and averaged. The 30-second period was chosen because the SNS effect usually reached a plateau after 30 seconds. Because there is an overhang of the SNS effect that usually fades within 20 seconds after termination of SNS, the first spontaneous sinus cycle length after cessation of SNS was measured to calculate SNRTc. PR, QRS, QT, and QTc were measured during SNS and atrial pacing for 30 seconds. For this purpose, the last 5 beats before the cessation of SNS were averaged and compared with the intervals with atrial pacing done before the onset of SNS.

The right and left atrial (distal CS) effective refractory periods were determined with and without SNS (n = 4). For this purpose, the atria were paced at 120 bpm from the SNS site. The extrastimulus in the right or left atrium was then coupled to the local atrial deflection (10-ms decrement in extrastimulus, 7-beat baseline pacing train, 2-second interval after each sequence). To determine the ventricular effective refractory period and to assess ventricular vulnerability to ventricular tachycardia or fibrillation, programmed stimulation was performed with and without SNS at 2 cycle lengths (500 and 400 ms) in the right ventricle with up to 3 extrastimuli until the effective refractory period was met or the coupling interval reached 180 ms (n = 4).

Histology
To create microscopic images, sequential sectioning was performed orthogonal to the axis of the CS from the left atrial appendage to the CS orifice (n = 2). Each segment included 7 to 20 mm of the adjoining left atrium. From the paraffinized tissue blocks, 2-μm-thick sections were taken, mounted on charged slides, and stained as indicated below. Transmural sections were deparaffinized and rehydrated through a graded ethanol series. The sections were then treated with 3% hydrogen peroxide to inactivate endogenous peroxidase, followed by incubation with Serum-Free Protein Block (DAKO, Carpinteria, Calif) for 10 minutes to reduce nonspecific staining. For immunohistochemical staining, the sections were incubated at room temperature with primary antibodies for 1 hour, then with biotinylated secondary antibodies (DAKO) for 30 minutes, followed by ABCComplex/horseradish peroxide (DAKO) for 30 minutes. The source of staining was anti-tyrosine hydroxylase as a marker for adrenergic nerves.

Statistical Analysis
All data are expressed as mean ± SD. The dose-response and kinetics of systolic LV pressure changes to SNS were evaluated with...
repeated-measures ANOVA. The relationship and the strength of
correlation between the systolic LV pressure changes over time after
the initiation or cessation of HFS were quantified by regression
analysis; \( R^2 \) was the coefficient of determination. The paired \( t \) test
was used to compare differences in continuous variables before
(control) and during SNS. Two-way repeated-measures ANOVA
was used to examine the effect of SNS before and after \( \beta \)-receptor
blockade. The effect of SNS on regional LV function was analyzed
by 2-way repeated-measures ANOVA. Values of \( P<0.05 \) were
considered significant. Statistical analysis was done with SPSS
software version 14.0 (SPSS Inc, Chicago, Ill).

The authors had full access to and take full responsibility for the
integrity of the data. All authors have read and agree to the
manuscript as written.

**Results**

In all 20 sheep, sympathetic nerves along the CS could be
identified next to the branching of the great cardiac vein (GCV)
and LMV. At this side, a selective increase of LV inotropy was
observed during SNS. HRA indicates high right atrium; OCB,
occlusion balloon catheter.

Figure 1. Left anterior oblique view of SNS site inside the CS.
Retrograde occlusion venography illustrating a multielectrode
catheter (') next to the branching of the great cardiac vein (GCV)
and LMV. At this side, a selective increase of LV inotropy was
observed during HFS. HRA indicates high right atrium; OCB,
occlusion balloon catheter.

SNS during atrial pacing at a constant rate significantly
augmented LV pressure (Figure 2) from 97±19 to
137±32 mm Hg (\( P<0.001 \)). Similarly, SNS during right
ventricular pacing significantly increased LV systolic pressure
(100±22 versus 143±33 mm Hg; \( P=0.003; n=8 \)). SNS
coupled to the ventricular pacing stimulus during induced
atrial fibrillation (AF) also resulted in a significant LV pressure increase
(93±10 versus 126±29 mm Hg; \( P=0.04; n=5 \)).

Likewise, rate of pressure development increased from
1143±334 to 1728±632 mm Hg/s (\( P=0.004 \)), and rate of
diastolic relaxation increased from 531±128 to
888±331 mm Hg/s (\( P=0.001 \)). A significant increase in the
slope of the end-systolic pressure-volume relationship was
observed during SNS (2.3±0.8 versus 3.1±0.6 mm Hg/mL;
\( P=0.04 \); Figure 3). SNS increased cardiac output from
3.5±0.8 to 4.4±0.8 L/min (\( P<0.001 \); Table 1). The dose-
response curve of SNS revealed a sigmoid shape (Figure 4)
with a quick exponential onset or offset (\( n=6; R^2=0.68; \)
\( P<0.001 \)) of the pressure increase within 20 seconds after
SNS initiation or cessation (\( P<0.05 \) versus baseline; \( n=6; \)
\( P<0.001 \), ANOVA). No significant change in right ventricular
pressure (22±3 versus 21±3 mm Hg; \( n=5; P=0.61 \))
ocurred during SNS. SNS did not significantly change total
systemic vascular resistance (1525±571 versus 1461±463
dynes \( \cdot \) s \( \cdot \) cm\(^{-5} \); \( P=0.32 \)) or pulmonary vascular resistance
(75±34 versus 67±14 dynes \( \cdot \) s \( \cdot \) cm\(^{-5} \); \( P=0.34 \)). The base-
line transcardiac norepinephrine gradient without SNS was
0.15 nmol/L (CS, 2.6 nmol/L; aorta, 2.7 nmol/L; \( n=2 \)). After
20 minutes of SNS, plasma levels of norepinephrine in-
creased to 12.7 nmol/L inside the CS compared with 8.9
nmol/L inside the aorta. This led to an increase in the
transcardiac norepinephrine gradient to 3.7 nmol/L (\( n=2 \)).
SNS-mediated effects were abolished by \( \beta_1+2 \)-receptor or
\( \beta_1 \)-receptor blockade (Table 2).

**Hemodynamics**

Figure 2. SNS during atrial pacing. The arrow (left) indicates the
onset of SNS. After 30 seconds of continued SNS (‘), a signifi-
cantly increase in systolic LV pressure occurred (right). A indicates
atrial deflection; S, stimulation artifact; and V, ventricular
deflection.
Regional LV Function

During SNS, a homogeneous increase in circumferential and radial strain was observed at all transversal levels \( (P=0.003 \) and \( P=0.004, \) 2-way ANOVA; Table 3). The interlevel difference in circumferential strain at baseline was not altered by SNS \( (P=0.86 \) and \( P=0.74; \) Table 3).

Analysis of longitudinal segments revealed an increase in circumferential and radial strain in all segments \( (P=0.02 \) and \( P=0.01, \) 2-way ANOVA; Table 4). There was no statistically significant interaction between SNS and segments; ie, the magnitude of the effect of SNS did not vary significantly by segment type \( (P=0.91 \) and \( P=0.94; \) Table 4).

Cardiac Electrophysiology

The sinus cycle length immediately after cessation of SNS did not change significantly compared with the sinus cycle length immediately before SNS \((712\pm117 \) versus \( 736\pm128 \) ms; \( P=0.57).\) Likewise, the SNRTc was not shortened by SNS \((134\pm83 \) versus \( 136\pm86 \) ms; \( P=0.53).\) No change in the PR, QT, or QTc interval was observed during SNS (Table 3). SNS led to a significant shortening of QRS width \((74\pm15\) versus \( 67\pm11 \) ms; \( P=0.004).\) This SNS-mediated shortening of ventricular conduction velocity was abolished by \( \beta \)-receptor blockade. SNS did not change the right ventricular refractory period \((353\pm6 \) ms without SNS versus \( 337\pm15 \) ms with SNS; \( P=0.19),\) right atrial refractory period \((253\pm10 \) versus \( 243\pm15 \) ms; \( P=0.42),\) or left atrial refractory period \((243\pm6 \) versus \( 240\pm10 \) ms; \( P=0.67).\)

Programmed ventricular stimulation during SNS did not induce ventricular tachycardia or fibrillation. In 2 sheep, SNS induced AF, which terminated spontaneously within 5 minutes, whereas in 3 sheep, AF lasted >5 minutes and was terminated by electric cardioversion.

Continuous SNS

The increase in LV systolic pressure could be maintained during 4 hours of continuous SNS (Figure 5). Likewise, cardiac output was continuously augmented, whereas total peripheral resistance did not change during SNS. Four hours of continuous SNS did not induce atrial or ventricular arrhythmia.

Histology

Postmortem inspection of the stimulation sites within the CS did not show macroscopic lesions. Microscopic analysis showed a slight denudation of the endothelium at the catheter stimulation site in 1 animal. Microphotographs showed nerve bundles in the fibrous and fatty tissue surrounding the CS close to the LMV. There was an intense positive staining for tyrosine hydroxylase, indicating a sympathetic origin of these nerve fibers (Figure 6).

Discussion

The present study introduces an approach to selectively increase LV contractility by intracardiac electric neural stimulation with transvenously introduced electrode catheters. The major advantages of this approach are the following: There were no changes in sinus node function, atroventricular conduction, or peripheral vessel tone; positive inotropic effects were independent of preload and afterload; because of the short half-life of the electrically released neurotransmitter, the effect can be readily adjusted to the medical needs;
and the neural structure can be accessed rapidly on a percutaneous-transvenous route.

Previous anatomic and functional studies found distinct projections of sympathetic efferent fibers to the heart. Anatomic studies in the canine and human heart demonstrated that cardiopulmonary neural efferents of both cervicothoracic ganglia are interconnected in the mediastinum immediately cranial to the heart and project onto the heart as 3 major sympathetic nerves to innervate the ventricles: the right and left coronary cardiac nerves (coursing along the right and left coronary arteries) and the left lateral cardiac nerve. The left lateral cardiac nerve courses adjacent to the left atrial appendage and anterior to the left pulmonary veins onto the left lateral myocardium. In dogs, it is the offspring of the ventrolateral nerve. Besides these 3 major nerves, small cardiac nerves arise from various cardiopulmonary plexus and the thoracic vagal nerves that innervate overlapping regions of the LV or right ventricle.21

On the basis of functional and anatomic analyses, most likely sympathetic efferent fibers of the left lateral cardiac nerve were stimulated in the present study. The positive inotropic effects were obtained in all segments of the LV, but the magnitude of the increase was less and not significant in septal and inferoseptal segments. This is in line with results during epicardial stimulation of the ventrolateral nerve in dogs. The septum also contributes to right ventricular function, and right ventricular pressure did not change during SNS; these findings may be taken as evidence for a different sympathetic neural input to the right ventricle and septum. In accordance with this, other authors have demonstrated that the right ventricular lateral wall is innervated mainly by sympathetic fibers crossing the right anteroventricular groove.

Table 2. Hemodynamic Effects of SNS

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>SNS</th>
<th>Δ</th>
<th>Control</th>
<th>SNS</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVSP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β1+2-blockade (n=4)</td>
<td>98±23</td>
<td>138±34*</td>
<td>40±19</td>
<td>90±26</td>
<td>93±26</td>
<td>3±3</td>
</tr>
<tr>
<td>β1-blockade (n=4)</td>
<td>100±20</td>
<td>131±23†</td>
<td>31±5</td>
<td>84±9</td>
<td>82±6</td>
<td>−2±4</td>
</tr>
<tr>
<td>All β-blockade (n=8)</td>
<td>98±20</td>
<td>135±27†</td>
<td>37±14</td>
<td>87±18</td>
<td>89±17</td>
<td>2±1</td>
</tr>
<tr>
<td>RPD, mm Hg/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β1+2-blockade (n=4)</td>
<td>1075±272</td>
<td>1650±755*</td>
<td>575±517</td>
<td>913±233</td>
<td>913±233</td>
<td>0±0</td>
</tr>
<tr>
<td>β1-blockade (n=4)</td>
<td>1017±144</td>
<td>1300±300*</td>
<td>188±103</td>
<td>973±180</td>
<td>1000±141</td>
<td>38±48</td>
</tr>
<tr>
<td>All β-blockade (n=8)</td>
<td>1046±208</td>
<td>1475±528*</td>
<td>429±410</td>
<td>943±206</td>
<td>957±187</td>
<td>14±37</td>
</tr>
<tr>
<td>RoR, mm Hg/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β1+2-blockade (n=4)</td>
<td>513±85</td>
<td>825±150*</td>
<td>312±118</td>
<td>425±98</td>
<td>435±124</td>
<td>10±80</td>
</tr>
<tr>
<td>β1-blockade (n=4)</td>
<td>426±36</td>
<td>651±71*</td>
<td>225±36</td>
<td>438±75</td>
<td>425±125</td>
<td>−13±85</td>
</tr>
<tr>
<td>All β-blockade (n=8)</td>
<td>470±61</td>
<td>738±111*</td>
<td>268±103</td>
<td>432±87</td>
<td>425±125</td>
<td>−7±25</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

*P<0.05, †P<0.01 vs control.
laterally, whereas the septum receives inputs from nerve fibers that cross the lateral right atrioventricular groove and from fibers coursing alongside the left anterior descending coronary artery. The observed positive inotropic effects in the anterior segments of the LV during SNS support the previous description of a considerable overlap of innervation between right and left sympathetic neural inputs to the heart.

At present, there is only limited anatomic evidence of a similar cardiac sympathetic nerve distribution along the inferior CS in humans. Thus, we do not know whether stimulation of these neural structures in man elicits comparable functional effects. The similarity of intracardiac parasympathetic neuralstructures in humans, dogs, and sheep, however, may be taken as initial evidence for a similar course of autonomic fibers alongside the left anterior descending coronary artery. Hemodynamic increase in the LV sympathetic tone during SNS may increase the heterogeneity of ventricular refractory periods, thus promoting ventricular arrhythmias at least in coronary artery disease or HF.

AF was induced in 5 animals and mostly terminated spontaneously. The probable reason was local refractory period shortening at the CS stimulation site, which was overlying the left atrium. HFS is capable of stimulating local nerve endings that spread inside the local atrial tissue, which may have shortened the local refractory period. Likewise, Lemery and colleagues reported an increase in systemic arterial pressure during HFS next to the left pulmonary veins. This may also be taken as preliminary evidence for comparable sympathetic structures in humans.

The evidence for stimulating local efferent cardiac sympathetic fibers in the study presented here is multifold. First, the positive inotropic effect during HFS was abolished by β-receptor blockade. Second, immunohistochemistry demonstrated tyrosine hydroxylase–positive fibers close to the CS stimulation site. Third, increased outflow of cardiac norepinephrine into the CS was measured during SNS. Likewise, other authors have shown in isolated hearts of dog, sheep, and humans that peripheral neural stimulation also elicits sympathetic efferent effect. Changes in LV contractility during neural stimulation inside the CS might still be due in part to afferent stimulation with reflex central sympathetic activation. The lack of changes in sinus rate or peripheral vessel resistance during SNS in our study, however, supports the idea of a predominant efferent local sympathetic response versus a central reflex increase of the sympathetic tone.

Ventricular proarrhythmia is an important concern in any attempt to increase sympathetic neural tone. Accordingly, accelerated idioventricular rhythms were observed during epicardial sympathetic neural stimulation of the ventrolateral cardiac nerve in healthy open-chest dogs. Of note, short-term intraoperative stimulation of mediastinal cardiac nerves in patients undergoing coronary artery bypass surgery has been performed without eliciting malignant ventricular arrhythmias. We did not observe ventricular arrhythmia in this short-term study with a maximal SNS duration of 4 hours. Because pentobarbital is known to increase baseline sympathetic tone, it seems unlikely that the anesthetics used in the present study might have been responsible for this lack of ventricular arrhythmia during SNS. Nevertheless, an asymmetrical increase in the LV sympathetic tone during SNS may increase the heterogeneity of ventricular refractory periods, thus promoting ventricular arrhythmias at least in coronary artery disease or HF.

Table 4. Longitudinal Radial and Circumferential Strain During SNS

<table>
<thead>
<tr>
<th>Strain</th>
<th>Septal</th>
<th>Inferior</th>
<th>Posterior</th>
<th>Lateral</th>
<th>Anterior</th>
<th>Anteroseptal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=6)</td>
<td>−6.7±4.9</td>
<td>−7.9±4.8</td>
<td>−8.7±3.3</td>
<td>−8.3±6.2</td>
<td>−7.7±5.5</td>
<td>−7.2±4.3</td>
</tr>
<tr>
<td>SNS (n=6)</td>
<td>−8.2±6.1</td>
<td>−9.7±5.2</td>
<td>−14.3±4.3</td>
<td>−14.2±8.0</td>
<td>−12.5±6.1</td>
<td>−11.5±5.0</td>
</tr>
<tr>
<td>Δ</td>
<td>−1.5±3.5</td>
<td>−1.8±3.9</td>
<td>−5.5±4.2</td>
<td>−5.8±4.4</td>
<td>−4.7±3.4</td>
<td>−4.3±3.1</td>
</tr>
</tbody>
</table>

Each longitudinal segment (eg, septal) comprised basal, midventricular, and apical segments. The P values for circumferential and radial strain, as determined by 2-way ANOVA, were 0.02 and 0.01 for SNS, 0.31 and 0.82 for segment, and 0.91 and 0.94 for the SNS-segment interaction.
refractory period at more remote atrial sites (eg, distal CS) during SNS also supports the idea that a local neural response caused AF rather than a stimulation of nerve fibers that innervate a larger part of the atria.

**Potential Clinical Implications**

There are potential scenarios in which access to the identified neural structure may be beneficial. First, during acute HF, SNS via a catheter inside the CS might be used as an adjunct to intravenous catecholamine treatment. Likewise, during chronic end-stage HF, SNS via an implantable lead may intermittently augment LV contractility before overt decompensation develops. For example, fluid or pressure sensors might indicate a deterioration of LV function and trigger short-term low-intensity SNS to counteract the loss of cardiac output. However, this would certainly require additional implantation of a defibrillator in case of proarrhythmia caused by SNS. In the initial stages, one could also envision intermittent hospital-based inotropic therapy via an implanted SNS lead under the close surveillance of an HF specialist.

Finally, there is recent evidence that left stellate ganglionic blockade may hemodynamically stabilize patients with severe ventricular arrhythmias. Therefore, one could imagine that catheter ablation of the sympathetic nerves around the CS may be developed as a last-resort antiadrenergic therapy in these patients. However, at this time, we do not know whether this may cause denervation hypersensitivity or a dysbalance in sympathetic innervation, which in turn might favor the development of ventricular arrhythmias in the midterm.

**Study Limitations**

SNS in humans may stimulate afferent sympathetic nerves, which may cause sensations of discomfort. This was also observed occasionally in humans during stimulation of parasympathetic fibers in the proximal CS with voltages comparable to those in this study. In later human studies with active fixation leads, the stimulation strength was reduced almost 10-fold, and sensations of discomfort were rare.

The many statistical comparisons in a small sample of animals may have led to a type I error. In addition, in the present study, the effects during HFS were abolished by β1-blockade, which indicates that predominantly efferent sympathetic fibers were excited. We did not apply atropine during SNS to unmask concomitant parasympathetic effects at the SNS site. However, the observation that SNS after β-blockade did not decrease the parameters of LV contractility or induce sinus node slowing or PR prolongation supports the hypothesis that predominantly sympathetic fi-

---

**Table 5. Electrophysiological Effects of SNS**

<table>
<thead>
<tr>
<th></th>
<th>QRS</th>
<th>PR</th>
<th>QT</th>
<th>QTc</th>
<th>RR</th>
<th>SNRT*</th>
<th>SNRTc*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=18), ms</td>
<td>74±15</td>
<td>194±49</td>
<td>315±69</td>
<td>435±94</td>
<td>502±5</td>
<td>831±90</td>
<td>134±83</td>
</tr>
<tr>
<td>SNS (n=18), ms</td>
<td>67±111†</td>
<td>178±42</td>
<td>306±68</td>
<td>423±93</td>
<td>501±3</td>
<td>848±97</td>
<td>136±86</td>
</tr>
<tr>
<td>Δ, ms</td>
<td>−7±6</td>
<td>−16±14</td>
<td>−9±8</td>
<td>−13±9</td>
<td>−1±2</td>
<td>17±9</td>
<td>2±6</td>
</tr>
</tbody>
</table>

*n=5.
†P<0.01 vs control.

---

**Figure 5.** LV systolic pressure (LVSP; A), cardiac output (CO; B), and total peripheral resistance (TPR; C) during short-term SNS. The positive inotropic effects could be maintained for at least 4 hours. †P<0.05 vs control (n=4).
by guest on April 23, 2017

Meyer et al Sympathetic Control of Ventricular Contractility

Figure 6. Microphotographs of the SNS site. The stimulation site was close to the takeoff of the LMV from the great cardiac vein (GCV). Immunohistochemical staining of tyrosine hydroxylase (TH), a marker of sympathetic nerve fibers, showing multiple TH-positive fibers (arrows) close to the SNS site (arrowhead) next to the branching of the GCV and LMV.

ners were stimulated. In contrast, ≈2 cm proximal to the SNS site inside the CS ostium, parasympathetic (PR prolongation) but not sympathetic effects were elicited by HFS. This is evidence for a distinct anatomic course of parasympathetic and sympathetic neural fibers across the CS in sheep.

The transcardiac norepinephrine gradient is only a rough estimation of cardiac catecholamine production. It does not acknowledge changes in norepinephrine reuptake as a potential modifier of CS norepinephrine levels during SNS.

For the determination of SNRT, an SNS period of 30 seconds was chosen. Because the maximal SNS effect was observed 30 seconds after initiation of SNS, an SNS influence on the sinus node function might have been missed with this short SNS period. However, because noticeable positive inotropic effects already started within 10 seconds after SNS onset, a parallel sinus node effect should have been detected by this protocol. However, because we do not know whether the sinus node might react with a different latency than the LV to SNS inside the CS, we cannot completely exclude that SNS might have affected the sinus node. We also did not deliver the SNS stimuli during sinus rhythm because we did not have the appropriate software solution to deliver the HFS triggered to the local atrial electrogram. Such a technique might have directly shown the effect of SNS on sinus node function.

Changes in preload during SNS may have affected LV inotropy. For example, increased superior vena cava return, increased pulmonary venous return to the left atrium resulting from stimulated venous contraction or increased atrial contractility may have contributed to the augmented LV contractility.

The present study was not designed to investigate the complex interplay of SNS impulse parameters to achieve a positive inotropic effect. Thus, different patterns with less energy consumption and equal or better SNS effects might exist that might be favorable for any future implantable device solution. Theoretically, a window of stimulus strength might exist at which positive inotropic effects can be elicited but no arrhythmias occur. This was, however, not investigated in the present study.

In awake and possibly moving patients, a deflatable stimulation catheter may not provide stable contact inside the CS at the SNS site. Thus, distinct catheter designs (eg, expandable basket design, epicardial leads) will have to be developed. In addition, downstream stimulation inside the LMV might also yield positive inotropic effects. This would be very intriguing because a specific permanent lead might be implanted in the branching vein.

Conclusions Cardiac nerve fibers that innervate the LV are amenable to transvenous electric catheter stimulation. This may permit direct interference with and modulation of the sympathetic tone of the LV.

Disclosures None.

References
During worsening of congestive heart failure, an intrinsic counterregulatory increase in humoral and neural sympathetic tone tries to compensate for the loss of ventricular contractility. This sympathetic hyperactivity might contribute to even more deterioration of heart failure. Antiadrenergic pharmacological β-receptor blocker therapy has been shown to decrease mortality in heart failure but cannot be applied to all patients because of systemic side effects like arterial hypotension and bradycardia. On the other hand, in the end stage of acute heart failure, catecholamine treatment is often needed to override β-receptor downregulation and to immediately augment left ventricular contractility. However, this is not cardioselective in that it also affects systemic vascular tone, thereby increasing cardiac afterload and potentially diminishing peripheral organ perfusion. This study provides experimental evidence for the presence of sympathetic neural fibers alongside the coronary sinus that selectively innervate the left ventricle and can be electrically stimulated by transvenously introduced electrode catheters. Because the obtained increase in left ventricular contractility is not accompanied by tachycardia or an increase in peripheral vascular resistance, such an approach might reduce the likelihood of peripheral organ damage. On the other hand, catheter ablation of the sympathetic nerves around the coronary sinus may be developed as a selective antiadrenergic therapy of the last resort in patients with severe ventricular arrhythmias (eg, to stabilize patients) during an electrical storm.
Augmentation of Left Ventricular Contractility by Cardiac Sympathetic Neural Stimulation

Christian Meyer, Obaida R. Rana, Erol Saygili, Christopher Gemein, Michael Becker, Kay W. Nolte, Joachim Weis, Thomas Schimpf, Christian Knackstedt, Karl Mischke, Rainer Hoffmann, Malte Kelm, Dainius Pauza and Patrick Schauerte

Circulation. published online March 8, 2010;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2010/03/08/CIRCULATIONAHA.109.874263.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/