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Selective Increase of Cardiac Neuronal Sympathetic Tone

A Catheter-Based Access to Modulate Left Ventricular Contractility

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OBJECTIVES This study was designed to develop a technique to selectively increase the sympathetic tone to the heart by cardiac sympathetic nerve stimulation (SNS).

BACKGROUND Access to the cardiac sympathetic neurons may allow modulating the adrenergic tone of the heart while avoiding systemic side effects.

METHODS Cardiac sympathetic nerves course within neural sleeves along the subclavian artery. Because of this proximity, transvascular SNS was attempted with electrode catheters inside the subclavian artery in 16 pigs.

RESULTS Right/left (R-/L-) SNS (20 Hz) during ventricular pacing at 200/min evoked a >100% increase of left ventricular systolic pressure (baseline: 51 ± 1 mm Hg; L-SNS: 118 ± 26 mm Hg; R-SNS: 116 ± 33 mm Hg; $p < 0.001$) while systemic vascular resistance remained unchanged. There was a sigmoid dose-response curve with rapid on- and offset of the effect during SNS initiation/cessation. Positive inotropic effects persisted for 12 h of continued SNS (n = 4). Besides positive dromotropic effects, L-SNS/R-SNS yielded a 41% and 77% sinus rate increase, respectively.

CONCLUSIONS The neural adrenergic tone to the heart can be selectively increased by catheter stimulation of cardiac efferent sympathetic nerves. (J Am Coll Cardiol 2005;46:1354–9) © 2005 by the American College of Cardiology Foundation

The sympathetic nervous system exerts its effects via humoral and neural pathways. Access to organ-specific autonomic neurons would allow therapeutic modulation of the autonomic tone of a target organ while avoiding undesired systemic side effects observed during pharmacologic sympathetic stimulation or blockade. A selective elevation of the cardiac parasympathetic neural tone has recently been obtained in humans (1). The present study introduces a percutaneous approach for identification and stimulation of sympathetic nerves, which exclusively innervate the heart.

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METHODS

Animal preparation and instrumentation. In 16 pigs (71 ± 6 kg), anesthesia was induced with 400 mg azaperone intramuscularly and maintained by sodium pentobarbital (bolus: 16 mg/kg, infusion: 5 to 20 mg/kg/h) and N_2O/O_2 (Dräger-Sulla-808V/Dräger, Lübeck, Germany). Six surface electrocardiogram limb leads were recorded. After heparinization (1,000 IE/h), multipolar electrode catheters were inserted into the coronary sinus, high right atrium, and right ventricular apex via femoral/jugular veins.

Hemodynamic measurements. A pigtail catheter was introduced into the left ventricle (LV) (n = 16) and a Swan-Ganz-Catheter (Becton/Dickinson, Sandy, Utah) into the pulmonary artery (n = 6) for pressure recording and calculation of cardiac output and total peripheral resistance (TPR) during sinus rhythm and ventricular pacing at 200/min. The rates of LV systolic pressure increase (end-diastole to peak-systole) and decrease (aortic valve closure to beginning of diastole) were calculated.

Electrophysiologic measurements. The RR, PR, QRS-QT, and QT_c intervals were measured in lead II. The intervals between ventricular deflections in proximal and distal coronary sinus electrograms were averaged to calculate local conduction velocity by dividing inter-electrode distance by time.

Effective refractory periods (ERPs) were determined at the high right atrium, interatrial septum/left atrium (proximal/distal coronary sinus), and right ventricular apex (extrastimulus step-size: 2 ms; baseline cycle length: 350 ms). An atrial ERP heterogeneity index (1 · SD/mean · 100%) was calculated.

Sympathetic nerve stimulation (SNS). Efferent sympathetic cardiac nerves course within neural sleeves (ansae subclaviae) adjacent to both subclavian arteries (2). For SNS, deflectable electrode-catheters (Cordis-Corp., Baldwin Park, California) were introduced into the subclavian

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Abbreviations and Acronyms

AF	= atrial fibrillation
ERP	= effective refractory period
L-SNS/R-SNS	= left-sided/right-sided sympathetic nerve stimulation
LV	= left ventricle/ventricular
SNS	= sympathetic nerve stimulation
TPR	= total peripheral resistance

arteries via the femoral artery (Fig. 1). Sympathetic nerve stimulation was attempted over the distal electrode pair (20 Hz, 37.5 V, 2-ms pulse duration, Grass-S-88-stimulator/Astro-Med-Inc., West Warwick, Rhode Island). While gently rotating, advancing, or withdrawing the catheter, the SNS site was identified by an arterial pressure increase. After SNS, 5 min elapsed for heart rate and pressure normalization.

In eight pigs, SNS was performed before/after beta$_{1+2}$-receptor blockade (propranolol, 0.2 mg/kg intravenously). In four pigs, L-SNS at 37.5 V was continued over 12 h during ventricular pacing at 200/min.

Statistical analysis. Data are expressed as mean values ± 1 SD. Repeated-measures analysis of variance with Dunnett's post-test was used for repeated measures. The Student *t* test was applied for quantitative variables. A p value <0.05 was considered significant.

RESULTS

In all 16 pigs cardiac sympathetic nerves along the subclavian arteries could be identified 1 to 2 cm proximal to the offspring of the thoracic artery within 10 min (Fig. 2). At the effective site the catheter position remained stable throughout the experiment.

Inotropy, chronotropy, and dromotropy. Sympathetic nerve stimulation more than doubled LV systolic pressure

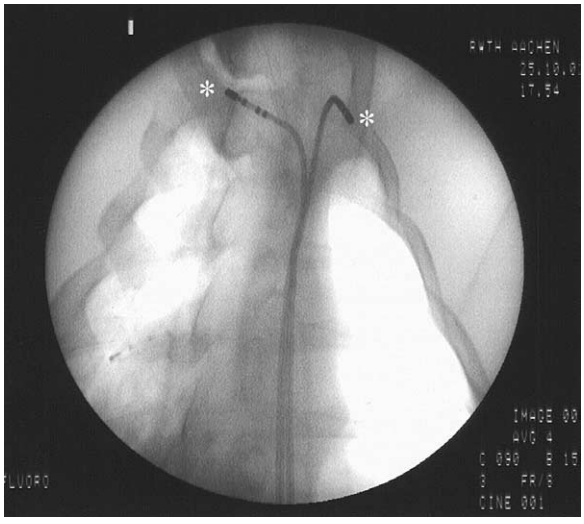

Figure 1. Anterior-posterior view of electrode catheters with their tips (*) at sympathetic nerve stimulation sites in both subclavian arteries.

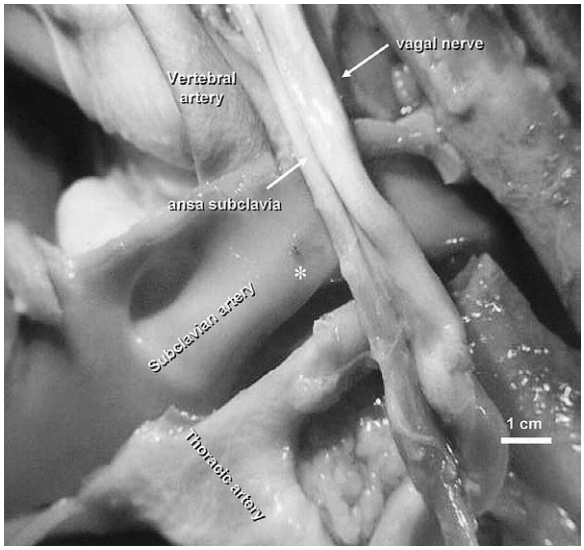

Figure 2. Sympathetic nerve stimulation site in right subclavian artery. Before connective tissue dissection, there was a 1.5 to 2 cm separation of the vagal nerve and ansa subclavia. *Radiofrequency burn.

(Fig. 3) independent of a concomitant sinus rate increase (Fig. 4). The dose-response curve revealed a sigmoid shape with a quick on-/offset of the inotropic effect within 20 to 30 s after SNS initiation/cessation (Fig. 5). Right-sided/left-sided sympathetic nerve stimulation (R-SNS/L-SNS, respectively) increased cardiac output during sinus rhythm by 60% but did not increase TPR (Table 1).

During R-SNS/L-SNS, a 43%/26% shortening of the sinus cycle length occurred. Likewise, the PR interval declined from 127 ± 17 ms to 107 ± 14/105 ± 9 ms during L-SNS/R-SNS ($p < 0.01$). All SNS-mediated effects were abolished by propranolol (Table 1).

Depolarization and repolarization. Sympathetic nerve stimulation decreased right ventricular and atrial ERPs without changing atrial ERP heterogeneity (Table 2). Propranolol prevented the ERP shortening. Sympathetic nerve stimulation did not significantly change QT_c time but shortened QRS width and increased local ventricular conduction velocity (Table 3).

Arrhythmias. Programmed stimulation during SNS did not induce ventricular fibrillation. Right-sided SNS at 37.5 V elicited wide QRS tachycardias (cycle length 350/390 ms) in 2 of 16 pigs, which terminated within 30 s after SNS cessation. This cycle length was slightly shorter than the preceding sinus cycle length, consistent with an accelerated idioventricular rhythm. Right-sided SNS (L-SNS) at 37.5 V induced atrial fibrillation (AF) in 5 of 12 (2 of 12) pigs, which dissipated within 60 s after SNS cessation.

Long-term efficacy and safety. Despite a slight decrease of the positive inotropic response during the first 2 h of continued SNS, a more than 90% increase of LV systolic pressure, rate of systolic pressure development, and cardiac output could be maintained for 12 h of SNS, whereas TPR was not significantly altered (Figs. 6A to 6D).

Postmortem inspection of the subclavian arteries revealed