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Vagal neurostimulation in patients with coronary artery disease ☆

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Abstract

We tested the hypotheses that (1) progression of coronary artery disease (CAD) increases sympathetic inflow to the heart, thus impairing cardiac blood supply, and (2) reduced sympathetic tone improves cardiac microcirculation and ameliorates severity of anginal symptoms. Electrical irritation of the nerve auricularis—a sensitive ramus of the vagus nerve—provides a central sympatholytic action. Using this technique, we studied the effects of vagal neurostimulation (VNS) on hemodynamics, the content of atrial noradrenergic nerves and the microcirculatory bed of CAD patients. VNS was performed in the preoperative period of CAD patients with severe angina pectoris. The comparison groups consisted of untreated patients with CAD or Wolff–Parkinson–White syndrome. Atrial tissue of patients with this syndrome ($n = 6$); with effort angina ($n = 14$); with angina at rest ($n = 10$); and with severe angina treated with VNS ($n = 8$) contained the following volume percentages of noradrenergic nerves: $1.7 \pm 0.1\%$, $1.3 \pm 0.3\%$, $0.5 \pm 0.1\%$ ($p < 0.05$ vs. the other groups) and $1.3 \pm 0.2\%$, respectively. In these groups, cardiac microcirculatory vessels (diameter, 10–20 μm) had the following densities: $2.7 \pm 0.2\%$, $3.4 \pm 0.2\%$, $2.0 \pm 0.4\%$ ($p < 0.05$ vs. the other groups) and $3.3 \pm 0.3\%$, respectively. VNS treatment abolished angina at rest, decreased heart rate and blood pressure. It improved left ventricular ejection fraction from $50 \pm 1.5\%$ to $58 \pm 1.0\%$ ($p < 0.05$), also changing left ventricular diastolic filling. The ratio of time velocity integrals of the early (E_i) to late (A_i) waves increased from 1.07 ± 0.12 to 1.65 ± 0.17 after VNS ($p < 0.05$). In electrocardiograms of VNS-treated patients, QRS- and QT-duration were shortened, the PQ-interval did not change, but T-wave configuration improved. In the postoperative period, heart failure occurred in 90% of the control group, vs. 12% in patients treated with VNS ($p < 0.05$). We conclude that CAD is characterized by overactivity of sympathetic cardiac tone. Vagal stimulation reduced sympathetic inflow to the heart, seemingly via an inhibition of norepinephrine release from sympathetic nerves. VNS' sympatholytic/vagotonic action dilated cardiac microcirculatory vessels and improved left ventricular contractility in patients with severe CAD.

Keywords: Angina pectoris; Atrial tissue; Ejection fraction; Microcirculation; Nerve stimulation; Norepinephrine; Vagus; Ventricular filling

1. Introduction

Autonomic interactions in the physiology of normal and pathological heart are important, as evidenced by many studies (Cordero et al., 1995). The sympathetic and parasympathetic drives of the autonomic nervous system work in a reciprocal fashion: an increase in the activity of one component causes or is due to a decrease in the activity of the other (Levy and Martin, 1989). At the level of neuroeffector interactions, norepinephrine release from sympathetic nerve terminals inhibits acetylcholine release from neighboring vagal fibers, whereas acetylcholine prevents the release of norepinephrine (Randall and Ardell, 1988; Levy and Martin, 1989; Vanoli, 1994). Dysfunction of the autonomic nervous system contributes to the pathogenesis of the most important cardiovascular diseases, including coronary artery disease (CAD), hypertension, congestive cardiac failure, life-threatening arrhythmias and sudden cardiac death (Vanoli, 1994; Esler and Kaye, 1998; Julius and Nesbitt, 1998). Neural imbalance correlates with the severity of cardiac disease, with marked sympathetic activation and abnormally low levels of parasympathetic cardiac activity (Shvalev et al., 1980; Dae et al., 1995; Schomig et al., 1995; Miwa et al., 1998). Sympathetic excitation shortens the refractory period of ventricles, reduces the threshold of ventricular fibrillation and leads to

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peripheral and coronary vasoconstriction (Shvalev et al., 1980; Verrier, 1991; Kollai et al., 1994).

Drugs diminishing the sympathetic influence on the cardiovascular system fit the basic medication for cardiac patients (Maseri, 1995; Adams, 1996). Widely used neurostimulation techniques—transcutaneous nerve and spinal cord stimulation—may modulate sympathetic tone (Cordero et al., 1995; Borjesson et al., 1997). However, the use of vagotonic stimulus for reducing sympathetic activity is currently insignificant. This is related, in part, to limited knowledge on how to achieve tonic parasympathetic activation. We made use of the ramus auricularis, a sensitive nerve of the vagus nerve beginning with the ganglion superior (Knorre, 1974). The nerve innervates the auditorium passage and an area of the external auricle (Knorre, 1974; Chlopov et al., 1988). The electrical resistance of the skin area innervated with the nerve auricularis changed in cardiac patients (Saku et al., 1993). Recently, we have found that impulse current irritation of the nerve auricularis or vagal neurostimulation (VNS) influences ATP content and expression of stress proteins in atrial tissue of patients with CAD (Zamotrinsky et al., 1997). Belkina et al. (1999) reported the beneficial effects of VNS on hemodynamics and cardiac output in rats with heart failure. The vestibular and autonomic systems interact functionally. Vestibular stimulation increases sympathetic outflow in cardiac and splanchnic vascular beds in experimental models (Biaggioni et al., 1998).

The aims of our study were three-fold: First, to investigate the effect of CAD on the density of cardiac noradrenergic nerves and microcirculatory bed; second, to study the effects of vagal neurostimulation on these nerves and the microcirculation in patients with angina at rest; and third, to compare hemodynamics and symptoms of patients with severe angina at baseline and after VNS. We hypothesized that (1) CAD progression gradually increases sympathetic cardiac tone, thus affecting cardiac microcirculation; (2) increases in vagal activity inhibit sympathetic inflow to the heart, thereby improving cardiac blood supply in patients with severe angina pectoris.

Myocardial ischemia decreased the number of cardiac noradrenergic nerves. Vagal stimulation increased the density of cardiac noradrenergic plexuses. In CAD patients, vagal activation improved cardiac blood supply and left ventricular contractility.

2. Materials and methods

2.1. Study population

The study was performed during 1997–1999. All patients involved gave their informed written consent to participate in the study. In 1996, the Russian Academy of Medical Sciences (RAMS) accepted vagal neurostimulation to treat cardiac patients. Eighteen patients with CAD were randomly divided into, either the VNS-treated or the non-treated group. All patients were male, aged 48–58 years, with stable angina pectoris [class IV of the Canadian Cardiovascular Society (CCS, Maseri, 1995)]. Daily, the patients experienced anginal attacks at rest and under a low workload (tolerance to bicycle exercise testing: ≤ 25 W). None of them had diabetes mellitus or atrial fibrillation. Their left ventricular ejection fraction (EF) was in the range of 49–59%. After admission, the patients spent 25–30 days in the hospital awaiting surgery. During that period, the groups received similar pharmacotherapy (Table 1). Beta-blockade was unusual, due to a RAMS-instruction for the preoperative management of patients with impaired left ventricular contractility.

2.2. Additional groups of cardiac patients

We studied atrial tissue of patients suffering from angina at rest, who were on conventional therapy only ($n = 10$), patients with angina at effort (CCS class II, $n = 14$), and patients with Wolff–Parkinson–White syndrome (non-ischemic heart pathology, $n = 6$). Histology data from these groups were compared to understand how various degrees of angina (myocardial ischemia) influence the number of cardiac noradrenergic nerves and the microcirculatory bed. To study how simple needle irritation of the auricle might influence the clinical course, four CAD patients in CCS class III–IV were subjected to traditional auricular acupuncture. Cardiac tissue from these patients

Table 1
Patients with CAD: daily peroral medication and performance before electrical nerve and surgical interventions

Drug/performance	CCS class IV, VNS group	CCS class IV	CCS class II
Long-acting nitrates	8/8	10/10	0/14
Calcium blockers	7/8	8/10	12/14
Beta-blockers	1/8	3/10	2/14
ACE-inhibitors	3/8	4/10	2/14
Aspirin	8/8	10/10	14/14
Diuretics	1/8	1/10	2/14
Glycerol trinitrate, 2–40 tablets/day	8/8	10/10	occasionally
Tolerance to bicycle test	≤ 25 W	≤ 25 W	≥ 75 W
Ejection fraction (%)	49–51	49–58	55–72

was not analyzed, because they did not respond clearly to acupuncture (see Section 3).

2.3. Clinical endpoints

For VNS-treated patients, heart rate, blood pressure, left ventricular ejection fraction, nitrate use, and PQ-, QRS- and QT-duration were compared before and after the VNS course. Patients were given a questionnaire in which they noted any symptoms and their consumption of glycerol trinitrate. The consumption of this nitrate, a free choice of the patients, was used to measure the anti-anginal efficacy of the VNS treatment. The daily dependence on glycerol trinitrate, 2–40 tablets/day, was possibly due to nitrate tolerance which developed in our patients as a result of extended medication with high doses of long-acting nitrates. Heart rate and blood pressure were recorded before and after each VNS procedure. Daily averages of blood pressure and heart rate were calculated for each patient at baseline and after the VNS course. Every patient underwent Doppler echocardiography (Ultramark-9, Atlanta, GA, USA) before and after the VNS course. Left ventricular diastolic function was evaluated using the pulsed-wave mode. Left ventricular filling (transmitral flow) was assessed as the ratio of time velocity integrals of the early (A) to late (E) waves (A_i/E_i). B-mode ultrasound analysis and Simpson's formula were used to calculate left ventricular ejection fraction (EF). One highly qualified technician, blinded regarding patient medication and VNS treatment, performed the echo-studies.

Electrocardiograms were recorded when patients were free from angina. The duration of the PQ-, QRS- and QT-intervals were calculated in a standard way, in the second standard lead. VNS-treated and non-treated patients with angina at rest underwent coronary artery bypass grafting of three to four vessels. During the operation, St. Thomas' Hospital cardioplegia was used. In all patients, the aortic cross-clamp time exceeded 90 min. The same surgical team operated on all patients included in this study. In the early postoperative period, the occurrence of transient heart failure which required infusion of either dopamine or dopamine/epinephrine was compared between the two groups. Heart failure was assessed as a spontaneous drop of blood pressure below 100/70 mm Hg. Cardiac arrhythmias were a reason for heart failure in about 40% of the cases; they were treated by infusion of antiarrhythmics, followed by inotropic drugs. In the other cases, the reasons for heart failure were unclear. Patients who experienced massive postoperative bleeding were excluded from our study. In the case of stable hemodynamics, no inotropic cardiac support was required for postoperative recovery. This recovery took place in the Anesthesiology Department, where doctors were blinded as to whether patients received VNS treatment or conventional medication only.

2.4. Technique of vagal neurostimulation

Neurostimulation was performed in patients in the supine position, monitored electrocardiographically. An impulse current generator was connected to a pair of electrodes, attached to short acupuncture needles put into the skin, to a depth of 0.1–0.3 mm. The area situated near the auditory passage that contains endings of the nerve auricularis was used for neurostimulation (Fig. 1). Transcranial impulse current stimulation of the left and right afferent trunks of the vagus nerve and brain stem structures was performed, using stimulation parameters described previously (Zamotrinsky et al., 1997). The VNS course consisted of 10 stimulation procedures lasting 15 min, repeated for 10 consecutive days. Vagal stimulation is a painless procedure, not requiring local anesthesia. After a VNS procedure, patients were at rest for 10–15 min, then they led their usual life. Medication, except glycerol trinitrate and beta-blocker withdrawal, did not vary during the VNS course.

2.5. Histological analysis of atrial tissue

Histological analysis was performed in a blinded, randomized fashion. Part of the right heart auricle was resected during surgery. This tissue was frozen immediately and kept in liquid nitrogen until analysis. Noradrenergic nerves were visualized in standard histological cardiac

Fig. 1. Topography of afferent endings of some cranial nerves on the auricular surface: (1) tenth cranial; (2) seventh cranial; (3) salivary gland. The area where electrodes were placed for vagal neurostimulation is indicated by an ellipse (Chlopov et al., 1988).

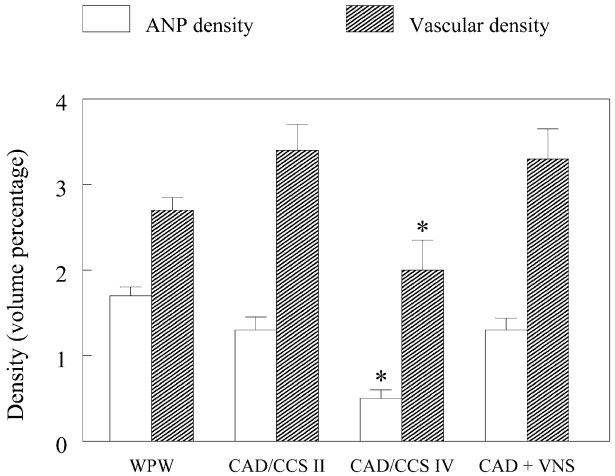

Fig. 2. Density of microcirculatory vessels and adrenergic nerve plexuses (ANP) in atrial tissue of the four patient groups studied. WPW = patients with Wolff–Parkinson–White syndrome ($n = 6$); CAD/CCS II and CAD/CCS IV = patients with effort angina ($n = 14$) and angina at rest ($n = 10$), respectively; CAD + VNS = CAD patients in CCS class IV, treated with vagal neurostimulation ($n = 8$). Mean ± SEM $^{*}p < 0.05$ compared to the corresponding values in all other groups.

sections by a modification of Falck's method (Shvalev et al., 1980). Sections were incubated in 2% glyoxylic acid, pH 7.4, at 20°C, for 10 min. During the incubation, norepinephrine became fluorescent. Fluorescent microscopy, excitation at 395 nm and emission at 521 nm, allowed visualization of neural structures containing significant amounts of the mediator (i.e., nerve trunks and plexuses). The technique used was not sensitive enough to detect nerves with little norepinephrine (Shvalev et al., 1980).

Blood vessels were visualized by staining alkaline phosphatase in their walls (Lojda et al., 1982). Sections were incubated in medium containing 0.025% naphtol AS-BI phosphate and 0.1% fast blue RR (Sigma, St. Louis, MO, USA) at 37°C, for 30 min. Then, they were studied by light microscopy, focusing on microcirculatory vessels (arteriolar and venous capillaries, diameter 10–20 μm). To calculate the vessel and nerve density, a point method with a standard glass counter was used (Shvalev et al., 1980), the density was expressed in volume percentage. For each cardiac sample, mean vascular and nerve densities were calculated from observations on 20 different section areas.

2.6. Statistical analysis

The non-parametric sign test was used to compare the incidence of symptoms at baseline and after VNS. The Wilcoxon matched-pairs test was used to compare electrocardiographic, histological and clinical measurements. Data are presented as mean ± SEM. Differences with $p < 0.05$ were regarded as significant.

3. Results

3.1. Cardiac adrenergic nerve and vascular density

Fig. 2 shows density data on atrial noradrenergic nerves and microcirculation vessels, both in patients with CAD and Wolff–Parkinson–White syndrome. The number of noradrenergic nerve plexuses was decreased in the CAD patients ($p < 0.01$). The degree of reduction in noradrenergic cardiac plexuses of CAD patients depended on the severity of anginal symptoms experienced. It varied from 17% to 85% of the neural density in patients with non-ischemic pathology. Worsening of CCS class in CAD patients resulted in a progressive decrease of noradrenergic nerve density. In patients with severe angina, vagal stimulation considerably increased the density of noradrenergic plexuses: 1.3 ± 0.2% in eight VNS-treated patients, vs. 0.5 ± 0.1% in 10 non-treated patients ($p < 0.05$). Fig. 3 illustrates this VNS-induced increase, depicting the typical distribution of noradrenergic nerves in atrial tissue of a non-treated (panel A) and a VNS-treated patient (panel B).

Cardiac vascularisation was more prominent in patients with mild angina and those with severe angina, treated

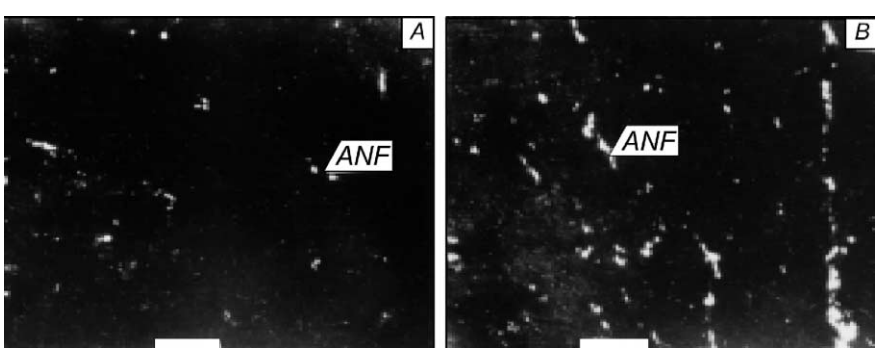

Fig. 3. Distribution of adrenergic nerves in atrial tissue of patients with angina at rest: (Panel A) untreated control patient. (Panel B) VNS-treated patient. In the photographs, the adrenergic nerve fibers (ANF) show up in white. Horizontal bar corresponds to 20 μm.

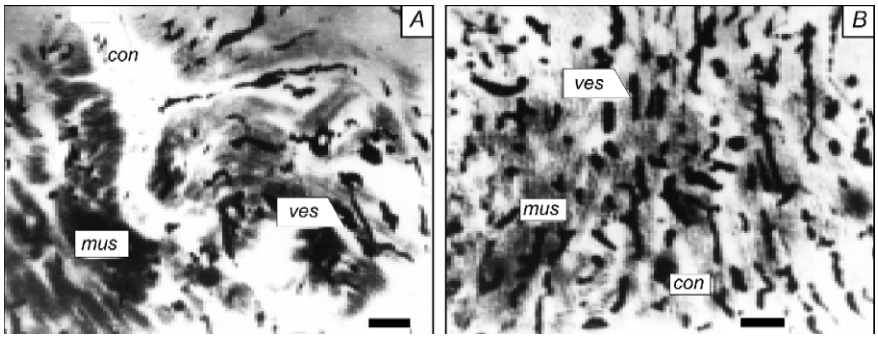

Fig. 4. Cardiac microcirculatory bed in patients with angina at rest: (Panel A) untreated control patient. (Panel B) VNS-treated patient. In the photographs, blood vessels (ves) show up in black, muscle tissue (mus) in grey, and conjunctive tissue (con) in white. Horizontal bar indicates 40 μm.

with VNS; atrial tissue from patients with severe angina, who were on conventional medication, showed a lower density of cardiac microcirculatory vessels ($p < 0.05$ compared to the other groups, Fig. 2). Fig. 4 shows typical microcirculation patterns of a non-treated (panel A) and a VNS-treated patient (panel B) with severe angina pectoris, which is more extensive in the latter.

3.2. Clinical endpoints of VNS treatment

Table 2 summarizes clinical endpoints of VNS applied in the preoperative period of patients with severe angina. The time-course of response is characterized by the accumulative hemodynamic effects of consecutive VNS procedures. At the beginning of the VNS course (four to five procedures), each procedure influenced heart rate and blood pressure. Initially, a decrease in heart rate from 72–84 to 50–56 beats/min during a procedure was routinely observed. Just after the procedure, systolic blood pressure increased by 10–15 mm Hg, diastolic blood pressure either decreased or remained the same. These hemodynamic changes returned to baseline level within 15–20 min. However, during the VNS course, heart rate and blood pressure progressively decreased (despite the transient increase of systolic blood pressure after a VNS procedure). After the first four to five interventions, the VNS procedures lost efficacy on heart rate and blood pressure, and became effective on angina. The dependence of patients on vasodilators (glycerol trinitrate) diminished, their blood pressure and heart rate became chronically lower than those at the beginning of the VNS course.

VNS treatment shortened QRS- and QT-duration, had no impact on the PQ-interval, and augmented T-wave amplitude in chest leads (Table 2 and Fig. 5). At baseline 7/8 CAD patients had altered T-wave configuration in some or all chest electrocardiographic leads (i.e., the wave was negative, biphasic, flattened). After the VNS course, all seven patients showed T-wave improvement ($p < 0.05$): negative or biphasic waves became positive; if the wave was initially flattened, it increased in amplitude (Fig. 5). Echo-studies revealed an average increase of left ventricular contractility of 16% ($p < 0.05$). Basic parameters of transmitral flow also changed: The echo-area for the late phase (A) of left ventricular filling reduced, whereas the area for the earlier one (E) increased. As a result, the ratio between the passive (earlier) and active (late) phases of

Table 2
Changes produced by vagal neurostimulation in patients with angina at rest

Variable	Baseline	After VNS
Heart rate (beats/min)	76 ± 3	$63 \pm 2^{*}$
SBP/DBP (mm Hg)	130/80	$120^{*}/75$
Left ventricular diastolic filling (E_i / A_i)	1.07 ± 0.12	$1.65 \pm 0.17^{*}$
Ejection fraction (%)	50.1 ± 1.5	$58.4 \pm 1.0^{*}$
Glycerol trinitrate (tablets/day)	8.7 ± 7.4	0^{*}
PQ-interval (s)	0.16 ± 0.02	0.15 ± 0.02
QRS-interval (s)	0.09 ± 0.01	$0.06 \pm 0.01^{**}$
QT-interval (s)	0.40 ± 0.03	$0.37 \pm 0.02^{*}$

Systolic (SBP) and diastolic (DBP) blood pressure data are given as the mean observed; other values are expressed as mean ± SEM ($n = 8$).
* $p < 0.05$ Compared to baseline values.
** $p < 0.01$ Compared to baseline values.

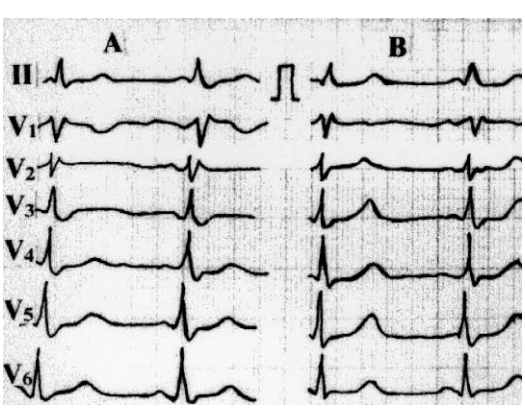

Fig. 5. Electrocardiograms before (A) and after (B) the VNS treatment of a CAD patient. This patient received glycerol trinitrate before, but not after the VNS course. The administration of calcium antagonists did not vary.

Table 3
Comparative effects of VNS and acupuncture in CAD patients

Variable	Vagal neurostimulation		Ear acupuncture	
	Start	End	Start	End
Heart rate	acute decrease	no effect	increase[a]	no effect
Systolic blood pressure	acute increase	no effect	increase[a]	no effect
Glycerol trinitrate use	no effect	no use[b]	no effect	no effect
Sensation in the chest	warmth	warmth	no effect	no effect
Tolerance to physical load	no effect	increase	no effect	no effect

The table lists effects found in all or the majority of patients. 'Acute' refers to changes developed during the procedure.

[a]Changes appeared at the beginning and disappeared by the end of the procedure. The number of patients undergoing acupuncture was quite small ($n = 4$), preventing a statistical comparison between the two groups.

[b]$p < 0.01$. Between drug consumption at baseline and after VNS.

ventricular filling increased in our population by 50% ($p < 0.05$). VNS-related changes in left ventricular contractility and transmitral blood flow were observed in all eight VNS-treated patients.

During a VNS procedure, patients usually felt a warm sensation inside their chest. It appeared just after electrical irritation started and was present during the whole procedure. Patients noted that their respiration improved. If patients experienced anginal attacks or chest discomfort while subjected to VNS, they felt a rapid reduction of chest pain during the procedure (i.e., in one session). In this manner, VNS rendered an anti-anginal effect similar to that of glycerol trinitrate. Sometimes patients fell asleep during the procedure. Table 3 compares typical symptoms of patients treated either with VNS or with needling acupuncture of the same auricular area (the acupuncture course consisted of eight procedures).

Early in the postoperative period (1–7 days after surgery), heart failure developed in 1/8 VNS-treated patients and in 9/10 of non-treated patients ($p < 0.05$).

4. Discussion

We hypothesized that CAD progression increases sympathetic inflow to the heart and that reduced sympathetic tone improves cardiac microcirculation, ameliorating anginal symptoms. We found that myocardial ischemia decreased the number of cardiac noradrenergic nerves. Microvessels were constricted in patients with angina at rest, whereas those with effort angina showed more microvessels. Vagal stimulation increased the density of cardiac noradrenergic plexuses. In CAD patients, vagal activation improved cardiac blood supply and left ventricular contractility.

4.1. Coronary artery disease and cardiac sympathetic nerves

The question whether worsening of anginal symptoms increases sympathetic cardiac tone in CAD patients is based on the following rationale. First, cardiac sympathetic excitation and vagal depressor reflexes occur within a few seconds of ischemia (Verrier, 1991; Kollai et al., 1994; Vanoli, 1994). Second, catecholamine depletion in cardiac sympathetic nerves is common in patients with stable, unstable or variant angina (Dae et al., 1995; Schomig et al., 1995; Hartikainen et al., 1997; Miwa et al., 1998). Third, catecholamine depletion takes place during (prolonged) myocardial ischemia (Shvalev et al.,1980; Dae et al., 1995). The progressive reduction of noradrenergic plexus density observed in our patients with effort and rest angina indicates that CAD progression increases sympathetic cardiac tone. We stress that sympathetic activity is directly related to the amount of released mediator (Levy and Martin, 1989). However, Falck's method measures the opposite. This technique allows estimation of norepinephrine stored in nerves, not the total density of noradrenergic nerves. Nerves with little or no norepinephrine are invisible, epinephrine and dopamine stain weakly. Sympathetic nerve content depends on mediator synthesis, release and uptake. Ischemia stimulates release and inhibits uptake (Randall and Ardell, 1988; Schomig et al., 1995; Du et al., 1998; Gurtner et al., 1998). Thus, atrial tissue of healthy people contains 5–8% of noradrenergic plexuses, tissue obtained from patients who died from myocardial infarction contain only 0.3–0.7% (Shvalev et al., 1980; Du et al., 1998). Restoration of noradrenergic nerve content in VNS-treated patients may be due to norepinephrine accumulation in the nerves, via vagal-mediated inhibition of mediator release (Levy and Martin, 1989). We like to stress our focus on noradrenergic nerves in right heart appendage. No real evidence exists that this tissue was exposed to ischemia. However, changes in atrial noradrenergic nerves seem to reflect the severity of ischemia in other cardiac regions; ventricular ischemia exhausts sympathetic nerve content in all parts of the heart (Shvalev et al., 1980).

4.2. Cardiac microvasculature and sympathetic activity

We studied the microvasculature in hearts with or without significant occlusion of the main coronary arteries. In patients with mild CAD or effort angina, an enhancement of vascular density was observed. This increase may be due to angiogenesis, induced by short ischemic episodes (Yamamoto et al., 1984). Increased anginal symptoms in our patients paralleled deterioration of their cardiac microcirculatory bed and loss of cardiac noradrenergic plexuses. This finding corresponds to animal data showing that

ischemia-evoked dysfunction of small coronary arteries depends on the severity of the ischemic challenge (Conger and Weil, 1995). We suppose that the lesion of the microcirculatory bed in patients with rest angina was due to vasospasm of neural origin. The neural nature of the microvasculature damage follows from the observation that patients with interrupted sympathetic cardiac activity had increased vascular density. We suppose that VNS treatment provided coronary vasodilation. It is unlikely that angiogenesis played a key role in the period patients were treated with VNS. Vagal stimulation could dilate constricted vessels, either by an endothelium-dependent mechanism or by a reduction in released norepinephrine (Young and Vatner, 1986). In the regulation of regional myocardial blood flow, the tone of coronary resistance vessels (diameter, 100–200 μM) is critical (Chilian et al., 1986). We were unable to study these arteries. Further study of small coronary arteries is needed to clarify blood supply regulation during myocardial ischemia or vagal activation.

4.3. Clinical setting

Discussing clinical endpoints of vagal stimulation, we want to point out that our patients were on strong medical therapy. Obviously, the extensive medication could disguise some hemodynamics effects of VNS. The differences in glycerol trinitrate use by the VNS-treated patients at baseline and after the treatment were substantial (Table 1). Dilation of the cardiac microvasculature is the most likely explanation for the anti-anginal effects of VNS, as shown, e.g., by reduction in nitrate use and improvement of T-wave configuration. VNS treatment had no impact on atrioventricular conduction, whereas anti-adrenergic drugs typically prolong PQ-duration (Adams, 1996). The reason for this difference remains unclear. Surprisingly, VNS shortened the duration of electrical ventricular systole, but had little effect on the duration of electromechanical systole (QRS- and QT-intervals, respectively, Table 2). The positive inotropic effect of VNS is predictable; beta-blockers, after prolonged administration, increase left ventricular contractility (Adams, 1996; van Campen et al., 1998). Compared to systolic function, which hardly improved, parameters of left ventricular diastolic filling (transmitral flow) changed substantially. The regulation of diastolic ventricular function has been poorly investigated (Thomas and Vagueiro, 1999). Our data on transmitral flow could indicate that parasympathetic activity plays a critical role in ventricular relaxation. Vagal stimulation reduced the incidence of transient heart failure in the postoperative period. It is likely that sympathetic–parasympathetic interactions play a key role in the stabilization of hemodynamics of VNS-treated patients. Concomitant with changes in autonomic activity, the brain varies its neuropeptide production (Chao et al., 1999). We believe that neuropeptides play a role during VNS: Patients often fall asleep during neurostimulation; they become much more optimistic regarding surgery. However, we were unable to measure changes in neuropeptide balance due to VNS. In addition, we could not determine whether the VNS-induced effects were due to increased vagal or reduced sympathetic activity.

4.4. Parasympathetic activation

The ramus auricularis is a sensitive nerve of the vagus nerve beginning with the ganglion superior (Knorre, 1974). We consider this nerve a conductor connecting central structures of the vagus nerve with the external world. Our study, in which VNS restores noradrenergic nerve content, indicates that repeated electrical irritation of the nerve auricularis results in tonic activation of the central vagus nerve structures. An increase in vagal tone improves cardiac blood supply in patients with severe angina via dilation of spastic cardiac microvessels. In addition, vagal stimulation improves left ventricular contractility and especially, ventricular filling of patients with CAD. Future studies of vagal-mediated changes in hemodynamics and cardiac performance of healthy individuals and patients with cardiovascular disorders are required to define areas of application of the neurostimulation technique.

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