Improving Myocardial Perfusion by Percutaneous Coronary Intervention Reduces Central Sympathetic Activity in Stable Angina

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ABSTRACT

Background: By stimulating sympathetic afferents, repetitive myocardial ischemia induces a state of increased sympathetic tone.

Hypothesis: Removing the ischemic trigger by revascularization using percutaneous coronary intervention (PCI) might thus reduce central sympathetic activity in symptomatically stable angina patients.

Methods: A total of 20 patients with stable angina $\geq$ New York Heart Association (NYHA) class II with persistent symptoms despite maximal pharmacological therapy and a clinical indication for PCI, were included in our study. Sympathetic nervous system activity was measured before and 1 month after PCI by a combination of techniques: direct muscle sympathetic nerve activity (MSNA), neurochemical (plasma catecholamine levels), and heart rate variability (HRV).

Results: All patients completed the study. After PCI there was a significant reduction in MSNA (pre-PCI 72 ± 4 to post-PCI 53 ± 4 burst/100 beats, $P < .05$) and low frequency/high frequency (LF/HF) ratio (3.7 ± 0.6 vs 2.4 ± 0.4 , $P < .05$) consistent with a decline in sympathetic activity. Plasma norepinephrine levels were reduced after PCI, but this difference did not reach statistical significance (1.84 ± 0.17 vs 1.73 ± 0.13 nmol/L, $P =$ not significant).

Conclusion: Coronary revascularization by PCI reduces sympathetic activity in patients with established myocardial ischemia.

Introduction

Sympathetic activation has been closely correlated with myocardial ischemia.^{1,2} The most likely explanation is stimulation of sympathetic afferents in the myocardial wall due to ischemia-induced release of a number of afferent-stimulating substances.^{3,4} If the ischemic stimulus is strong enough, a reflex increase in central sympathetic output occurs, despite current pharmacological interventions.^{2–5} In myocardial infarction, as well as in unstable angina, this state of sympathetic hyperactivity appears to be protracted for several months after the occurrence of the ischemic event, suggesting a persistent change in central autonomic balance.¹ Patients with documented coronary artery disease (CAD) and exercise-provoked angina (stable angina) show a similar state of sympathetic hyperactivity, although the persistence of this effect in time is less well established.⁶ As myocardial ischemia seems to be the trigger of this state of sympathetic hyperactivity, removing this trigger would be expected to reduce sympathetic

overactivity. Thus, improving myocardial perfusion by percutaneous coronary intervention (PCI) might have beneficial effects on central sympathetic activity in ischemia-triggered sympathetic hyperactivity. We hypothesized that a revascularization procedure in patients with stable angina on maximal pharmacological treatment should decrease central sympathetic activity. We tested this hypothesis in a group of patients with stable angina who underwent PCI.

Methods

Participants

The patients that participated in this study met the following criteria: stable angina, which was defined as chest discomfort that occurs and is predictable and reproducible at a certain level of exertion which was relieved by rest or nitroglycerin. Signs of angina remained despite optimal pharmacological treatment (regulation of blood pressure, heart rate, and other risk factors like lipid levels, were already optimal). Other inclusion criteria included: planned

for PCI; age between 24 and 75 years; and sinus rhythm. Exclusion criteria were: diabetes, chronic heart failure, a left ventricle ejection fraction of <40%, known chronic disease of the autonomic nervous system, treatment with tricyclic antidepressants, α_1 -adrenoreceptor inhibitors, or α_2 -adrenoreceptor inhibitors. Ischemia was confirmed by a positive ischemia detection test prior to PCI (myocardial scintigraphy or exercise test) in 18 patients and 2 patients had a classic history of angina. All patients underwent a ventricular angiogram to assess ventricular function or, if ventricular angiography was not possible, echocardiography. For adequate heart rate variability analysis, patients needed to have a sinus rhythm. Successful PCI was defined as: no significant coronary artery pathology had to persist; all stenoses of $\geq 60\%$ should be reduced by $\geq 20\%$; and residual stenosis should be <50% for each vessel. The institutional review committee approved the study and informed consent was obtained from all patients before participation in the study. The study was performed in accordance with the Declaration of Helsinki.

Study Protocol

Sympathetic activity was assessed using 3 different approaches: measurement of muscle sympathetic nerve activity (MSNA) by microneurography, heart rate variability (HRV), and arterial plasma catecholamine concentrations. Measurements were performed before and 1 month after PCI. All experiments started at 8:00 AM after an overnight (10 h) fast with the patient in a supine position in a quiet temperature-controlled room (23°C–24°C). All subjects had to abstain from caffeine, tea, alcohol, chocolates, and smoking for at least 12 hours. All experiments were carried out after voiding to prevent reflex sympathoexcitation. After complete instrumentation, 30 minutes of rest were included to attain stable baseline before data collection. Hereafter, HRV measurement was performed for 10 minutes. Finally, arterial blood samples were drawn and microneurography was performed.

Sympathetic Nerve Traffic (Microneurography)

Muscle sympathetic nerve activity was measured as previously described.^{7,8} In short, the peroneal nerve was localized at the site of the fibula head using transdermal electrical impulses (40–60 mV, 0.2 ms, 1 Hz) through a small electrode. After localization, a sterile Tungsten microelectrode was inserted manually through the skin in the underlying peroneal nerve posterior to the fibular head. A second reference electrode was placed subcutaneously approximately 3 cm from the recording electrode. An electrode position within a muscle nerve fascicle was identified by evoking muscle twitches by electrical stimuli (1–5 mV, 0.2 ms, 1 Hz) and provoking afferent, mechanoreceptive activity by the stretching of the appropriate muscle. The MSNA signal was confirmed

using the Valsalva maneuver. From the original signal, multi-unit MSNA bursts were obtained as the average voltage after filtering (bandwidth, 700–2000 Hz) and integrating (time constant, 0.1 s). Bursts were identified using an automated computer program Midac Software 12.0 Nijmegen, Netherlands with prefixed settings to exclude observer bias. A preset triangle with a base of 0.8 seconds, correlated to the known delay between the R-peak in the EKG and the postganglionic burst, was used to scan the MSNA signal and identify sympathetic bursts. Hereafter, the maximal and average amplitude were calculated and potential bursts were correlated to a percentage of the maximal amplitude. The computer-derived measures were visually confirmed by an investigator so that noise artifacts were not being counted and if found, the noise artifacts were removed. Only bursts with a sufficient discriminating signal-to-noise ratio (≥ 3) were analyzed.^{8,9} Microneurography recordings were performed under basal conditions (patient in supine position) and quantified as bursts per 100 beats. This quantification has shown to have high intraindividual reproducibility.¹⁰ All measurements were performed between 9:30 and 11:30 A.M. to prevent confounding by circadian variation.^{11,12}

Heart Rate Variability

Using a 2-channel Holter (Medilog 4500-3, Oxford Instruments Ltd, Abingdon, England) a 10 minute EKG recording was performed for each patient at each visit. Ectopic beats and arrhythmias were excluded using the Oxford scanning software version 6.0 Oxford Instruments Ltd, Abingdon, England. R-R interval selection was performed using a beat-to-beat filter set at N-N-N, whereby the interval being considered must start and end in a “normal” beat and so must the preceding R-R interval. Rejected intervals were interpolated over the invalid area. Before converting the interval tachogram to frequency domain, the mean R-R interval was calculated from the tachogram and subtracted from each R-R interval to reduce spectral leakage. A Fast Fourier transformation was performed from the interpolated tachogram resampled at 292 msec, using the Oxford spectral analysis software package version 2.1 Oxford Instruments Ltd, Abingdon, England. Results from the 10 minute interval were averaged to form a composite spectrum. Total power between 0.003 and 0.40 Hz was calculated. This represents the total variance for a 10 minute interval. Power was quantified as total power, high frequency (HF) 0.15 to 0.40 Hz, and low frequency (LF) 0.04 to 0.15 Hz power.

Arterial Plasma Catecholamine Levels

Arterial blood samples were drawn from an arterial catheter after 40 minutes of rest. Plasma catecholamine concentrations were measured using high performance liquid pressure analysis with fluorometric detection.¹³ Within-run and between-run coefficient of variance (cv)’s

or plasma epinephrine were 4.1% and 8.1% at a level of 0.166 nmol/L and for norepinephrine 4.1% and 6.1% at a level of 1.76 nmol/L, respectively. Analytical detection limits were 0.003 and 0.002 nmol/L for epinephrine and norepinephrine respectively. Catecholamines were collected in ice-chilled 10 mL Vacutainer tubes (Becton-Dickenson Co., Franklin Lakes, NJ) containing 0.2 mL of a solution of Ethylene glycol-bis(beta-aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA) (0.25 mol/L) and glutathione (0.20 mol/L).

Statistical Analysis

Data are expressed as mean $\pm$ SEM unless indicated otherwise. Differences between visits were assessed using parametric (Student *t* test for paired observations) or non-parametric (paired Wilcoxon) tests as appropriate. A 2-tailed *P* value of $<.05$ was considered to be statistically significant. It was calculated that at least 9 patients were needed (with each patient as its own control) in order to detect a 15% reduction in MSNA based on resolution of ischemia after PCI, with a power of 80% at a significance level of .05. Per visit success rate for retrieval of adequate MSNA signal was estimated at 70%, as reported in the literature.¹⁴ Patient inclusion was continued until sufficient paired observations were collected. Power spectral data and plasma catecholamines are presented for all patients and each was sufficiently powered.

Results

A total of 20 patients were included in the study to retrieve paired MSNA data in 11 patients, corresponding with a per visit success rate of 75%. Patients with and without successful MSNA did not differ in body mass index, age, gender, and medication use. For this reason results on power spectral analysis and plasma catecholamines are presented for all patients. Patient characteristics are shown in Table 1. All patients remained on the same medication at both visits. All but 1 patient used β -blockers (metoprolol or atenolol, *n* = 15, mean dosage, 80 mg/d; bisoprolol, *n* = 4, mean dosage, 3.75 mg/d). Remaining medication: aspirin, *n* = 20; β -blocker, *n* = 18; statin, *n* = 16; angiotensin-converting enzyme inhibitors (ACEI), *n* = 4; and calcium channel blockers, *n* = 5. All patients received stent implantation. In those patients where clopidogrel was added for stent implantation, measurements were performed after discontinuation of clopidogrel (1 mo after PCI and stent implantation, according to clinical protocols). In 5 patients, a drug-eluting stent was used and measurements were performed during clopidogrel administration. Results did not differ between the patients with and without a drug-eluting stent or on different medication. Using the predefined criteria, PCI was successful in all patients. At the second visit, all patients were free of angina.

Table 1. Baseline and Procedural Characteristics

Variable	Statistic
Age (yrs)	59 $\pm$ 8
Sex (male/female)	13/7
BMI (kg/m ²)	27.9 $\pm$ 3.8
Hypertension, n (%)	5 (25%)
Prior MI, n (%)	1 (5%)
Prior PCI, n (%)	6 (30%)
Prior CABG, n (%)	1 (5%)
NYHA class	2.9 $\pm$ 0.6
Fasting blood glucose (mmol/L)	5.9 $\pm$ 0.6
Positive ischemia detection test, n (%)	18 (90%)
CAD angiographic grade	
1-vessel disease (n)	17
2-vessel disease (n)	3
Vessel with significant lesions	
LAD (n)	14
RCA (n)	6
RCX (n)	3
Number of stents implanted	1.4 $\pm$ 0.6
Abbreviations: BMI, body mass index; MI, myocardial infarction; PCI, percutaneous intervention; CABG, coronary artery bypass grafting; NYHA, New York Heart Association CAD, coronary artery disease; LAD, left anterior descending; RCA, right coronary artery; RCX, ramus circumflex.	

After PCI, MSNA significantly decreased from 72 $\pm$ 4 bursts/100 beats pre-PCI to 53 $\pm$ 4 bursts/100 beats post-PCI, *P* < .05 (Figure 1). Similar results were found when MSNA was expressed as bursts/minute (42 $\pm$ 2 bursts/min pre-PCI vs 30 $\pm$ 3 post-PCI, *P* < .05). After PCI, the LF/HF ratio was significantly lower (2.4 $\pm$ 0.4) compared to pre-PCI, (3.7 $\pm$ 0.6; *P* < .05), consistent with a reduction in sympathetic dominance (Figure 2). For those patients with successful microneurography, values for the LF/HF ratio were 4.5 $\pm$ 1.0 pre-PCI and 2.5 $\pm$ 0.8 post-PCI. Total spectral power and LF/HF values before and after PCI did not differ significantly. Arterial plasma norepinephrine concentrations tended to be lower after PCI, but this was not significant (1.84 $\pm$ 0.17 pre-PCI vs 1.73 $\pm$ 0.13 nmol/L post-PCI). For those patients with successful microneurography, values were 1.94 $\pm$ 0.36 nmol/L pre-PCI and 1.59 $\pm$ 0.16 nmol/L post-PCI. Plasma epinephrine levels were significantly lower

Figure 1. Mean MSNA before and 1 month after PCI. Abbreviations: MSNA, muscle sympathetic nerve activity; PCI, percutaneous coronary intervention * $P < .05$.

Figure 2. Mean LF/HF ratio before and 1 month after PCI. Abbreviations: LF/HF, mean low frequency/high frequency ratio; PCI, percutaneous coronary intervention * $P < .05$.

at the second visit (0.33 ± 0.03 vs 0.22 ± 0.02 nmol/L, $P < .05$).

Systolic blood pressure was significantly reduced 1 month after PCI, (146 ± 7 vs 136 ± 6 mm Hg, $P < .05$; Figure 3), while diastolic blood pressure, mean arterial pressure, and heart rate remained unchanged.

Discussion

This study provides evidence that revascularization by PCI is able to reduce central sympathetic outflow in patients with stable angina. This conclusion is based on the finding that MSNA, representing central sympathetic outflow, significantly decreased after PCI. In accordance, sympathovagal balance shifted towards reduced sympathetic predominance (reduction in LF/HF ratio). Plasma norepinephrine levels appeared to be lower after PCI, albeit

Figure 3. Changes in systolic, diastolic, and MAP before and 1 month after PCI. Abbreviations: MAP, mean arterial pressure; PCI, percutaneous coronary intervention * $P < .05$.

not significantly. Finally, systolic blood pressure fell significantly in the absence of any change in cardiovascular medication.

Myocardial ischemia is closely related to an increase in central sympathetic activity.^{2,15} Sympathetic afferents residing in the myocardial wall are triggered by a number of substances released during ischemia.^{3–5} When afferent stimulation is sufficient, a reflex mechanism ensues, increasing central sympathetic outflow, with the degree of ischemia being correlated with the degree of central sympathoexcitation.² This state of increased sympathetic tone seems to persist beyond the ischemic event.¹ To our knowledge, there are no studies that have shown that reversal of ischemia by PCI reduces central sympathetic tone. In our patient group, sympathetic nervous system activity was indeed clearly increased. Baseline MSNA levels were similar to those of patients with acute onset unstable angina (72 ± 4 bursts/100 beats vs 78 ± 4 bursts/100 beats for unstable angina) and clearly increased compared to patients with asymptomatic stable CAD (54 ± 4 bursts/100 beats).² This strongly suggests that ischemia is an important determinant of sustained sympathetic stimulation. Improving myocardial perfusion by successful PCI should therefore improve myocardial oxygenation, reduce afferent stimulation, and subsequently decrease central sympathetic outflow. The present study does show a significant reduction in central sympathetic nerve traffic after PCI. It should, however, be noted that “complete” revascularization was based on angiographic findings (no remaining stenosis $\geq 50\%$) and thus any persistent microvascular ischemia cannot be excluded. The elimination of anginal symptoms in our patients, however, supports improved myocardial oxygenation. The reduction in MSNA is in accordance with the observed change in sympathovagal balance as assessed by heart rate spectral analysis.

As MSNA is the best measure for central sympathetic activity, our study was specifically designed to have sufficient power to detect an effect of PCI on MSNA. Based on power calculations, at least 9 paired successful microneurography measurements were needed to assess potential changes in MSNA after PCI reliably. As such, 20 patients were included, resulting in sufficiently high-quality MSNA data in 11 patients. This corresponds to a 75% success rate per visit, which is still in the upper range of the values proposed in the literature.¹⁴ The relatively high failure rate in retrieving adequate MSNA data for analysis is a well-known limitation of this technique. Although nerve activity recording failure is at least in part operator related, it occurred randomly in our study. Comparing baseline characteristics between those patients with and without successful microneurography showed no significance between group difference and HRV; catecholamine and hemodynamic analysis were therefore performed for the group as a whole to identify a significant effect. For all these parameters, calculated statistical power was sufficient.

As stated, central sympathetic activity was clearly increased, despite β -blocker treatment in all patients. Increased sympathetic activity has proven to be detrimental in CAD.¹⁶ Current therapy in ischemic heart disease has mainly focused on shielding the β -adrenergic receptor from high sympathetic tone. Although effective, this solves only part of the problem. α -Adrenergic receptor mediated effects and consequences of increased norepinephrine concentrations have proven to be vicious effects of increased sympathetic tone.^{15,17} It was demonstrated that carvedilol, a combined α - and β -adrenergic receptor blocker had superior hemodynamic and metabolic effects compared to single β_1 -receptor blockade in conscious dogs with dilated cardiomyopathy and clear sympathoexcitation.¹⁸ These results were in accordance with those obtained in the carvedilol or metoprolol European trial (COMET) trial, which compared carvedilol and metoprolol.¹⁹ These findings suggest that strategies aimed at reducing sympathetic tone at a central level might be beneficial.

Several factors might have confounded our results. First, MSNA prior to PCI could have been increased by anxiety based on unfamiliarity with study protocol and the pending PCI. Reduction in MSNA after PCI could then be explained by reduced anxiety. Whether this also explains the drop in systolic blood pressure remains uncertain. Although heart rate did not differ between the 2 sessions, patients generally reported being relaxed and measurements were taken after at least 30 minutes of rest; this possibility, though unlikely, cannot be excluded. Secondly, it is possible that angiographically restored myocardial perfusion improved left ventricular function and cardiac output. A reduction in central sympathetic activity could then solely be based on the improved hemodynamic state rather than on a reduction in myocardial ischemia. It seems highly improbable,

however, that myocardial function improves without improvement of myocardial oxygenation. Differentiating reduced sympathetic afferent stimulation from improved cardiac output as the mechanism for reduced central sympathetic activity is difficult. Catecholamine levels are variable. The lack of a significant reduction in plasma norepinephrine levels might be explained by the fact that plasma norepinephrine levels are determined by release, metabolism, and re-uptake of neuronal released norepinephrine, possible obscuring increased release from the presynaptic neuron.²⁰

In summary, the present study shows that cardiac revascularization by PCI reduces central sympathetic activity in patients with clinically established myocardial ischemia, which may add beneficial effects to the increased myocardial perfusion.

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