Sympathetic and cardiac baroreflex function in panic disorder

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Background Recent reports have demonstrated increased cardiac risk, and an association with essential hypertension in patients with panic disorder. The cause is not known, but possibly involves sympathetic nervous activation. In this study, we evaluated the arterial baroreflex control of vascular sympathetic nervous outflow and cardiac baroreflex function in panic disorder patients.

Methods and Results We studied nine patients suffering from panic disorder and ten healthy subjects. Microneurographic recording of muscle sympathetic nerve activity (MSNA) was made with simultaneous recording of blood pressure (BP) and electrocardiogram (ECG). The relationship between MSNA and spontaneous diastolic BP (DBP) changes was assessed at rest and was defined as the arterial baroreflex control of MSNA. Cardiac baroreflex function was assessed using the sequence method. Anxiety was assessed using Spielberger's anxiety state and trait inventory. The slopes of the relationship between MSNA and DBP were more negative (steeper) in the panic disorder group compared with the control subjects (-5.97 ± 0.45 versus -3.06 ± 0.43 bursts/100 heart beats per mmHg, $P < 0.001$). Panic disorder patients had significantly higher state and trait anxiety scores. The slope of the relationship between MSNA and diastolic BP was significantly related to the trait anxiety of the subjects. There was no difference between the cardiac baroreflex sensitivity between the two groups.

Conclusion Patients with panic disorder exhibit enhanced reflex gain of the arterial baroreflex control of MSNA but no change in the cardiac baroreflex. While any clinical significance this observation might have in relation to increased cardiac risk in panic disorder, or to concordance with essential hypertension, remains to be elucidated, increased reactivity of vasoconstricting sympathetic nerves may be a trait characteristic in this cohort. *J Hypertens* **20**:2445–2451 © 2002 Lippincott Williams & Wilkins.

Introduction

No more than 50% of clinical coronary heart disease is explicable in terms of classic cardiac risk factors such as high blood pressure (BP), dyslipidemia, cigarette smoking, obesity and diabetes. There exists a growing body of evidence linking psychological abnormalities, particularly depressive illness [1–4] and anxiety states [5,6] with clinical cardiovascular events and atherosclerosis development [7]. Given the nature of the symptoms accompanying a panic attack, such as: intense anxiety, palpitations, chest pain, and hyperventilation, patients often believe they are experiencing a heart attack but, following clinical cardiac evaluation, are assured they are not. However, recent studies indicate that anxiety disorders, including panic disorder, are indeed accompanied by a significantly increased risk of sudden death [5,6,8,9]. An association has recently also been estab-lished between panic disorder and essential hypertension [10].

Although the mechanism of increased cardiac risk attributable to panic disorder is at present uncertain, the classic symptoms accompanying a panic attack are consistent with some form of autonomic nervous dysfunction. Patients with panic disorder exhibit a more pronounced heart rate response to orthostatic challenge [11]. Yet, while power spectral analysis of cardiac rhythms demonstrates reduced parasympathetic [12,13] and increased sympathetic activities [14] in panic disorder patients, plasma noradrenaline concentrations have yielded conflicting results [11,15,16]. The resting rate of spillover of noradrenaline to plasma from the heart is normal in panic disorder patients and, in response to laboratory mental stress, increases to the

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same extent observed in control subjects [17]. While heart rate increases during panic attacks, BP responses are less consistent [17].

To our knowledge, concurrent cardiac baroreflex and arterial baroreflex control of muscle sympathetic nerve activity (MSNA) has not been documented in panic disorder patients, but would merit some attention given evidence linking anomalies in baroreflex function and cardiac morbidity. The analysis of vagal reflexes has significant prognostic value following myocardial infarction [18], and reduced heart rate variability has been described in panic disorder patients [13,14]. Earlier reports indicate that cardiac baroreflex modulation is a central feature of the cardiovascular manifestations of changes in arousal [19], and have demonstrated that high levels of anxiety sensitivity are related to the development of spontaneous panic attacks [20]. Indeed, consistent with altered cardiac baroreflex function, panic disorder patients have been observed to exhibit a greater fall in BP and less bradycardia than controls after injection of clonidine [21]. In this study, we sought to further examine autonomic function in panic disorder by concurrently examining the arterial baroreflex control of MSNA and cardiac baroreflex sensitivity in response to spontaneous fluctuations in BP.

Methods
Subjects
Nine patients with panic disorder (four female/five male, aged 45 ± 4 years; range, 29–57) and 10 healthy control subjects (seven female/three male, aged 35 ± 5 years; range, 19–58) participated in this study. Subjects were recruited by local advertisement. Diagnosis of panic disorder was made according to DSM-IV criteria [22] and patients were included if they had more than two panic attacks per month, no major depression before the onset of the panic attacks, and no other psychiatric or chronic medical illness. Patients were not on any medication. The healthy subjects were recruited by local advertisement and underwent a comprehensive clinical and physical examination to screen for any previously undiagnosed medical conditions prior to their acceptance in the experimental protocol. Exclusion criteria included a history of major illness, previous psychiatric therapy, cardiovascular disease, and current drug medication. The research protocol conformed to the relevant guidelines of the National Health and Medical Research Council of Australia and was approved by the Alfred Hospital Human Research Ethics Committee. All participants gave written informed consent prior to their participation.

Experimental protocol
On the experimental day, Spielberger's State-Trait Anxiety Inventory (STAI) was used to assess the anxiety proneness (trait anxiety) and the situational
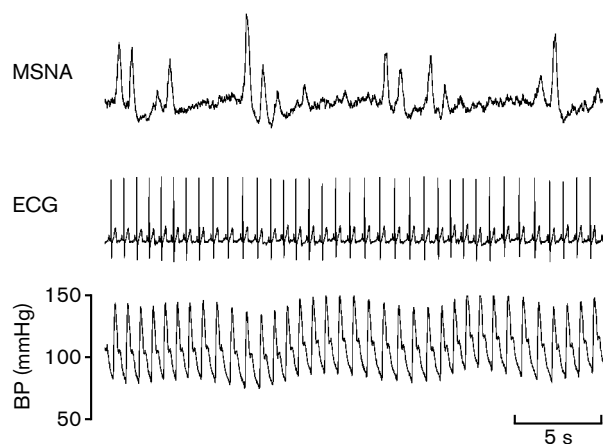
anxiety (state anxiety) of each subject [23]. This was administered immediately prior to the commencement of the study. The STAI consists of two separate 20-item questionnaires. The first required the respondent to assess how they 'generally feel' (anxiety trait), while the second questionnaire required subjects to report the intensity of their feelings of anxiety 'right now, at this moment' (anxiety state). Subjects rated their degree of agreement with the 20 items on each questionnaire using a four-point Likert-type scale. Raw scores thus potentially range from a minimum of 20 to a maximum of 80 for each scale. Low scores indicate low anxiety proneness on the 'trait' scale, and relative calm on the 'state' scale. The construction and validity of Spielberger's inventory has been reviewed [23].

All studies were performed with subjects in the supine position. BP was measured using either brachial artery catheterization (eight patients in the panic group and five in the control one) or using a Finapres BP monitor positioned on the middle finger (model Datex-Ohmeda 2300). Resting Finapress BP was verified during the experiment by brachial auscultation. Heart rate and cardiac interval were determined from the lead III electrocardiographic recording (ECG).

Muscle sympathetic nerve activity
Multiunit postganglionic sympathetic activity was recorded using microneurography in a muscle fascicle of the peroneal nerve at the fibular head, as described previously [24]. The needle was adjusted until satisfactory spontaneous MSNA was observed in accordance to previously described criteria [25,26] (Fig. 1). The nerve

Fig. 1

Simultaneous recording of resting muscle sympathetic nerve activity (MSNA), as assessed from microneurographic nerve recording of impulses in the peroneal nerve, electrical activity of the heart (ECG) and blood pressure (BP) recording in a 36-year-old subject suffering from panic disorder. Note that the sympathetic bursts tend to occur predominantly during spontaneous BP reduction.

signal was amplified ($\times 50\,000$), filtered (bandpass, 700–2000 Hz) and integrated. BP, ECG and MSNA were digitized with a sampling frequency of 1000 Hz (PowerLab recording system, model ML785/8SP; ADI Instruments, Sydney, Australia). After an acceptable nerve-recording site was obtained, resting measurements were performed over a 20-min period.

MSNA was expressed as burst frequency (bursts/min) and burst incidence (bursts/100 heart beats). Relative burst amplitude was calculated by attributing the value of 100 to the largest burst that occurred during the analysed period and expressing all other burst amplitudes as a percentage of the maximum burst.

Assessment of spontaneous arterial baroreflex control of MSNA

Over a 3 to 5 min resting period, diastolic pressures of individual heart beats were grouped in intervals of 2 mmHg and, for each interval, the percentage of diastoles associated with a sympathetic burst was plotted against the mean of the pressure interval (threshold diagram). Muscle sympathetic bursts were advanced by 1.3 s to compensate for baroreflex delay [27]. The threshold (T_{50}) was defined as the diastolic BP (DBP) at which 50% of the diastoles were associated with a burst, and the sensitivity or reflex gain was defined as the slope of the regression line (Fig. 2).

Assessment of spontaneous cardiac baroreflex function

The sequence method of estimation of baroreflex sensitivity has been described by Parati *et al.* [28]. This procedure identifies the 'spontaneous' sequences of three or more consecutive beats in which systolic BP (SBP) progressively rose and cardiac interval progressively lengthened (type 1 sequences), or SBP progressively fell and cardiac interval progressively shortened (type 2 sequences), with a lag of one beat. For each sequence, the linear correlation coefficient between cardiac interval and SBP was computed and the sequence validated when $r > 0.85$. The slope between cardiac interval and systolic BP was calculated for each validated sequence. The percentage of beats involved in such baroreflex sequences (%) and the average slope were calculated for each recording.

Statistical analysis

All baseline variables between the groups were compared using a two-tailed unpaired t-test. Sympathetic baroreflex relations were analysed by weighted linear regression (by number of beats in each diastolic range). $P < 0.05$ was considered significant. Values are reported as mean $\pm$ SEM.
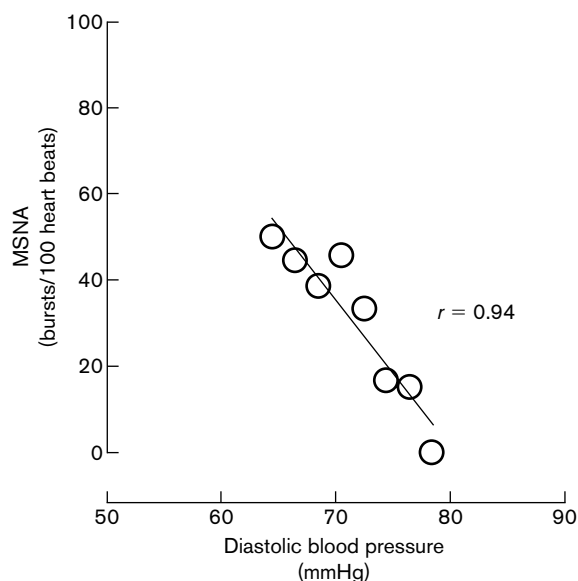
Results

Demographic data, resting values of BP, heart rate, MSNA and anxiety state and trait scores for the two groups are presented in Table 1. No significant differences were observed for BP, heart rate or MSNA between the patients and the control subjects. Patients with panic disorder had significantly higher Spielberger anxiety state and trait scores.

Arterial baroreflex control of MSNA

There was a strong inverse relationship between MSNA and DBP in all nine patients with panic disorder and in nine of the 10 control subjects. Sympathetic baroreflex diagrams indicated that MSNA increased by $5.97 \pm 0.45\%$ ($R = -0.90$)/mmHg decrease in DBP in the panic disorder patients. This was significantly greater than that observed in the control subjects where MSNA increased by $3.06 \pm 0.43\%$ ($R = -0.75$)/mmHg reduction in DBP ($P < 0.001$, Fig. 3). The T_{50} was not different between the two groups of subjects (72 ± 4 mmHg in the group of patients with panic disorder and 68 ± 6 mmHg in the controls, $P = 0.51$).

The range of variation in DBP over the resting periods was not different between the two groups (15 ± 2 and 18 ± 3 mmHg, $P = 0.43$, in the panic disorder and control groups, respectively). There occurred no difference in the slopes of the baroreflex diagrams between the subjects when they were divided according to the way their BP was assessed (radial artery versus Finapres). There was no relation between the slope and age or gender of the subjects. In all subjects combined, Spielberger's anxiety trait scores (but not state scores)
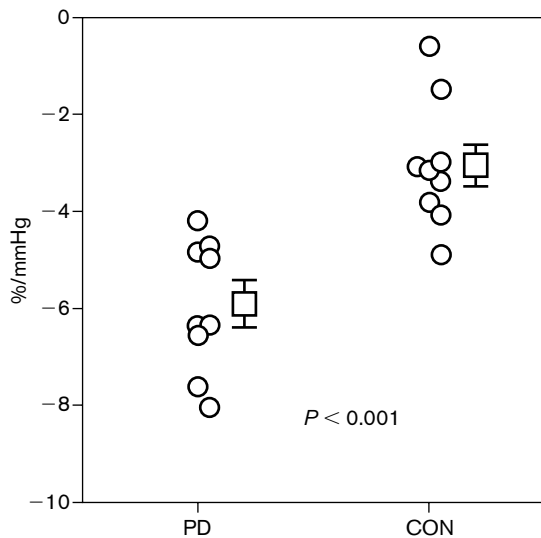
Fig. 2

Example of diagrams describing the relationship between muscle sympathetic nerve activity (MSNA) and spontaneous diastolic blood pressure changes in one control subject.

Table 1 Demographic characteristics of panic disorder patients and controls

	Panic disorder	Controls	P value (t test)
n, (female/male)	9 (4/5)	10 (7/3)	
Age (years)	45 ± 4 (29−57)	35 ± 5 (19−58)	0.129
Trait anxiety	48 ± 3	30 ± 2	0.001
State anxiety	47 ± 4	30 ± 3	0.009
BMI (kg/m^2)	26 ± 2	25 ± 2	0.664
SBP (mmHg)	137 ± 3	129 ± 5	0.23
DBP (mmHg)	72 ± 3	71 ± 5	0.76
HR (bpm)	73 ± 3	68 ± 2	0.144
MSNA (bursts/min[1])	34 ± 5 (11−51)	25 ± 3 (12−46)	0.132
MSNA (bursts/100 heart beats)	47 ± 7 (14−69)	37 ± 5 (23−74)	0.230
Median burst amplitude	41 ± 2	46 ± 4	0.215

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; MSNA, muscle sympathetic nerve activity.

Fig. 3

Slope of the sympathetic baroreflex function in the panic disorder (PD) patients and controls (CON) calculated from the baroreflex diagrams. Units are percentage increase in muscle sympathetic nerve activity/ mmHg decrease in diastolic blood pressure.
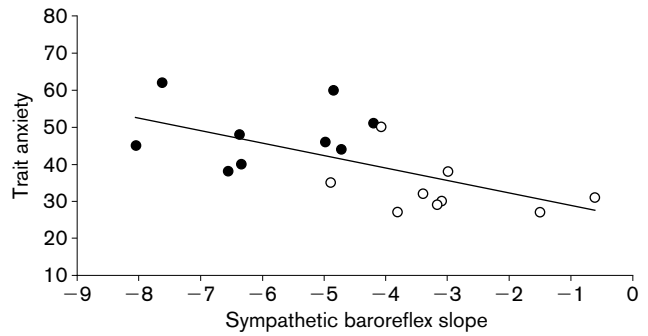
Fig. 4

Correlation between trait anxiety and the sympathetic baroreflex sensitivity. Open circles, controls; closed circles, panic disorder patients. $P < 0.01$, $R = 0.6$.

were significantly related to the slope of the relationship between diastolic BP and MSNA (Fig. 4, $P < 0.01$, $R = 0.6$).

Cardiac baroreflex sensitivity
Altered cardiac baroreflex sensitivity was not evident in panic disorder. There occurred no difference in the slope of the cardiac baroreflex between the two groups (18 ± 5 and 29 ± 7 ms/mmHg, $P = 0.87$ for the panic disorder and control groups, respectively). The percentage of beats involved in baroreflex sequences was 53 ± 6% in the panic disorder patients and 48 ± 8% in the control subjects ($P = 0.23$). Anxiety state and trait scores bore no association to cardiac baroreflex sensitivity.

Discussion
Although acknowledged as distressing and disabling,

until recently anxiety disorders, such as panic disorder, were not considered to constitute a risk to life. Kawachi and colleagues [6], in their prospective examination of over 30 000 male health professionals, found that subjects with a high level of phobic anxiety were at sixfold increased risk of developing fatal coronary heart disease. The mechanism of increased cardiac risk in panic disorder is uncertain, but autonomic dysregulation, such as to induce global increases in sympathoexcitation and possible genesis of ventricular tachyarrhythmias, combined with coronary artery spasm [29], are likely to be of prime importance. Our results indicate that while resting sympathetic function appears normal in panic disorder [17] there occurs a marked alteration in sympathetic baroreflex function favouring substantially greater responses in sympathetic nerve firing to spontaneous fluctuations in DBP. The sensitivity of the sympathetic baroreflex is significantly related to the underlying degree of anxiety proneness.

In this study, arterial baroreflex control of MSNA was analysed by relating each spontaneous sympathetic burst to the DBP of the heartbeat, during which the burst was generated without recourse to utilizing

vasoactive substances, such as phenylephrine or sodium nitroprusside. While pharmacological interventions undoubtedly induce a more pronounced range in DBP, such techniques may alter intracardiac pressure and impact on cardiopulmonary receptor function [30]. Our results were expressed as BP sensitivity for occurrence of sympathetic bursts. Recently, Kienbaum and colleagues [31] demonstrated the utility and reproducibility of this approach, with burst incidence providing a more robust indicator of baroreflex control than burst amplitude alone, or burst amplitude and incidence in combination. The mean resting baroreflex gain (slope of the relationship between MSNA and DBP) in their study based on observations in 60 healthy subjects was -3.9% and was similar to that documented in the present report. Differentiation of sympathetic nerve burst strength and amplitude has previously been observed [32]. Indeed, Kienbaum *et al.* [31] postulated that the baroreflex mechanisms regulating the incidence and strength of sympathetic bursts are not identical and suggested that the modulation of each occurs at two sites within the central nervous system.

BP recordings were obtained invasively from more subjects with panic disorder than from controls thereby raising the possibility that differences in methodology may induce a bias in the estimation of the slope of the sympathetic baroreflex function. Kienbaum *et al.* [31] found that the relationship between cardiac intervals and MSNA was also a good estimate of the sympathetic baroreflex function. Although arterial baroreceptors primarily sense the BP-induced distension of the vessel wall, the duration of the cardiac interval seems to influence the occurrence of sympathetic bursts [31]. We estimated the sympathetic baroreflex function by calculating the slope of the relationship between MSNA and cardiac intervals [extracted from the electrocardiogram (ECG) recordings] and found a steeper slope in panic disorder subjects than controls (0.37 versus 0.27%, $P = 0.017$, data not shown). This observation is independent of any possible bias associated with BP recording methodology.

We found a direct relation between the slope of the sympathetic baroreflex and the subjects' trait anxiety. Whether anxiety proneness impacts directly on brain neurotransmission in panic disorder, so as to favour a more pronounced sympathetic activation in response to fluctuations in BP remains to be unequivocally demonstrated. While the principal neuronal circuitry involved in the reflex regulation of the cardiovascular system resides in the medulla, reciprocal connections between the medulla, pons, midbrain and hypothalamus are essential for the integration of behaviourally significant responses [33]. Indeed, a degree of central dysfunction within noradrenergic, serotonergic and amino acid neuronal pathways has been demonstrated in patients with

panic disorder. γ-aminobutyric acid (GABA) receptor density in the brain stem appears diminished [34] and brain noradrenergic activity may be augmented [35] in patients with panic disorder. GABA plays a critical role in the inhibitory projection between the caudal and rostral ventrolateralmedulla; a projection believed to be the key to the negative feedback homeostatic character of the baroreceptor reflex arc [36]. Recent experimental data support the hypothesis that GABA receptors are of primary importance in determining the gain of the sympathetic baroreflex control to the vasculature [37]. Whether decreased GABA receptor sensitivity or alterations in brain monoaminergic neurotransmission is responsible for the alteration in baroreflex sensitivity in panic disorder remains to be elucidated.

An association between essential hypertension and panic disorder has recently been reported. Prevalence of panic disorder was found to be approximately trebled in patients with essential hypertension [10]. There are some points of similarity in the neural pathophysiology of both disorders. Adrenaline has been documented to be a sympathetic nerve co-transmitter in both [17,38], attributable it seems, to neuronal uptake of adrenaline from plasma. Adrenaline sympathetic co-transmission in essential hypertension has been taken to be evidence that mental stress is operative in its pathogenesis [39]. Another point of similarity is the phenotypic evidence of faulty neuronal re-uptake of noradrenaline present in both [39]. In panic disorder (unpublished observations), such an abnormality might augment arousal responses in the heart in particular, such as to sensitise panic sufferers to symptom development. There are, however, also pathophysiological areas of dissimilarity, a case in point being elevation of sympathetic tone at rest in essential hypertension [40,41] but not in panic disorder [17]. Augmentation of the neural arterial baroreflex in panic disorder, presented here, but not in essential hypertension [42] is another difference.

The concept of psychosomatic heart disease has gained a degree of credibility with the publication of a number of reports indicating that anxiety disorders are accompanied by a significantly increased risk of sudden death [5,6,8,9]. While a number of factors including altered cardiac baroreflex sensitivity have been proposed to account for the increased morbidity, direct evidence is lacking. Moreover, the present study failed to demonstrate an impaired cardiac baroreflex function in patients with panic disorder. Watkins *et al.* [43] demonstrated an association between anxiety and reduced cardiac baroreflex control of heart rate in older individuals. Patients with panic disorder exhibit a reduction in heart rate variability [44] and a more pronounced diminution in BP following clonidine administration [21]. Impaired autonomic function, as indicated by reduced heart rate variability and/or decreased cardiac baroreflex function,

is evident in diabetes [45], hypertension [42] and heart failure [46], conditions where the risk of cardiac mortality is major.

Whether altered sympathetic baroreflex function is responsible for the increased cardiac risk associated with panic disorder remains problematic. Indeed, increased arterial baroreflex gain may help to regulate the BP more efficiently when patients experience a panic attack. In support of our observation, Lucini *et al.* [47] recently demonstrated that psychological stress in healthy young students induces greater vascular, as opposed to cardiac, responses to standing-induced sympathetic excitation. In a large group of subjects, Young *et al.* [48] demonstrated that subjects with a high level of anxiety displayed less BP increase to mental arithmetic than subjects with low or medium level of anxiety. This finding suggests that a high level of anxiety is accompanied by autonomic dysfunction, which is in accordance with our observation that the sensitivity of the baroreflex was related to the degree of trait anxiety of the patients. While resting cardiac and MSNA appears normal in panic disorder [17], we have demonstrated a marked alteration in sympathetic baroreflex function, resulting in noticeable alterations in MSNA in response to spontaneous fluctuations in DBP. The ability of the baroreflex to modify heart rate remained unaltered. This suggests that the differential behaviour of the baroreflex control in panic disorder is due to a central alteration limited to the sympathetic nervous system. It must be emphasized that our finding of altered sympathetic baroreflex control has been demonstrated in patients between panic attacks and free of significant demonstrable cardiovascular dysfunction. Patients experiencing episodic chest pain of anginal quality during a panic attack may exhibit signs of cardiac ischemia [29]. Whether the acute development of coronary artery spasm, combined with the alteration in sympathetic control we describe, underpins the increased cardiovascular morbidity seen in these patients remains conjectural but clearly warrants further investigation.

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