

# Sympathetic Activity in Patients With Panic Disorder at Rest, Under Laboratory Mental Stress, and During Panic Attacks

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**Background:** The sympathetic nervous system has long been believed to be involved in the pathogenesis of panic disorder, but studies to date, most using peripheral venous catecholamine measurements, have yielded conflicting and equivocal results. We tested sympathetic nervous function in patients with panic disorder by using more sensitive methods.

**Methods:** Sympathetic nervous and adrenal medullary function was measured by using direct nerve recording (clinical microneurography) and whole-body and cardiac catecholamine kinetics in 13 patients with panic disorder as defined by the *DSM-IV*, and 14 healthy control subjects. Measurements were made at rest, during laboratory stress (forced mental arithmetic), and, for 4 patients, during panic attacks occurring spontaneously in the laboratory setting.

**Results:** Muscle sympathetic activity, arterial plasma concentration of norepinephrine, and the total and cardiac norepinephrine spillover rates to plasma were similar in

patients and control subjects at rest, as was whole-body epinephrine secretion. Epinephrine spillover from the heart was elevated in patients with panic disorder ( $P=.01$ ). Responses to laboratory mental stress were almost identical in patient and control groups. During panic attacks, there were marked increases in epinephrine secretion and large increases in the sympathetic activity in muscle in 2 patients but smaller changes in the total norepinephrine spillover to plasma.

**Conclusions:** Whole-body and regional sympathetic nervous activity are not elevated at rest in patients with panic disorder. Epinephrine is released from the heart at rest in patients with panic disorder, possibly due to loading of cardiac neuronal stores by uptake from plasma during surges of epinephrine secretion in panic attacks. Contrary to popular belief, the sympathetic nervous system is not globally activated during panic attacks.

*Arch Gen Psychiatry.* 1998;55:511-520

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SINCE ITS first recognizable descriptions during the 19th century, panic disorder has been conceptually linked with the sympathetic nervous system. In his 1871 study of "irritable heart" in soldiers, Da Costa<sup>1</sup> attributed the malady to "hyperaesthesia of the cardiac nerve centres." More recently, increased cardiovascular mortality, including sudden death, has been reported in patients with panic disorder and in men with high levels of phobic anxiety.<sup>2-6</sup> These findings may provide indirect evidence of sympathetic involvement in panic disorder, because the cardiac sympathetic nerves have a critical role in the development of fatal ventricular arrhythmias.<sup>7-10</sup> Studies of patients with panic disorder using measurements of venous plasma norepinephrine levels to assess sympathetic nervous activity

have, however, failed to consistently show differences between patients and healthy subjects at rest.<sup>11-20</sup> This may, perhaps, be because plasma norepinephrine concentration values in samples

*For editorial comment  
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obtained from the antecubital venous site provide a flawed measure of sympathetic tone. The notion of a "generalized" sympathetic tone is now discounted; regionalized and highly differentiated responses are recognized with many different stimuli.<sup>21</sup> Antecubital venous concentrations of norepinephrine, which primarily reflect activity in muscle and skin sympathetic nerves to the forearm, cannot be used to infer cardiac sympathetic tone, for example. Esler et al<sup>22</sup> previously reported that laboratory-

## PARTICIPANTS AND METHODS

### PARTICIPANTS

Thirteen patients were recruited primarily by advertising in local newspapers. After screening by telephone, they were examined for a diagnosis of panic disorder according to criteria in the *DSM-IV*.<sup>26</sup> Patients were excluded if they had any of the following: (1) less than 1 panic attack every 2 weeks, (2) major depression that preceded the onset of the panic attacks or other psychiatric illness, or (3) a chronic medical illness. As a consequence of the method of recruitment, most patients were not receiving medications for the panic disorder. Three patients who had been taking medication stopped at least 2 weeks before the study (**Table 1**). In some circumstances, patients with primary cardiac arrhythmias can be misdiagnosed as having panic disorder.<sup>27</sup> Accordingly, all patients were clinically assessed by a cardiologist (M.D.E.) participating in the study. In each patient, mitral valve prolapse was excluded by echocardiography, and the electrocardiogram revealed no evidence of Wolff-Parkinson-White syndrome.

Seven healthy female control subjects were recruited by advertising in local newspapers and at employment services and were reimbursed a small amount for their time and effort. The 7 male control subjects were drawn from a large database for the study of sympathetic nervous function in healthy male volunteers who underwent testing in the research cardiac catheter laboratory during the period of the study and the preceding 2 years. The men qualified for inclusion in the study only if all measures of whole-body and regional sympathetic nervous function and of epinephrine secretion had been performed identical to the measurements done in patients with panic disorder. The control subjects were aged between 25 and 70 years and had no history of chronic illness. Exclusion criteria for control subjects included the following: (1) use of medications other than simple analgesics within 2 weeks of the study, (2) a history of psychiatric illness, (3) overweight (>125% of ideal

body weight), and (4) for women, a positive pregnancy test on the day that study testing was performed.

All participants underwent clinical screening for any previously undiagnosed medical condition. Although drug screening was not performed, to the best of our knowledge, all were free of substance or alcohol abuse. Before the study, the levels of depression and anxiety were determined for all patients and the female control subjects by using the Spielberger State-Trait Anxiety Inventory (STAI-Form X<sup>28</sup>) and the Beck Depression Inventory.<sup>29</sup> The research protocols conformed to the relevant guidelines of the National Health and Medical Research Council of Australia and were approved by the Alfred Hospital (Melbourne, Australia) Human Research Ethics Committee. All participants gave written informed consent for their participation.

### PROCEDURES

#### Catheterization

We used an isotope dilution technique, concurrently administering radiolabeled epinephrine and norepinephrine<sup>21</sup> to measure the rates of whole-body and cardiac spillover of both catecholamines. Blood samples were obtained from coronary sinus and brachial or radial arterial catheters that were percutaneously inserted after administration of local anesthesia under strict aseptic conditions, and coronary sinus blood flow was measured by thermodilution.<sup>9,22,25</sup> Blood flow values were converted to plasma flow values by using the hematocrit measurements of the participants. Caffeinated beverages, alcohol, and tobacco smoking were forbidden during the 12 hours preceding the study, which took place in the morning after a light breakfast.

During the study, levo-[7-<sup>3</sup>H]-norepinephrine and levo-[N-methyl-<sup>3</sup>H]-epinephrine (New England Nuclear Corp, Boston, Mass) were infused continuously into a peripheral vein at a constant rate of 0.018 to 0.037 MBq/min. Blood samples for catecholamine measurement (10 mL) were obtained simultaneously from the arterial and

induced mental stress in human subjects causes activation of cardiac sympathetic nerves with minimal change in the venous plasma concentration of norepinephrine.

We attempted to overcome some of these difficulties. Tracer levels of labeled norepinephrine and epinephrine were infused, and whole-body spillover rates to plasma of the endogenous catecholamines were derived. One previous study applied similar methods to the study of panic disorder, measuring arterialized venous concentrations along with infusions of tritiated norepinephrine. Villacres et al<sup>23</sup> found no elevation in resting whole-body norepinephrine spillover rates in panic disorder, but did find a 3-fold increase in arterIALIZED plasma concentrations of epinephrine. In addition, we assessed cardiac sympathetic function directly by isotope dilution, using central venous catheterization to sample from the coronary sinus. The sympathetic nerve firing rates in muscle were measured by

using the electrophysiologic technique of clinical microneurography.<sup>24</sup>

Relatively few studies have been conducted of the physiological changes occurring during "spontaneous" panic attacks. During the course of our study, several patients experienced spontaneous panic attacks, providing us with an opportunity to measure whole-body and regional sympathetic responses. We compared these changes with those seen with a neutral form of stress, ie, forced mental arithmetic.<sup>22,25</sup>

## RESULTS

### RESTING SYMPATHETIC FUNCTION IN PANIC DISORDER

Demographic data and resting catecholamine results for patients and control subjects are given in Table 1. A profile of the 2 groups for age, body mass index, and results

coronary sinus catheters and placed in chilled tubes containing an anticoagulant and antioxidant (ethyleneglycol-tetraacetic acid and reduced glutathione), following which the plasma was separated by centrifugation and stored at  $-80^{\circ}\text{C}$  until assayed.<sup>25</sup>

#### Microneurography

The sympathetic activity to skeletal muscle blood vessels was measured by using well-established techniques.<sup>24,30</sup> Multiunit postganglionic sympathetic nerve activity was recorded at rest by using a tungsten microelectrode (Titrone Medical Instruments, Iowa City, Iowa) that was inserted through the intact unanesthetized skin into the peroneal nerve at the fibular head. The needle was adjusted until spontaneous sympathetic nerve activity was recorded; the activity was identified according to proved criteria.<sup>24,30</sup>

#### Forced Mental Arithmetic

Simulated mental stress was generated in the laboratory by using a cognitive challenge paradigm.<sup>22,25</sup> Each subject rapidly subtracted 1-digit numbers from a 3-digit number for 10 minutes. The test for all participants was supervised by one staff member at the Baker Medical Research Institute, Melbourne, Australia, who was unaware whether participants were patients with panic disorder or healthy volunteers. This staff member changed the subtractions as required to maintain the complexity of the challenge according to the participants' differing mathematical abilities. Blood samples were obtained at rest and during the last 2 minutes of stress testing, and blood pressure, heart rate, and sympathetic nerve activity measurements were averaged over 2 minutes at rest and during stress to correspond with these catecholamine values.

#### Panic Attacks

Four patients experienced spontaneous panic attacks during the study. They were told that the study could be

stopped at any time, but all chose to continue to allow measurements to be made. Sympathetic nerve firing was measured in all 4 patients, and whole-body catecholamine kinetics were measured in 3. Of the 4 patients, 3 completed the Acute Panic Inventory.<sup>31</sup> They were asked to complete the inventory for "a typical panic attack" and "today's attack."

Owing to the technical complexity of the study, measurement of all variables was not possible in all subjects (range, 6-14 measurements in each group). Anxiety and depression scores were not available for male control subjects.

#### Catecholamine Kinetics

The plasma concentrations of epinephrine and norepinephrine were measured by using high-performance liquid chromatography with electrochemical detection. Fractions of the eluant leaving the electrochemical cell were collected for measurement of hydrogen 3-labeled catecholamines by liquid scintillation spectroscopy. Whole-body catecholamine spillover rates were calculated by using isotope dilution.<sup>32</sup> Norepinephrine and epinephrine spillover from the heart was calculated by application of the Fick principle as described previously.<sup>21</sup>

#### STATISTICAL METHODS

Unpaired analyses between control subjects and patients with panic disorder were performed by using the Student *t* test or the Mann-Whitney rank sum test (when the samples were not normally distributed or had unequal variances). Responses to mental stress were analyzed by using the paired *t* test or the Wilcoxon signed rank test as appropriate. When significant responses occurred in control and patient groups, the increments in the relevant measures were compared by using unpaired *t* tests or the Mann-Whitney rank sum test as described. Correlations were tested with the Pearson product moment correlations. The null hypothesis was rejected if  $P < .05$ . All results are expressed as mean  $\pm$  SD.

on the anxiety and depression indices is given in **Table 2**. Patients with panic disorder had significantly higher resting heart rates than did control subjects ( $76.4 \pm 10.07$  beats/min vs  $65.7 \pm 9.57$  beats/min) ( $n = 13$ ;  $t_{2,4} = -2.78$ ,  $P = .01$ , unpaired *t* test). The systolic and diastolic blood pressure measurements were similar in the 2 groups. The heart rate was unrelated significantly to state or trait anxiety levels.

The resting arterial norepinephrine concentrations and whole-body norepinephrine spillover were not significantly different between patients and control subjects (Table 1 and **Figure 1**). While there was a trend for higher arterial concentrations of epinephrine and higher whole-body epinephrine secretion, the differences were not statistically significant (Table 1 and Figure 1). Neither norepinephrine nor epinephrine rates of release were significantly correlated with the indices of state or trait anxiety or depression. The muscle sympathetic nerve activity also was similar in patients and con-

rol subjects at rest (**Figure 2**). Cardiac sympathetic activity as measured by the spillover of norepinephrine from the heart was somewhat higher in patients than in control subjects, but not significantly so (Figure 1).

Cardiac epinephrine spillover was significantly higher in patients with panic disorder than in control subjects ( $P = .01$ ; Figure 1). Cardiac spillover of epinephrine was not significantly correlated with cardiac norepinephrine spillover.

#### SYMPATHETIC FUNCTION DURING LABORATORY MENTAL STRESS

There was a significant and sustained increase in heart rate and systolic blood pressure with cognitive challenge, which was not significantly different between patients and control subjects (**Table 3**). Muscle sympathetic nerve activity did not change significantly during the challenge. The arterial plasma concentration of norepinephrine and whole-

**Table 1. Demographic Data and Resting Catecholamine Results for Control Subjects and Patients\***

Sex	BMI, kg/m <sup>2</sup>	Trait Anxiety	State Anxiety	Duration of Illness, y	Frequency of PA per Month†	Medication Taken in Last 3 mo‡
<b>Controls</b>						
F	27.58	27	26	NA	NA	...
F	19.36	28	32	NA	NA	...
F	25.32	33	37	NA	NA	...
F	21.74	50	35	NA	NA	...
F	24.31	34	36	NA	NA	...
F	22.55	27	24	NA	NA	...
F	21.25	27	24	NA	NA	...
M	22.84	ND	ND	NA	NA	...
M	25.71	ND	ND	NA	NA	...
M	22.86	ND	ND	NA	NA	...
M	24.93	ND	ND	NA	NA	...
M	22.86	ND	ND	NA	NA	...
M	29.04	ND	ND	NA	NA	...
M	31.62	ND	ND	NA	NA	...
<b>Patients</b>						
F	20.15	45	41	4	>2	Imipramine hydrochloride
F	25.65	40	56	1	>2	...
M	26.24	60	47	20	8	...
M	26.76	48	50	>1	12	...
M	24.83	44	50	0.3	4	...
M	26.11	62	38	1.2	>2	Paroxetine, diazepam
F	19.68	46	43	>1	4	...
F	17.67	38	55	0.3	4	Alprazolam
F	33.33	51	68	>1	4	...
F	20.31	54	39	9	4	...
F	22.66	49	50	2	4	...
F	19.86	31	34	26	2	...
M	33.14	38	30	34	2	...

\*BMI indicates body mass index; PA, panic attacks; NA, not applicable; ellipses, no medication given; and ND, not done.

†Frequency over last 2 months.

‡The 3 patients taking medication stopped taking it at least 2 weeks prior to the study.

body norepinephrine spillover increased significantly in both groups. There also was a significant increase in whole-body epinephrine secretion (Table 3). The magnitude of these changes in catecholamine release was similar among patients and control subjects.

#### SYMPATHETIC NERVOUS AND ADRENAL MEDULLARY FUNCTION DURING PANIC ATTACKS

Four patients experienced acute episodes of anxiety during the study that they described as “similar to normal panic attacks” and that met criteria of the the DSM-IV.<sup>26</sup> One patient experienced several episodes. Arterial plasma samples were obtained from 3 patients within 3 to 5 minutes of the onset of the panic attack, enabling catecholamine responses to be analyzed. For the fourth patient, arterial and coronary sinus plasma samples were obtained approximately 10 minutes after an attack.

The heart rate increased in 3 patients, with a mean increase of 27% (Table 4). One patient had a brief (approximately 30-second) episode of atrial fibrillation. The blood pressure increased in 3 patients; however, the changes generally were small (average mean blood pressure increase, 7.2%). The whole-body norepinephrine spillover

increased slightly in all 3 patients in whom it was measured, with a mean increase of 15% (Table 4). The secretion of epinephrine increased dramatically during panic attacks, with a mean increase of 153% (Figure 3). Microneurography recordings were made for all 4 patients. Changes in muscle sympathetic nerve burst frequency were inconsistent, but generally small (mean decrease of 5 bursts per minute). In 2 patients, the muscle sympathetic nerve burst amplitude increased despite no significant change in burst frequency (Figure 4). In the 1 patient in whom it was measured, there was a marked increase in cardiac epinephrine spillover after the panic attack from 2.0 pmol/min (resting, before the panic attack) to 33.1 pmol/min (10 minutes after panic attack). There was a minimal change in the cardiac norepinephrine spillover (0.23 nmol/min after the panic attack compared with 0.26 nmol/min resting).

#### COMMENT

##### RESTING SYMPATHETIC FUNCTION IN PANIC DISORDER

Whole-body norepinephrine spillover, a sensitive measure of overall sympathetic nervous system activity,<sup>21,33</sup>

Arterial Norepinephrine, nmol/L	Arterial Epinephrine, pmol/L	Whole-Body Norepinephrine Spillover Rate, ng/min	Whole-Body Epinephrine Spillover Rate, ng/min	Cardiac Norepinephrine Spillover Rate, ng/min	Cardiac Epinephrine Spillover Rate, ng/min
0.52	198	267	128	ND	ND
1.35	527	588	231	28.77	-0.08
1.10	313	678	202	30.2	1.86
1.14	252	532	149	17.96	0.49
1.29	318	514	143	13.64	1.86
0.73	313	363	169	ND	ND
1.18	938	371	277	ND	ND
1.07	445	396	226	6.60	0.71
0.94	406	530	268	6.40	-1.44
0.95	423	461	215	38.86	-4.04
0.50	170	228	85	4.60	-0.09
1.32	428	356	129	35.88	-0.16
2.11	466	721	218	8.49	0.60
1.40	285	453	111	13.95	0.07
1.09	395	581	233	44.51	0.37
1.38	445	703	258	27.50	3.23
1.21	307	431	112	8.90	-0.51
1.53	653	932	418	ND	ND
0.82	648	374	338	14.89	-1.09
1.32	379	485	142	16.81	4.56
1.31	845	540	373	17.80	4.84
0.70	779	318	393	ND	ND
1.31	302	291	76	ND	ND
2.02	318	836	135	69.00	4.03
1.26	582	426	192	ND	ND
1.06	1125	391	446	35.30	1.42
0.87	214	449	121	ND	ND

**Table 2. Age, Sex, Body Mass Index, and Anxiety and Depression Profiles of Patient and Control Groups\***

	Control Subjects	Patients With Panic Disorder
Age, y	38.9 ± 18.22	41.8 ± 8.80
Sex, M/F	7:7	5:8
Body mass index, kg/m <sup>2</sup>	24.4 ± 3.28	24.3 ± 4.46
Trait Anxiety†	32.3 ± 8.36 (n = 7)	46.6 ± 8.87‡
State Anxiety†	30.6 ± 5.77 (n = 7)	46.2 ± 10.25§
Depression	1.43 ± 2.57 (n = 7)	6.23 ± 4.09¶

\*Unless otherwise indicated, values are expressed as mean ± SD. Psychometric scales were not available for all controls.

†Spielberger State Trait Anxiety Inventory (STAI-Form X<sup>28</sup>).

‡Patients vs controls: P = .003 unpaired t test.

§Patients vs controls: P = .002 unpaired t test.

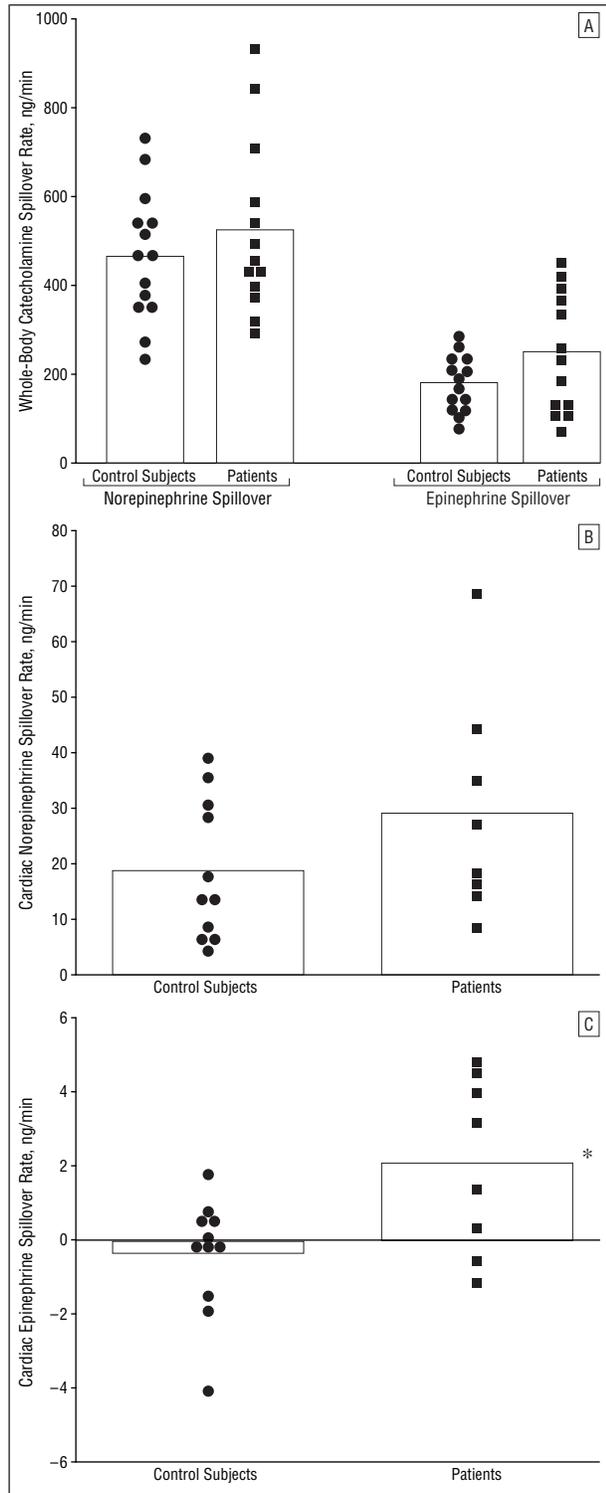
||Beck Depression Inventory.<sup>28</sup>

¶Patients vs controls: P = .01 unpaired t test.

was similar in patients and control subjects, arguing against any generalized increase in sympathetic activity in panic disorder. While a subset of patients had high whole-body epinephrine secretion rates, across the group of patients this difference was not significant. These findings are similar to those of the only

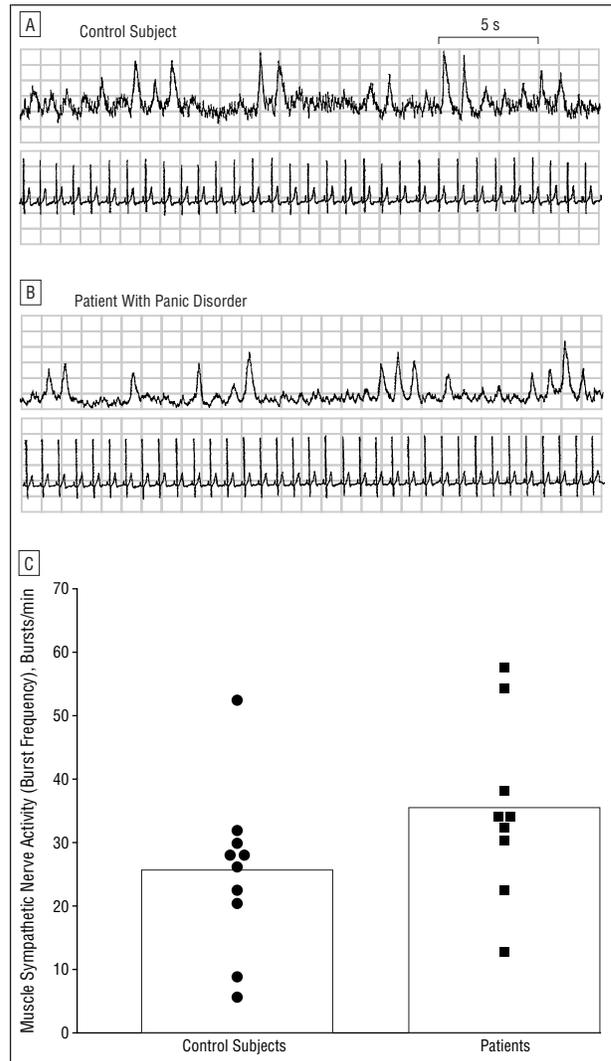
previous study to have measured norepinephrine kinetics in panic disorder, which found elevated plasma concentrations of epinephrine but normal norepinephrine spillover.<sup>23</sup>

By using methods that readily detect small changes in efferent sympathetic activity in skeletal muscle<sup>24,25,30</sup> and in the heart,<sup>9,21,25</sup> we also found regional sympathetic nervous activity to be normal in patients with panic disorder while they were at rest. Muscle sympathetic nerve activity measured by microneurography was similar in patients and control subjects. This finding agrees with earlier reports of normal concentrations of antecubital venous plasma norepinephrine in panic disorder.<sup>11-17</sup> Although in several of these studies, the antecubital venous concentration of norepinephrine was considered to signify whole-body noradrenergic activity, this measure best reflects skeletal muscle sympathetic tone in the forearm.<sup>34,35</sup> Similarly, cardiac norepinephrine spillover was normal in patients with panic disorder, indicating normal resting cardiac sympathetic activity. Investigators using power spectral analysis of heart rate variability, in which individual components of variability are separated as a method of analyzing cardiac autonomic nervous control, have reported indirect evidence of decreased parasympathetic activ-



**Figure 1.** Whole-body catecholamine (A) and cardiac norepinephrine (B) spillover to plasma in patients with panic disorder and healthy control subjects at rest; overall and cardiac sympathetic activity were similar in the 2 groups. Cardiac epinephrine spillover (C) at rest was evident in patients with panic disorder only (asterisk indicates  $P = .01$ , patients vs control subjects).

ity<sup>36,37</sup> or increased resting cardiac sympathetic activity.<sup>38</sup> The methodological limitations of this technique are now apparent, especially for the study of sympathetic nervous function; the low-frequency component of heart rate variability, sometimes used as a measure of



**Figure 2.** Sympathetic nerve activity to skeletal muscle blood vessels at rest. Sample microneurograms and accompanying electrocardiograms from a healthy control subject and a patient with panic disorder are shown (A and B). Muscle sympathetic nerve burst frequencies were similar in patients and control subjects (C).

cardiac sympathetic tone, is determined primarily by arterial baroreflex function and cardiac adrenergic receptor sensitivity rather than cardiac sympathetic nerve firing rates.<sup>39</sup>

Epinephrine spillover from the heart was evident at rest in patients with panic disorder. The concentration of epinephrine in the healthy human heart is low, and cardiac release of epinephrine is undetectable at rest.<sup>40</sup> It previously has been suggested that stress-induced elevation of plasma epinephrine might lead to buildup of stores of epinephrine within sympathetic nerves<sup>41</sup>; yet to date, there is little direct evidence of this phenomenon in humans. The release of epinephrine from the heart shown in the present study in patients with panic disorder is presumably attributable to loading of sympathetic nerves by uptake from plasma during the epinephrine surges accompanying panic attacks. One patient had a large increase in cardiac epinephrine spillover shortly after a panic attack. There is evidence that co-release of epinephrine from

the heart might potentiate cardiac stress responses by its action on presynaptic neuronal  $\beta$ -adrenergic receptors, augmenting release of norepinephrine from the cardiac sympathetic nerves.<sup>42,43</sup> There was no clear evidence of this, however, in our study, as cardiac norepinephrine spillover values were normal at rest and in response to mental stress.

### SYMPATHETIC FUNCTION IN PANIC DISORDER DURING LABORATORY-INDUCED MENTAL STRESS

There were no differences in the responses of patients with panic disorder and control subjects to cognitive challenge. In a previous study of the reactivity of patients with panic disorder to forced mental arithmetic, Roth et al<sup>44</sup> similarly found that responses to laboratory-induced mental stress in panic disorder were unremarkable. Studies measuring reactivity to other laboratory stressors have given conflicting results.<sup>12,13,18,45-49</sup> Overall, our results give fur-

ther evidence that reactivity to neutral laboratory-induced stressors is unchanged in patients with panic disorder.

### SYMPATHETIC NERVOUS AND ADRENAL MEDULLARY FUNCTION DURING PANIC ATTACKS

There were consistently large increases in epinephrine secretion during spontaneous panic attacks, accompanied by proportionally smaller increases in norepinephrine spillover. This finding of a pattern of preferential adrenal medullary activation is in contrast to findings in a previous report on endocrine changes during spontaneous panic attacks. Cameron and coworkers<sup>50</sup> found a small increase in the antecubital plasma concentrations of norepinephrine during panic attacks but no change in epinephrine levels. The basis for this difference is unclear, but extraction of epinephrine across the forearm makes arterial plasma values more reliable than antecubital venous plasma concentrations for the detection of stress responses.<sup>21</sup>

Two of the 4 patients had large increases in muscle sympathetic nerve activity during panic attacks, while there was no change in 2 other patients who had shorter and less intense attacks. The increased neural activity was highly distinctive, involving an increase in amplitude of the multiunit bursts without a concomitant increase in burst frequency. This, to our knowledge, is without parallel in other circumstances of intense sympathetic nervous activation, in which the number of sympathetic bursts and the heart rate are quantitatively related, and the timing of bursts coincides with the nadir of diastolic blood pressure in the arterial pulse wave.<sup>21,24,30</sup> The distinctive pattern of nerve firing during panic attacks most likely represents recruitment of inactive sympathetic nerve fibers and a strong central synchronization of impulses that overrides the usual dominant influence of the arterial baroreflex.

**Table 3. Physiological and Sympathetic Nervous Response to Forced Mental Arithmetic\***

	Rest	Stress
Heart rate, beats/min	72.4 ± 10.3	82.7 ± 5.4†
Systolic pressure, mm Hg	133.2 ± 13.5	143.8 ± 20.1‡
MSNA, bursts/min	32.5 ± 15.4	32.9 ± 11.5
Arterial norepinephrine, nmol/L	1.25 ± 0.38	1.49 ± 0.43§
Norepinephrine spillover, ng/min	514.8 ± 168.2	636.8 ± 178.0
Arterial epinephrine, pmol/L	454 ± 198	496 ± 279
Epinephrine spillover, ng/min	199.9 ± 76.6	242.8 ± 128.4¶

\*Values are expressed as mean ± SD. MSNA indicates muscle sympathetic nerve activity.

†Stress vs resting:  $P < .001$ ,  $t_{16} = -5.66$ , paired  $t$  test.

‡Stress vs resting:  $P = .002$ ,  $t_{16} = -3.57$ , paired  $t$  test.

§Stress vs resting:  $P < .001$ ,  $t_{21} = -4.91$ , paired  $t$  test.

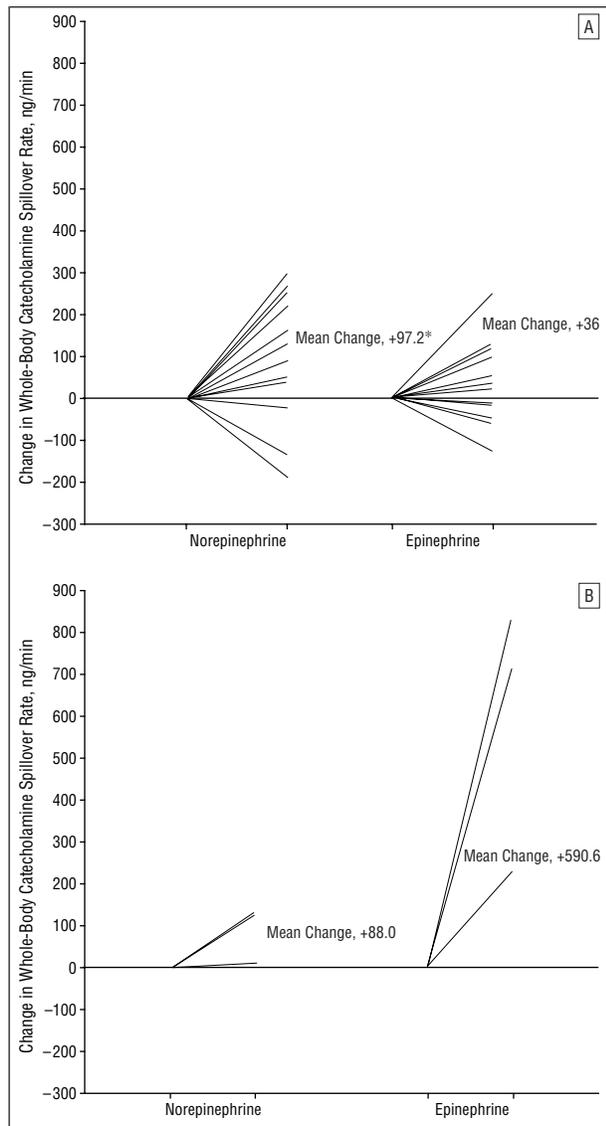
||Stress vs resting:  $P = .001$ ,  $t_{21} = -4.13$ , paired  $t$  test.

¶Stress vs resting:  $P = .04$ ,  $t_{21} = -2.19$ , paired  $t$  test.

**Table 4. Heart Rate, Blood Pressure, and Neurophysiological Changes During Spontaneous Panic Attacks\***

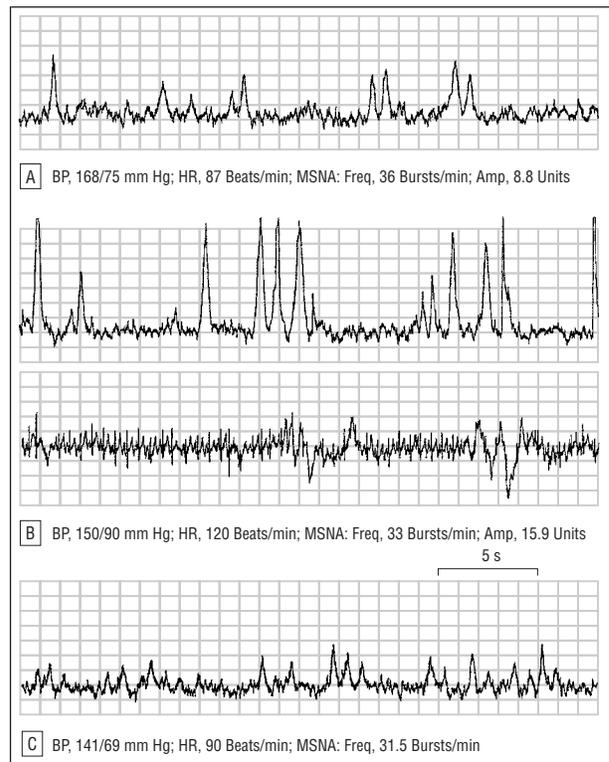
Patient No.	HR, Beats/min	BP, mm Hg	API	MNSA-Freq, Bursts/min	MSNA-Amp, Units	Arterial Norepinephrine, nmol/L	Arterial Epinephrine, pmol/L	Norepinephrine Spillover Rate, ng/min	Epinephrine Spillover Rate, ng/min	
1	Rest	68	143/85	...	34	10.7	1.52	631	963	431
	Attack	106	176/92	28	...	...	1.55	971	910	770
	1	85	...	...	...	...	1.62	971	1028	770
	3	110	161/92	...	...	...	...	...	...	...
	4	85	138/82	...	26	14.3	1.34	532	971	443
2	Rest	87	168/75	...	36	8.8	0.69	752	337	420
	Attack	108	150/90	25	34	15.9	0.74	1817	466	1247
3	Rest	60	138/73	...	38	12.7	1.03	648	469	306.5
	Attack	87	130/71	18	35	9.9	1.11	1937	597	1021
4	Rest	82	145/66	...	17	4.8	...	...	...	...
	Attack	85 (AF)	178/84	...	14	4.5	...	...	...	...

\*HR indicates heart rate; BP, blood pressure; API, Acute Panic Inventory<sup>31</sup>; MSNA, muscle sympathetic nerve activity; Freq, frequency; Amp, amplitude; AF, atrial fibrillation; and ellipses, not done.



**Figure 3.** Change in whole-body catecholamine spillover in patients with panic disorder during forced mental arithmetic (A) and panic attacks (B) (asterisk indicates  $P < .05$  for prestress vs stress). For a description of the forced mental arithmetic, see the "Participants and Methods" section.

It is interesting to note the differing characteristics of the 2 stress responses measured in this study. Cognitive challenge produced sympathoneural activation indicated by an increase in whole-body norepinephrine spillover, with some increase in epinephrine secretion. The sympathetic nervous activation did not involve all outflows, because muscle sympathetic activity was not increased, as noted previously with this stressor.<sup>30,51</sup> Earlier studies have shown that the sympathetic nervous activation occurring during laboratory-induced mental stress preferentially involves the sympathetic nerves of the heart and is paradoxically accompanied by reduced vascular resistance in the forearm, perhaps attributable to the vasodilator action of epinephrine in skeletal muscle blood vessels.<sup>34</sup> During panic attacks, there was a marked increase in the release of epinephrine, with a proportionally smaller change in whole-body norepinephrine spillover. The cardiac sympathetic response in a panic



**Figure 4.** Muscle sympathetic nerve activity (MSNA) and electrocardiograph recordings in a patient at rest (A), during a panic attack (B) (note movement artifact in electrocardiograph), and approximately 30 minutes later, at rest again (C). BP indicates blood pressure; HR, heart rate; Freq, sympathetic burst frequency, and Amp, sympathetic burst amplitude.

attack is, at present, uncertain. The reaction of skeletal muscle sympathetic nerves varied, apparently with the intensity of the panic attack, but in 2 of 4 patients, there was a highly distinctive pattern of increase in the size of the sympathetic burst without an increase in the burst rate, most likely representing a strong central synchronization of sympathetic outflow. These differing patterns of response provide further evidence against the nonspecificity implicit in the models of the stress response developed by Cannon and Selye and reported by Goldstein.<sup>52</sup>

## LIMITATIONS

It is difficult to achieve "resting" measurements in patients with anxiety disorders, especially in the context of involved and invasive studies such as ours. The elevated heart rate and rate of epinephrine secretion noted in a subset of patients may reflect anticipatory anxiety. It is also difficult to know how well the changes we measured during panic attacks represent those occurring spontaneously outside the laboratory. Patients rated the attacks they experienced as relatively mild compared with their usual attacks. The relatively small number of patients that can be studied in an invasive study imposes its own limitation, because how well they represent patients at large is necessarily somewhat uncertain.

A technical limitation is that large changes in regional sympathetic activity during panic attacks

might not be reflected in the measurements of whole-body norepinephrine spillover that we were able to make. Sympathetic activation in the heart could pass undetected, as the heart contributes only a small percentage of the total norepinephrine entering the plasma.

### THE POSSIBLE BASIS OF INCREASED CARDIAC RISK IN PANIC DISORDER

The possible neurobiological basis of the demonstrated link between phobic anxiety and sudden cardiac death<sup>53</sup> remains unresolved. From the epidemiological data, it is unclear whether this increased risk is specific for panic disorder or also applies to other anxiety disorders. In the present study, we demonstrated that patients with panic disorder do not have tonically increased cardiac sympathetic tone, which previously was shown to be linked with an increased risk of sudden cardiac death.<sup>7-10</sup> It is possible, but not yet demonstrated, that there may be a selective increase in cardiac sympathetic activity during panic attacks, predisposing to ventricular arrhythmias. Co-release of epinephrine from the sympathetic nerves of the heart could also trigger cardiac arrhythmias. Definitive information might be gained by measuring cardiac sympathetic activity during spontaneous panic attacks or possibly with pharmacological provocation of panic using techniques such as the inhalation of a carbon dioxide-rich gas mixture.<sup>54</sup> Ultimately, delineating the changes in neurotransmitter mechanisms in the central nervous system and in cardiac neural function may give the best clues to the underlying neurobiologic features of panic disorder and the pathophysiological basis for increased cardiac risk and lead to strategies for the protection of the heart in patients with panic disorder.

Accepted for publication October 31, 1997.

This study was supported by an institute grant from the National Health and Medical Research Council of Australia to the Medical Research Institute, Melbourne, Australia, and a project grant from the National Heart Foundation of Australia.

Presented in part at the Eighth International Catecholamine Conference, Monterey, Calif, October 1996; the Regional Meeting of the World Federation of Societies of Biological Psychiatry, Cairns, Australia, June 1996; and the 16th National Conference of the Anxiety Disorders Association of America, Orlando, Fla, April 1996.

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