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.

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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 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. 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. 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. This may, perhaps, be because plasma norepinephrine concentration values in samples obtained from the antecubital venous site provide a flawed measure of sympathetic tone. The notion of a “generalized” sympathetic tone is now discounted; regionally and highly differentiated responses are recognized with many different stimuli. 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 previously reported that laboratory-
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. 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.

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.

**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 subjects (Table 1 and significantly different between patients and control sub-
and whole-body norepinephrine spillover were not sig-
levels.
rate was unrelated significantly to state or trait anxiety
measurements were similar in the 2 groups. The heart
activity as measured by the spillover of norepinephrine from
heart was somewhat higher in patients than in con-
did not change significantly during the challenge. The
plasma was separated by centrifugation and stored at
an anticoagulant and antioxidant (ethyleneglycol-
tetraacetic acid and reduced glutathione), following which

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

Forced Mental Arithmetic
Simulated mental stress was generated in the laboratory by
using a cognitive challenge paradigm.22,25 Each subject rap-
ly 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 partici-
pants were patients with panic disorder or healthy volun-
tees. This staff member changed the subtractions as re-
quired 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 min-
utes 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 catechol-
amine kinetics were measured in 3. Of the 4 patients, 3
completed the Acute Panic Inventory.23 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 sub-
jects (range, 6-14 measurements in each group). Anxiety
and depression scores were not available for male con-
trol subjects.

Catecholamine Kinetics
The plasma concentrations of epinephrine and norepineph-ine were measured by using high-performance liquid chrom-
atography 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 catechol-
amine spillover rates were calculated by using isotope di-
lution.32 Norepinephrine and epinephrine spillover from
the heart was calculated by application of the Fick prin-
ciple as described previously.21

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 con-
trol 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 correla-
tions. The null hypothesis was rejected if $ P < .05 $. All re-
results are expressed as means$ \pm SD$. on the anxiety and depression indices is given in Table 2.
Patients with panic disorder had significantly higher rest-
ing heart rates than did control subjects (76.4$ \pm $10.0 beats/
min vs 65.7$ \pm $9.5 beats/min) ($n=13; t_2=−2.78, P=.01, un-
paired $ 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 sig-
nificantly different between patients and control sub-
jects (Table 1 and Figure 1). While there was a trend
for higher arterial concentrations of epinephrine and
higher whole-body epinephrine secretion, the differ-
ences were not statistically significant (Table 1 and Fig-
ure 1). Neither norepinephrine nor epinephrine rates of
release were significantly correlated with the indices of
state or trait anxiety or depression. The muscle sympa-
thetic nerve activity also was similar in patients and con-
trol subjects at rest (Figure 2). Cardiac sympathetic ac-
tivity 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 norepineph-ine 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 con-
trol subjects (Table 3). Muscle sympathetic nerve ac-
tivity did not change significantly during the challenge. The
arterial plasma concentration of norepinephrine and whole-
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 DSM-IV.26 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).

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

<table>
<thead>
<tr>
<th>Sex</th>
<th>Body Mass Index (BMI), kg/m²</th>
<th>Trait Anxiety</th>
<th>State Anxiety</th>
<th>Duration of Illness, y</th>
<th>Frequency of Panic Attacks per Month†</th>
<th>Medication Taken in Last 3 mo‡</th>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
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<td>27</td>
<td>26</td>
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</tr>
<tr>
<td>F</td>
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<td>28</td>
<td>32</td>
<td>NA</td>
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</tr>
<tr>
<td>F</td>
<td>25.32</td>
<td>33</td>
<td>37</td>
<td>NA</td>
<td>NA</td>
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</tr>
<tr>
<td>F</td>
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<td>50</td>
<td>35</td>
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</tr>
<tr>
<td>F</td>
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<td>34</td>
<td>36</td>
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<td>24</td>
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<td>27</td>
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<td>M</td>
<td>22.84</td>
<td>ND</td>
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<td>M</td>
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</tr>
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<td>22.86</td>
<td>ND</td>
<td>ND</td>
<td>NA</td>
<td>NA</td>
<td>...</td>
</tr>
<tr>
<td>M</td>
<td>24.93</td>
<td>ND</td>
<td>ND</td>
<td>NA</td>
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<td>22.86</td>
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<td>M</td>
<td>31.62</td>
<td>ND</td>
<td>ND</td>
<td>NA</td>
<td>NA</td>
<td>...</td>
</tr>
</tbody>
</table>

* 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.

COMMENT

RESTING SYMPATHETIC FUNCTION IN PANIC DISORDER

Whole-body norepinephrine spillover, a sensitive measure of overall sympathetic nervous system activity,21,33
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.

By using methods that readily detect small changes in efferent sympathetic activity in skeletal muscle and in the heart, 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. 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. 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-

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

<table>
<thead>
<tr>
<th>Control Subjects</th>
<th>Patients With Panic Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>38.9 ± 18.22</td>
</tr>
<tr>
<td><strong>Sex, M/F</strong></td>
<td>7:7</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td>24.4 ± 3.28</td>
</tr>
<tr>
<td><strong>Trait Anxiety†</strong></td>
<td>32.3 ± 8.36 (n = 7)</td>
</tr>
<tr>
<td><strong>State Anxiety†</strong></td>
<td>30.6 ± 5.77 (n = 7)</td>
</tr>
<tr>
<td><strong>Depression¶</strong></td>
<td>1.43 ± 2.57 (n = 7)</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, values are expressed as mean ± SD. Psychometric scales were not available for all controls.
†Spielberger State Trait Anxiety Inventory (STAI-Form X²).
‡Patients vs controls: P = .002 unpaired t test.
§Patients vs controls: P = .002 unpaired t test.
¶Beck Depression Inventory.
¶¶Patients vs controls: P = .01 unpaired t test.
ity or increased resting cardiac sympathetic activity. 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 cardiac sympathetic tone, is determined primarily by arterial baroreflex function and cardiac adrenergic receptor sensitivity rather than cardiac sympathetic nerve firing rates.

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. It previously has been suggested that stress-induced elevation of plasma epinephrine might lead to buildup of stores of epinephrine within sympathetic nerves; 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

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).

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).
the heart might potentiate cardiac stress responses by its action on presynaptic neuronal β-adrenergic receptors, augmenting release of norepinephrine from the cardiac sympathetic nerves.42,43 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 al44 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.12,13,18,45-49 Overall, our results give further 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 coworkers50 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.21,24,30

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.21,24,30 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

<table>
<thead>
<tr>
<th>Heart rate, beats/min</th>
<th>Systolic pressure, mm Hg</th>
<th>MSNA, bursts/min</th>
<th>Arterial norepinephrine, nmol/L</th>
<th>Norepinephrine spillover, ng/min</th>
<th>Arterial epinephrine, pmol/L</th>
<th>Epinephrine spillover, ng/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>Stress</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72.4 ± 10.3</td>
<td>82.7 ± 5.4†</td>
<td>133.2 ± 13.5</td>
<td>143.8 ± 20.1†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32.5 ± 15.4</td>
<td>32.9 ± 11.5</td>
<td>514.8 ± 168.2</td>
<td>636.8 ± 178.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>454 ± 198</td>
<td>496 ± 279</td>
<td>199.9 ± 76.6</td>
<td>242.8 ± 128.4</td>
<td>§ Stress vs resting: P = .001, t21 = −4.91, paired t test.</td>
<td>§ Stress vs resting: P = .001, t21 = −4.13, paired t test.</td>
<td>§ Stress vs resting: P = .001, t21 = −4.13, paired t test.</td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± SD. MSNA indicates muscle sympathetic nerve activity.
†Stress vs resting: P < .001, t21 = −5.66, paired t test.
‡Stress vs resting: P = .002, t16 = −3.57, paired t test.
§Stress vs resting: P < .001, t21 = −4.91, paired t test.
¶Stress vs resting: P = .04, t21 = −2.19, paired t test.

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

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>HR, Beats/min</th>
<th>BP, mm Hg</th>
<th>API</th>
<th>MNSA-Freq, Bursts/min</th>
<th>MNSA-Amp, Units</th>
<th>Arterial Norepinephrine, nmol/L</th>
<th>Arterial Epinephrine, pmol/L</th>
<th>Norepinephrine Spillover Rate, ng/min</th>
<th>Epinephrine Spillover Rate, ng/min</th>
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</thead>
<tbody>
<tr>
<td>1 Rest 68</td>
<td>143/85</td>
<td>...</td>
<td>34</td>
<td>10.7</td>
<td>1.52</td>
<td>631</td>
<td>963</td>
<td>431</td>
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</tr>
<tr>
<td>1 Attack</td>
<td>106</td>
<td>176/92</td>
<td>28</td>
<td>...</td>
<td>...</td>
<td>1.55</td>
<td>971</td>
<td>910</td>
<td>770</td>
</tr>
<tr>
<td>2 Rest 85</td>
<td>161/92</td>
<td>...</td>
<td>34</td>
<td>14.3</td>
<td>1.34</td>
<td>532</td>
<td>971</td>
<td>443</td>
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<tr>
<td>2 Attack</td>
<td>87</td>
<td>168/75</td>
<td>36</td>
<td>8.8</td>
<td>0.69</td>
<td>752</td>
<td>337</td>
<td>423</td>
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</tr>
<tr>
<td>3 Rest 108</td>
<td>150/90</td>
<td>25</td>
<td>34</td>
<td>15.9</td>
<td>0.74</td>
<td>1817</td>
<td>466</td>
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<tr>
<td>3 Attack</td>
<td>60</td>
<td>138/73</td>
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<td>469</td>
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<td>4 Rest 87</td>
<td>130/71</td>
<td>18</td>
<td>35</td>
<td>9.9</td>
<td>1.11</td>
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<td>587</td>
<td>1021</td>
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<tr>
<td>4 Attack</td>
<td>82</td>
<td>145/66</td>
<td>17</td>
<td>4.8</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<td></td>
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*HR indicates heart rate; BP, blood pressure; API, Acute Panic Inventory31; MSNA, muscle sympathetic nerve activity; Freq, frequency; Amp, amplitude; AF, atrial fibrillation; and ellipses, not done.
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. 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. 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 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.

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 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. 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. 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 neurobiological 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.

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