Destabilizing Effects of Mental Stress on Ventricular Arrhythmias in Patients With Implantable Cardioverter-Defibrillators

Rachel Lampert, MD; Diwaker Jain, MD; Matthew M. Burg, MD; William P. Batsford, MD; Craig A. McPherson, MD

Background—The incidence of sudden cardiac death increases in populations who experience disasters such as earthquakes. The physiological link between psychological stress and sudden death is unknown; one mechanism may be the direct effects of sympathetic arousal on arrhythmias. To determine whether mental stress alters the induction, rate, or termination of ventricular arrhythmias, we performed noninvasive programmed stimulation (NIPS) in patients with defibrillators and ventricular tachycardia (VT), which is known to be inducible and terminated by antitachycardia pacing, at rest and during varying states of mental arousal.

Methods and Results—Eighteen patients underwent NIPS in the resting-awake state (non-sedated). Ten underwent repeat testing during mental stress (mental arithmetic and anger recall). Induced VT was faster in 5 patients \( (P<0.03) \). VT became more difficult to terminate in 5 patients during mental stress; 4 required a shock \( (P<0.03) \). There was no change in ease of induction with mental stress. There was no evidence of ischemia on ECG or continuous ejection fraction monitoring. Eight patients received a shock in the resting-awake state and did not perform mental stress. Four underwent repeat NIPS after sedation; 3 then had induced VT terminated with antitachycardia pacing. All patients with an increase in norepinephrine of \( >50\% \) had alterations in VT that required shock for termination \( (P<0.01) \).

Conclusions—Mental stress alters VT cycle length and termination without evidence of ischemia. This suggests that mental stress may lead to sudden death through the facilitation of lethal ventricular arrhythmias. (Circulation. 2000;101:158-164.)

Key Words: stress • tachyarrhythmias • tachycardia • cardioversion • defibrillation

Sudden cardiac death increases in populations suffering disasters such as earthquake or war. Potential physiological mechanisms linking psychological stress and sudden death include coronary ischemia and direct modulation of arrhythmias via changes in autonomic tone. Mental stress can induce ischemia, both in laboratory protocols and in daily life. Whether mental stress influences arrhythmias, however, remains unknown.

Indirect evidence suggests that sympathetic arousal can trigger arrhythmic events. Ventricular tachycardia (VT), like sudden death, occurs more frequently in the morning, at the time of peak catecholamine levels and of lowest vagal tone, as demonstrated in patients with implantable cardioverter-defibrillators (ICDs). VT occurs more frequently on Mondays in working patients with ICDs, suggesting a role for stress. In addition, atrial and ventricular ectopy and nonsustained arrhythmias increase during the stress of being on-call in house officers and during exposure to a hostile environment in animals. Invasive studies in animals stress facilitates the induction of VT.

The population of patients with ICDs provides a unique opportunity to evaluate the effects of mental stress on human arrhythmias. Many patients have arrhythmias with well-defined, reproducible characteristics. In addition, their devices allow the performance of noninvasive serial electrophysiological (EP) studies. To determine whether increased sympathetic activation alters the induction, rate, or termination of ventricular arrhythmias, we performed noninvasive EP studies in patients with ICDs and sustained VT, at rest and during varying states of mental arousal and stress.

Methods

Patients

Eighteen patients with third-generation ICDs (Ventak PRxI, II, or Mini; Guidant/CPI) were invited to participate in the protocol. All provided written informed consent. The study was approved by the Yale University Human Investigation Committee.

In all patients, monomorphic VT had been induced and terminated with antitachycardia pacing (ATP) at least twice during previous noninvasive programmed stimulation (NIPS) performed with routine sedation (midazolam and fentanyl). Antiarrhythmic therapy at entry...
The unexpected behavior of the group 2 patients suggested that the awake state itself may have altered arrhythmic characteristics. To further evaluate this possibility, we retrospectively compared the 18 study patients while receiving the same antiarrhythmic regimen, both while awake and under conscious sedation (group 3). The records of all patients with induced VT terminated by shock in resting-awake state (group 2) underwent repeat NIPS during sedation. Patients with induced VT terminated by ATP or NSVT (group 1) underwent repeat NIPS during mental stress. Patients with induced VT terminated by shock in resting-awake state (group 2a) underwent repeat NIPS during sedation. R-2 pads indicate defibrillation pads; VEST, LVEF monitoring device.

Study Protocol

For comparisons among the groups, “state of arousal” was defined based on the protocol administered: from least aroused (sedated) to resting-awake to most aroused (mental stress).

Programmed Stimulation

A standard NIPS protocol was performed with drive cycle lengths (CLs) of 500 and 400 ms with up to 3 programmed extrastimuli (PES). Device settings, including ATP algorithms, programmed at prior NIPS, remained unchanged throughout the study protocol. Ventricular effective refractory periods were determined. The ease of VT induction was quantified ordinarily on the basis of the level of the pacing protocol at which sustained VT was induced: level 1 indicates induction at either CL with 1 PES; level 2, induction with 2 PESs; and level 4, completion of protocol without induction of sustained VT (noninducible). The ease of termination was also quantified ordinarily: level 1 indicates self-terminating (nonsustained VT [NSVT]); level 2, paced terminated; and level 3, shock terminated.

Mental Stress Protocol

The mental stress protocol was administered by a clinical psychologist (M.M.B.) as previously described. Room lights were dimmed, and a quiet state was maintained. For the resting-awake stage, patients were encouraged to relax by thinking about past relaxing situations. During the mental arithmetic stage, subjects were asked to serially subtract 7 from a 3-digit number. They were reminded to respond rapidly, and mistakes were corrected harshly. For anger recall, patients were asked to discuss an annoying or frustrating event, as the interviewer requested further details and asked irritating questions.

Radionuclide Angiography

Red blood cells were labeled with 20 to 25 mCi 99mTc according to the standard labeling technique. A gamma camera with a general all-purpose collimator interfaced with a minicomputer was positioned in the left anterior oblique view to measure baseline LVEF through the use of equilibrium radionuclide angiography. The miniature detector of an ambulatory left ventricular function monitoring device (C-Vest; Capintec) was then positioned over the left ventricular blood pool. The device was held in place with a semirigid plastic vest-like garment. Counts were acquired at 32 s⁻¹ and analyzed off-line with the use of a dedicated minicomputer to obtain 30-second averaged continuous trends of LVEF. The LVEF reported was the average value during the first 3 minutes of each stage, before the start of NIPS.

Catecholamine Analysis

Venous blood was continuously withdrawn at a rate of 1 mL/min with an exfusion pump (Dakmed). Separate samples were collected during each study phase and immediately placed on ice. Samples were spun and stored at −70°C at the Yale General Clinical Research Center. Norepinephrine levels were determined with radioenzymatic assay or high-performance liquid chromatography. All samples from a given subject were analyzed in the same batch. Correlations of catecholamine levels with arrhythmia characteristics were based on the sample before arrhythmia (the 1.5 mL within the tubing at the onset of the arrhythmia).
TABLE 1. Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1* (n=10)</th>
<th>Group 2 (n=8)</th>
<th>Group 3 (n=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69±3.2</td>
<td>68±1.6</td>
<td>70±3.5</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, n (% female)</td>
<td>1 (10)</td>
<td>0</td>
<td>10 (25)</td>
<td>0.06</td>
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<tr>
<td>Cardiac disease, n (%)</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>8 (80)</td>
<td>7 (87)</td>
<td>35 (87)</td>
<td></td>
</tr>
<tr>
<td>CM</td>
<td>1 (10)</td>
<td>1 (12)</td>
<td>1 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (10)</td>
<td>0</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmic therapy, n (%)</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>5 (50)</td>
<td>2 (25)</td>
<td>21 (53)</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>4 (40)</td>
<td>2 (25)</td>
<td>4 (10)</td>
<td></td>
</tr>
<tr>
<td>Sotalol</td>
<td>1 (10)</td>
<td>2 (25)</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2 (25)</td>
<td>13 (32)</td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>35±4</td>
<td>30±5</td>
<td>29±2</td>
<td>NS</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; CM, nonischemic cardiomyopathy. All values are mean±SEM.

*Group 1, patients undergoing mental stress protocol; group 2, patients shocked in the resting-awake state; group 3, retrospective control subjects. Details given in the text.

Resting-Awake Programmed Stimulation

In the resting-awake state, induced VT terminated with ATP or spontaneously in 10 patients (group 1) but required shock for termination in 8 patients (group 2). The baseline norepinephrine level was 3.06±0.50 nmol/L (518±84 pg/mL) in group 2 patients (levels were available in 4) and 2.78±0.41 nmol/L (471±69 pg/mL) in group 1 patients (levels were available in 6) (P=NS). However, during NIPS (before arrhythmia induction and shock delivery), norepinephrine increased by 34% in group 2 patients but only 10% in group 1 patients (P=0.01).

Patients Undergoing Mental Stress Protocol (Group 1)

Physiological Changes With Mental Stress

Heart rate and blood pressure increased and ventricular refractory periods decreased significantly with mental stress (Table 2). Norepinephrine levels rose during stress (Table 2).

TABLE 2. Physiological Changes With Mental Stress (Group 1)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Mental Stress</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>64±5</td>
<td>79±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>154±6</td>
<td>175±7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>80±4</td>
<td>100±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nmol/L*</td>
<td>2.78±0.32</td>
<td>3.78±0.43</td>
<td>0.03</td>
</tr>
<tr>
<td>pg/mL</td>
<td>471±54</td>
<td>640±72</td>
<td></td>
</tr>
<tr>
<td>Refractory periods, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL 500 ms</td>
<td>263±6</td>
<td>254±7</td>
<td>0.002</td>
</tr>
<tr>
<td>CL 400 ms</td>
<td>245±8</td>
<td>240±6</td>
<td>0.01</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>35±6</td>
<td>33±6</td>
<td>NS</td>
</tr>
</tbody>
</table>

BP indicates blood pressure. Values are mean±SEM.

*Available in 6 patients.

Changes in Arrhythmia Behavior During Mental Stress

VT was induced earlier in the protocol during mental stress in 3 of the 10 patients (2 with only NSVT induced during resting-awake, had sustained VT provoked by 2 PES during stress). In 6 patients, there was no change, and in 1 patient, induction occurred 1 stage later (Figure 2, P=NS). The mean induction stage at rest was 2.4±0.3; with stress, it was 2.0±0.2.

VT CLs decreased during mental stress: 5 patients (50%) had a decrease in CL of ≥20 ms (P=0.03). The mean CL was 353±24 ms in the resting-awake state and 314±20 ms with mental stress (P=0.12).

VT termination became more difficult during mental stress in 5 of the 10 patients (P=0.03) (Figure 3). This occurred in 1 patient during mental arithmetic, 3 during anger recall, and 1 during each of the stress tasks. One patient had NSVT at rest and pacer-terminated VT with stress. Four patients had pacer-terminated VT (3) or NSVT (1) induced at rest but VT induced during mental stress that required shock for termination. Of these, 1 required shock due to failure of ATP, 1 required shock due to induction of VT in a shock-only zone (Figure 4), and 2 received a shock after ATP during stress-accelerated VT, of whom 1 had VT of identical CL and morphology as that terminated with pacing in the resting state (Figure 5). (The other accelerated patient had NSVT at rest.) In the remaining 5 patients, VT was terminated with ATP both at rest and during mental stress. The mean stage of termination was 1.8±0.1 at rest and 2.4±0.1 with stress.
LVEF and ECG Changes
There were no ST or T-wave changes with mental stress in any patient. Mean LVEF was 35±6% at baseline and did not change with mental stress (Table 2). Only 1 of the 10 patients had a fall in LVEF of >5% (this patient did not show alterations in any parameter with mental stress).

Patients Studied Awake and Sedated (Group 2a)
Four patients who received a shock at baseline underwent repeat EP testing after receiving sedation. There was no change in induction stage (Figure 2). Induced VT was significantly slower after sedation (CL 295±36 ms awake and 370±23 ms sedated, P=0.05). In 3 patients, the VT CL increased by >20 ms. After sedation, 3 of the 4 patients had induced VT effectively terminated with ATP (in 1, the same VT had failed pacer termination awake, in 2, faster VTs had been induced awake). One of the 4 patients again required shock while sedated (Figure 3).

Relation of Catecholamine Levels to Arrhythmia Characteristics
Comparisons between changes in norepinephrine levels and changes in arrhythmia characteristics were made in the 9 patients with catecholamine levels available in 2 different states of arousal: 6 group 1 patients (mental stress versus resting-awake) and 3 group 2a patients (resting-awake versus sedation) (Table 3). Overall, in these patients, mean norepinephrine levels, which were measured during NIPS before the induction of VT, were higher in the more aroused state. Earlier induction and faster VT tended to correlate with a greater rise in catecholamine levels with arousal. The ease of VT termination correlated strongly with extent of arousal-induced catecholamine rise, as shown in Table 3. When patients were dichotomized based on change in norepinephrine level, all 5 patients with a >50% increase in norepinephrine level in the aroused state (before VT induction) had induced VT that required shock for termination, whereas VT in the 4 patients with a smaller increase in norepinephrine remained pacer terminated (P<0.001).

Retrospective Comparison Awake Versus Sedated States
Temporal variability in VT characteristics was compared between the study patients (groups 1 and 2), who had undergone a previous sedated study and the awake study protocol, and the control subjects (group 3), who had undergone 2 sedated studies on different days. All were receiving the same antiarrhythmic medications for both studies.

State of arousal did not influence VT induction, which occurred earlier in the second study in 17% of awake patients and 28% of sedated patients (P=NS). Mean VT CL decreased at the second study by 65±17 ms in the awake versus 17±12 ms in the sedated patients (P=0.03). Arousal state strongly influenced VT termination. Although all patients had pacer-terminated VT at the first, sedated, study, termination of VT at the second study required shock in 8 of 18 (44%) of the awake patients but only 4 of 40 (10%) of the sedated patients (P=0.002).
Discussion

This study shows that mental stress shortens CL and renders induced VT more difficult to terminate. Similarly, arrhythmias induced in the awake state are faster and more difficult to terminate than those induced in the sedated state in the same patient. These alterations in VT characteristics were associated with increased norepinephrine levels, which are known to rise during mental stress, but with no evidence of ischemia on ECG or LVEF. In these patients with a defined VT substrate, mental arousal destabilized the circuit, creating a potentially more dangerous arrhythmia. This suggests that psychological stress may facilitate sudden cardiac death by increasing the lethal potential of arrhythmias in susceptible patients.

Unexpectedly, despite the inclusion of only patients with reproducible termination of VT by ATP at previous sedated noninvasive EP study (and no change in antiarrhythmic medications), 40% received shocks for induced VT in the “resting” awake state. To evaluate whether the awake state itself altered VT, 4 patients receiving shocks while awake underwent repeat testing after sedation; 3 again had pacer-terminated VT. The environment of the EP laboratory and the ongoing NIPS protocol may have produced anxiety or fear in some patients, changing the “resting” awake state to that of heightened arousal. The far greater increase in norepinephrine during NIPS (before VT induction) in patients proceeding to receive shocks supports this hypothesis, underscoring the influence of sympathetic tone on arrhythmia behavior. Although a pharmacological effect of the sedating agents cannot be excluded, studies in isolated tissue preparations or denervated hearts, which evaluated the effects of drugs in the absence of autonomic mediation, have not shown either midazolam or fentanyl to alter ventricular refractory periods or other EP parameters.

To exclude the possibility that the unexpected changes in arrhythmia behavior were due only to day-to-day variability

| TABLE 3. Relationship of Plasma Norepinephrine to Arrhythmia Behavior During Mental Arousal |
|-----------------|-----------------|-----------------|
| Change in Norepinephrine Level From Least to Most Aroused State | Absolute Change, nmol/L (pg/mL) | Percent Change |
| Overall | 1.17±0.32 (199±162) | 76±22 <0.01 * |
| By change in arrhythmia behavior | | |
| Induction | | |
| Earlier in protocol | 1.55±0.56 (263±95) | 82±41 NS† |
| No change or later | 0.98±0.40 (167±67) | 73±29 |
| CL shortening, ms | | |
| ≥20 | 1.68±0.44 (285±75) | 115±30 0.1 † |
| <20 | 0.76±0.40 (130±67) | 46±27 |
| Termination | | |
| Requiring shock | 1.71±0.34 (290±58) | 124±17 <0.01 † |
| Not requiring shock | 0.50±0.38 (85±64) | 17±19 |

*P value for difference between least and most aroused.
†P value for difference in norepinephrine rise based on change in arrhythmia behavior.
Values are mean±SEM.
of response to EP testing, we retrospectively compared the consistency of response to NIPS over time in a group of similar patients (with inducible pacer-terminated VT) who had undergone 2 NIPS while sedated. The results of NIPS varied minimally between 2 sedated studies, unlike the dramatic changes seen with a second study in the awake state, again suggesting that due to lack of sedation, a higher state of arousal increased the lethal potential of VT.

The results of previous studies in animals support our findings. Both Lown et al., in a healthy canine model, and Kirby et al., in a porcine model of scar-related VT, found VT to be more readily inducible and faster in animals stressed by being lifted in a sling. The present study demonstrates that not only the primitive fight-or-flight responses of animals but the more complex human emotions of anger, anxiety, and performance stress alter arrhythmias. In addition, although these studies induced only rapid VTs or NSVTs, the selection of patients with stable monomorphic VT in the present study allowed an evaluation of the mode of VT termination as well.

Although multiple epidemiological studies have shown an increase in sudden cardiac death in populations undergoing the stress of natural disaster or war, the physiological link between stress and sudden cardiac death remains unexplained. Ischemia is often hypothesized to precipitate stress-induced cardiac events. Mental stress testing in the laboratory setting can induce ischemia, and anger can precipitate ischemia,4–7 and angina can precipitate myocardial infarction.25 To evaluate whether ischemia might underlie stress-induced changes in arrhythmia, both ECG and ambulatory LVEF (a more sensitive indicator of ischemia underlie stress-induced changes in arrhythmia, both ECG and ambulatory LVEF (a more sensitive indicator of ischemia than repolarization changes) were monitored. No changes were seen in 9 of the 10 patients, suggesting that direct effects of the sympathetic nervous system on the VT circuit, rather than ischemia, affected the stress-related changes in VT behavior. This further implies that stress may directly cause arrhythmic sudden death in susceptible patients through the facilitation of lethal arrhythmias.

Stress-induced changes in EP properties such as repolarization time and conduction velocity may underlie the effects of arrhythmias seen in the present study. Toivonen et al. showed changes in repolarization in healthy house officers exposed to the sudden stress of an on-call alarm. Repolarization also exhibits diurnal variation, further suggesting an influence of changing adrenergic tone. The signal-averaged ECG has shown changes with both mental stress28 and time of day, implying sympathetic effects on conduction. Analogous changes in the reentrant circuit in patients with monomorphic VT may explain the changes seen in the present study. Although refractory periods, conduction times, and the excitable gap of the VT circuit cannot be measured without invasive mapping, the changes seen in CL and response to overdrive pacing may reflect changes in these properties of the VT circuit.

Study Limitations

Patients who received a shock at baseline did not undergo mental stress because we believe that the risk of delivering a second shock with the patient awake was not acceptable. We cannot exclude the possibility that the changes seen could reflect regression to the mean as an artifact of the protocol (ie, would the patients who received a shock at baseline have been pacer terminated with mental stress?). However, three fourths of the patients who received a shock who underwent testing while sedated then had pacer-terminated VT, and catecholamine levels correlated with arousal state; artifactual changes in response seem highly unlikely. Similarly, the order of testing was not randomized. However, catecholamine levels returned to baseline between stressors, suggesting that the stressor itself, rather than a cumulative effect of testing, was responsible for the changes seen.

Only 1 woman was enrolled in the study (5%). Whether the effects of mental stress and arousal state on arrhythmia differ in women requires further evaluation.

Conclusions and Implications

Mental stress alters VT CL and termination, suggesting that autonomic arousal may lead to sudden death through the facilitation of lethal ventricular arrhythmias. Whether these results can be extrapolated to patients without a preceding history of VT is unknown. In patients with defibrillators, as well as in all patients at risk for ventricular arrhythmias, therapies aimed at blocking the sympathetic response to stress may decrease the frequency and lethality of arrhythmic events.

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References


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