Baroreflex Gain Predicts Blood Pressure Recovery During Simulated Ventricular Tachycardia in Humans

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Background—Despite similar degrees of left ventricular dysfunction and similar tachycardia or pacing rate, blood pressure (BP) response and symptoms vary greatly among patients. Sympathetic nerve activity (SNA) increases during sustained ventricular tachycardia (VT), and the magnitude of this sympathoexcitatory response appears to contribute to the net hemodynamic outcome. We hypothesize that the magnitude of sympathoexcitation and thus arterial baroreflex gain is an important determinant of the hemodynamic outcome of VT.

Methods and Results—We evaluated the relation between arterial baroreflex sympathetic gain and BP recovery during rapid ventricular pacing (VP) in patients referred for electrophysiological study. Efferent postganglionic muscle SNA, BP, and central venous pressure (CVP) were measured in 14 patients during nitroprusside infusion and during VP at 150 (n=12) or 120 (n=2) bpm. Arterial baroreflex gain was defined as the slope of the relationship of change in SNA to change in diastolic BP during nitroprusside infusion. Recovery of mean arterial pressure (MAP) during VP was measured as the increase in MAP from the nadir at the onset of pacing to the steady-state value during sustained VP. Arterial baroreflex gain correlated positively with recovery of MAP (r=0.57, P=0.034). No significant correlation between ejection fraction and baroreflex gain (r=0.48, P=0.08) or BP recovery (r=0.41, P=0.15) was found. When patients were separated into high versus low baroreflex gain, the recovery of MAP during simulated VT was significantly greater in patients with high gain.

Conclusions—These data strongly suggest that arterial baroreflex gain contributes significantly to hemodynamic stability during simulated VT. Knowledge of baroreflex gain in individual patients may help the clinician tailor therapy directed toward sustained VT. (Circulation. 1999;100:381-386.)

Key Words: nervous system, autonomic ■ tachycardia ■ ventricles
Study Patients
The study was performed at the Dallas Veterans Affairs Medical Center and was approved by the institutional review board. Informed consent was obtained from all patients, and all procedures were in accordance with institutional guidelines. All patients with clinical indication for programmed electrical stimulation were screened for the study. Patients were excluded if they had a history of insulin-dependent diabetes mellitus, history or signs of peripheral neuropathy, or a history of sustained atrial arrhythmias. All patients had an echocardiogram for assessment of left ventricular function and the presence of structural heart disease. A total of 21 patients were enrolled in this study, and complete data were acquired for 14. The recordings from these 14 subjects form the material of the present study.

Electrophysiological Studies
Patients were studied in the drug-free postabsorptive state after informed consent was obtained. Three quadripolar catheters were inserted percutaneously and positioned in the high lateral right atrium, in the right ventricular apex, and across the tricuspid valve for His bundle recording. Atrial and VP thresholds were measured, and pacing was performed at twice the pacing threshold.

Measurements
Efferent postganglionic muscle SNA was recorded from the right peroneal nerve as previously described. Briefly, a sterile microelectrode was inserted into a fascicle of the peroneal nerve near the fibular head. The nerve signals were amplified, filtered (70 to 2000 Hz), rectified, and discriminated. Raw nerve signals were integrated (time constant=0.05 seconds) to produce a mean voltage display for quantitative analysis. Muscle sympathetic neural bursts during sinus rhythm were readily recognized by their tight temporal relationship to the sinus cardiac cycle, their increasing frequency during Valsalva maneuvers, the occurrence of large bursts accompanying premature ventricular beats, and their failure to respond to arousal stimuli or stroking of the skin. SNA was quantified as total activity derived from the sum of the area of the SNA bursts for a given time period. Burst area was normalized to the average area of SNA bursts during the baseline period before VP. This baseline value was assigned a value of 100 U. This allows comparison of data among subjects. Area was used for these analyses because it more appropriately reflects the changes in SNA associated with the wide variations in arterial pressure that can occur during VT or pacing than burst amplitude. Most SNA data were quantified over 1-minute segments; however, data reported for the nadir of arterial pressure at the onset of pacing were acquired during a 10-second segment. Thus, all SNA data were quantified as units per 10 seconds. Arterial BP was directly recorded with a catheter inserted into the right femoral artery. CVP was continuously recorded with a catheter placed in the right atrium via the right femoral vein. Heart rate (HR) was derived from continuous ECG recording of $ \geq $ 2 leads (II and V$_1$).

Experimental Protocol
After acceptable recordings of SNA were obtained, the following protocol was performed: (1) baseline measurements for 5 minutes, (2) rapid right VP at 150 bpm for 1 minute, (3) recovery for 5 minutes, (4) intravenous administration of nitroprusside at doses of 0.5 to 1 $\mu$g $\cdot$ kg$^{-1}$$\cdot$min$^{-1}$ to achieve a drop in systolic BP of $\geq$ 20 to 30 mm Hg, and (5) recovery for 15 minutes.

SNA, BP, CVP, and HR were measured continuously during the study. Data were analyzed during VP and during nitroprusside infusion so that multiple data points at different arterial pressures were acquired to estimate baroreflex gain. Rapid VP was discontinued if systolic BP remained $<$ 85 mm Hg during sustained pacing. When pacing at 150 bpm was not tolerated, pacing was repeated at 120 bpm (n=2). During nitroprusside infusion, the drug was to be discontinued if systolic BP fell $<$ 85 mm Hg; however, this did not occur in any patient.

Table 1 summarizes the clinical data for the 14 patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Age, y</th>
<th>HTN</th>
<th>LVEF, %</th>
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<tbody>
<tr>
<td>1</td>
<td>Syncope</td>
<td>51</td>
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<td>2</td>
<td>VT</td>
<td>63</td>
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<td>45</td>
</tr>
<tr>
<td>3</td>
<td>VT</td>
<td>66</td>
<td>Yes</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>VT</td>
<td>67</td>
<td>Yes</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>Cardiac arrest</td>
<td>59</td>
<td>Yes</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>VT</td>
<td>51</td>
<td>No</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>SVT</td>
<td>37</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>Syncope</td>
<td>50</td>
<td>Yes</td>
<td>Normal</td>
</tr>
<tr>
<td>9</td>
<td>Syncope</td>
<td>77</td>
<td>Yes</td>
<td>35</td>
</tr>
<tr>
<td>10</td>
<td>Syncope</td>
<td>72</td>
<td>Yes</td>
<td>25</td>
</tr>
<tr>
<td>11</td>
<td>Atrial flutter</td>
<td>82</td>
<td>Yes</td>
<td>45</td>
</tr>
<tr>
<td>12</td>
<td>Dizziness</td>
<td>71</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>13</td>
<td>Syncope</td>
<td>64</td>
<td>No</td>
<td>25</td>
</tr>
<tr>
<td>14</td>
<td>Syncope</td>
<td>82</td>
<td>No</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Arterial baroreflex gain was defined as the slope of the relationship of change in SNA to the change in diastolic arterial pressure during nitroprusside infusion. Several data points were obtained from the averages of 30-second segments during nitroprusside infusion so that 5 to 8 total points were acquired and used to define this relationship. Diastolic arterial pressure was used to estimate baroreflex gain because SNA bursts during quiet rest correlate best with diastolic pressure. A linear correlation analysis was applied to determine the slope for which $r$ $>$ 0.80 in all patients. The baroreflex gain for HR control was derived similarly from the same data. Gain was estimated by the relationship of change in HR to change in SBP. Recovery of mean arterial pressure (MAP) during VP was measured as the absolute increase in MAP from the nadir at the onset of pacing to the steady-state value during sustained VP.

Statistical Analysis
All data were recorded online on a personal computer with WINDAQ data acquisition software (DATA Instruments). Data were analyzed post hoc with customized software. The following statistical analyses were performed. All data exhibited a normal distribution according to Kolmogorov-Smirnov tests; thus, parametric analyses were used. Linear correlation coefficients (Pearson’s) were obtained for all correlational analyses. Correlations with estimated EF also were performed. All comparisons between groups were made by use of Student’s $t$ test. Statistical significance was defined by $\alpha$ $=$ 0.05. All data in the Results section are presented as mean $\pm$ SEM.

Results
Clinical Characteristics
Four patients had no structural heart disease; the remaining 10 presented a diverse background of cardiovascular disease. Eight patients had hypertension, and 10 had various degrees of left ventricular dysfunction (ranging from mild to severe). Table 1 summarizes the clinical data for the 14 patients.

Response to Pacing
In all but 2 patients, pacing was performed at 150 bpm. In the remaining 2 patients, pacing was performed at 120 bpm because systolic BP remained $<$ 85 mm Hg during pacing at 150 bpm. At the onset of pacing, arterial pressure decreased abruptly while CVP increased; these hemodynamic changes
Baroreflex Gain

As pacing was sustained for 1 minute, arterial pressure recovered toward pre-pacing levels, CVP increased further, and SNA remained elevated (Figure 1). The estimates of baroreflex sympathetic gain during nitroprusside infusion were diverse, ranging from 1.2%/mm Hg to 3.5%/mm Hg. The relation of estimated arterial baroreflex gain to the recovery of MAP during VP is shown in Figure 2. Recovery of MAP during pacing correlated positively with baroreflex gain, with a correlation coefficient of 0.57 \( (P=0.034) \). Although the data were scattered, the correlation was significant, and the trend toward greater increases in MAP in patients with higher gains was clearly apparent. On inspection of the scattergram, the data appear to separate into 2 clusters of patients on the basis of their baroreflex gain: 8 patients constituted group 1 with high gain (>2.5%/mm Hg), and 6 patients made up group 2 with low gain (<2.5%/mm Hg).

Group comparisons were then performed. The responses to VP in these 2 groups are summarized in Table 2. Figure 3 summarizes the arterial pressure, CVP, and sympathetic neural responses in the 2 groups. Baseline SNA was greater in the patients with low gain \( (P=0.024) \) but increased less during VP compared with patients with high gain \( (P=0.033) \). CVP was slightly greater at baseline in the patients with low gain \( (P=0.12) \) and increased significantly during VP \( (P=0.046) \). MAP was slightly lower in the patients with low gain and decreased significantly at the nadir of pacing \( (P=0.028) \). The recovery of MAP during sustained VP was significantly greater in the patients with high gain, as seen in Figure 4. Because ventricular pump function contributes to the hemodynamic responses, baroreflex gain and MAP recovery during VP were correlated with EF. No significant correlation between EF and baroreflex gain \( (r=0.48, P=0.08) \) or BP recovery \( (r=0.41, P=0.15) \) was found.

Arterial baroreflex–HR gain also was determined. Baroreflex–HR gain correlated significantly with baroreflex–SNA gain \( (r=0.74, P<0.01) \) but insignificantly with MAP recovery \( (r=0.49, P=0.07) \) and EF \( (r=0.44, P=0.14) \). HR gain was greater \( (P=0.02) \) in the high-gain group of patients \( (1.1\pm0.1 \text{ bpm/mm Hg}) \) compared with the low-gain group \( (0.7\pm0.1 \text{ bpm/mm Hg}) \).

### Table 2. Baseline and Pacing Responses in Patients With High or Low Baroreflex Gain

<table>
<thead>
<tr>
<th></th>
<th>High Gain (n=8)</th>
<th>Low Gain (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baroreflex gain, ∆%/∆mm Hg</td>
<td>2.9±0.4</td>
<td>1.9±0.3</td>
</tr>
<tr>
<td>SBP/DBP, mm Hg</td>
<td>142±5/85±4</td>
<td>135±6/85±5</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
<td>8.1±0.7</td>
<td>10.3±1.2</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>69±3</td>
<td>76±4</td>
</tr>
<tr>
<td><strong>Responses to pacing (steady state)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacing rate, bpm</td>
<td>150±0</td>
<td>141±6</td>
</tr>
<tr>
<td>∆MBP, mm Hg</td>
<td>−13±2</td>
<td>−18±3</td>
</tr>
<tr>
<td>∆SNA, %</td>
<td>34±19</td>
<td>28±15</td>
</tr>
<tr>
<td>∆CVP, mm Hg</td>
<td>3.2±0.5</td>
<td>4.1±0.8</td>
</tr>
</tbody>
</table>

SBP, DBP, and MBP indicate systolic, diastolic, and mean BP, respectively.

**Discussion**

The major finding of this study is the positive correlation between baroreflex gain measured during nitroprusside infusion and recovery of MAP during rapid VP. The recovery of MAP during simulated VT was significantly greater in patients with high gain compared with patients with low gain. These data strongly suggest that baroreflex gain contributes significantly to hemodynamic stability during simulated VT.
Knowledge of baroreflex gain in the individual patient may help the clinician tailor therapy directed toward sustained VT.

**Determinants of Hemodynamic Response During VT/VP**

We used VP to simulate VT because it has been shown to result in similar hemodynamic changes. The hemodynamic response during sustained VT or VP is determined by several factors. The influence of HR on cardiac output is well known. An increase in HR results in shortening of diastole and a decrease in cardiac output. This effect is exaggerated in patients with left ventricular dysfunction. Hamer et al. and Saksena et al. found that VT rate contributes to the occurrence of syncope; however, this finding was consistent only with rates >200 bpm. Thus, factors other than rate probably contribute importantly to hemodynamic outcome and symptom tolerance when tachycardia rates are <200 bpm. Smith and colleagues developed a predictive model from a group of 16 patients with VT, including rate, EF, and sympathetic response. This model predicted that rate was the most important determinant of hemodynamic outcome, but their data also suggested that sympathetic response played a role in the hemodynamic outcome. This is particularly relevant to episodes of VT in which the rate is <200 bpm; under these conditions, pump function and reflex sympathoexcitation may play important roles. In the model discussed above, Smith et al. found that EF was also predictive but that this contribution was modest. Likewise, we found a modest correlation between EF and MAP recovery during VP ($r=0.41$). Loss of synchrony of atrial and ventricular systole is another important factor that can result in less diastolic ventricular filling and systolic emptying. In addition to the loss of active atrial emptying, retrograde VA conduction can result in atrial contractions when the AV valves are closed, possibly leading to a cardiodepressant reflex with further decrease in BP. Thus, several factors other than EF alone may contribute to hemodynamic outcome during tachycardias.

Myocardial ischemia and humoral responses also can affect the hemodynamic response to VT. In our study, we did not measure parameters of pump function, the degree of myocardial ischemia, or humoral changes associated with rapid VP. Future investigation of these factors should further the understanding of the determinants of hemodynamic outcome during tachyarrhythmias.

**Autonomic Changes During VT/VP**

More than a decade ago, sympathetic nerve mechanisms were shown to play a possible role in the determination of hemodynamic response during VT. This was first evidenced by an increase in plasma catecholamines and forearm vascular resistance. In addition, the sympathoexcitatory response seen in patients with symptomatic VT was shown to be maximal during the first 30 seconds and was due largely to stimulation of $\alpha$-adrenergic receptors. Smith et al. recorded muscle SNA directly from the peroneal nerve in 16 subjects during diagnostic induction of 19 episodes of sustained monomorphic VT. Average SNA increased in direct proportion to arterial pressure reductions at the onset of VT. The late recovery of BP during VT was related significantly to the magnitude of early sympathetic responses. Results of this study suggest that early sympathetic activity contributed to hemodynamic stability during tachycardia. This is consistent with the findings of Ellenbogen et al. described above. Landolina et al. compared HR variability and baroreflex sensitivity in patients with poorly tolerated VT (syncope or systolic BP <90 mm Hg) and in patients with well-tolerated VT. All patients had old myocardial infarctions and depressed EFs. Baroreflex sensitivity was calculated as the slope of the linear regression line relating...
systolic BP changes to RR-interval changes in response to phenylephrine injection. The study showed that the value of baroreflex sensitivity as an estimation of baroreflex control of HR correlated with hemodynamic tolerance during VT. Baroreflex-mediated HR responses are not important to the hemodynamic outcome of a tachyarrhythmia because the ventricular rate is not changed. Therefore, we focused on the baroreflex control of SNA. Baroreflex gain was calculated as the change in SNA divided by the change in arterial pressure during nitroprusside infusion. We chose nitroprusside instead of phenylephrine to measure baroreflex gain during unloading conditions comparable to the hypotension produced during VT. We used infusion rather than bolus for 2 primary reasons. First, in many of these patients, there was some background ectopy that was augmented in some patients with nitroprusside. Our experience with bolus injections was that the occurrence of frequent ectopy confounded the analysis of the arterial pressure–SNA relationship and resulted in poor correlation coefficients (r<0.60). This raised concerns about the reliability of gain estimates that we might derive from these patients. Although the use of bolus injection is the standard approach for assessing baroreflex function, the response to vasoactive drug infusion has also been used and is similarly impaired in disease processes such as congestive heart failure. The use of a nitroprusside infusion probably resulted in smaller gain estimates than would have been produced by a bolus injection, as suggested by the study of Sullebarger et al16; however, it is unlikely that this influenced the conclusions of this study. Second, the use of infusion produced a sustained hypotension similar to that experienced during the simulated VT (pacing) and thus is a reasonable model of the baroreflex stimulus experienced during these tachyarrhythmias.

We found that the gain of baroreflex control of SNA during hypotension was predictive of MAP recovery (r=0.59). This supports our hypothesis that baroreflex gain does contribute importantly to the hemodynamic outcome during VT. These data could be a coincidence of heart disease and associated depressed pump function; however, this correlation was stronger than the correlation of hemodynamic outcome with pump function (EF). Moreover, when Smith and colleagues4 denervated the arterial baroreceptors of dogs, MAP recovery during rapid pacing or VT was significantly impaired. Thus, it is likely that the significant correlation between baroreflex gain and MAP recovery is functionally important and that arterial baroreflex gain does play an important role in hemodynamic outcome when tachyarrhythmia is not too rapid. We recently showed that SNA response during VP was mediated primarily by the arterial baroreflex and that it was modulated by input from cardiopulmonary baroreceptors.3 Our findings are consistent with those of Landolina et al14: baroreflex gain was markedly reduced in patients with poorly tolerated VP, suggesting that baroreflex gain is an important determinant of BP recovery during VP. In our study, baroreflex–SNA gain was a better predictor than baroreflex–HR gain.

The role of arterial and cardiopulmonary baroreceptors varies among patients as suggested by our previous study.3 Moreover, previous studies in dogs also suggest that relative impairment of cardiopulmonary and/or arterial baroreceptors may affect the net hemodynamic response to ventricular tachyarrhythmias. Nevertheless, studies in both dogs and humans have shown that in patients with the substrate for VT, arterial baroreflexes tend to predominate in the control of SNA.3,4 The present study extends these findings to show that arterial baroreflex gain is a predictor of hemodynamic outcome during ventricular tachyarrhythmias.

The reduction in SNA response during pacing and possibly during nitroprusside infusion in group 2 could be due to the long-term elevation of SNA in these patients. That is, their baseline SNA levels may be near a maximum and thus do not have “room” to significantly increase. In general, this does not appear to be the case on inspection of the group averages. The mean SNA for group 2 was 629±117 U/10 s, which approximates a sympathetic burst frequency of 60% to 70% of heartbeats. This is not near a maximum. However, 2 patients did have baseline SNA ≈900 U/10 s; therefore, this may have been limiting in these individuals. A question of cause and effect arises. This relationship of low gain and high baseline SNA is not surprising because in many conditions in which impairment of arterial baroreflex gain occurs, there is a concomitant elevation of baseline SNA. Our data suggest that the impairment of baroreflex gain is a probable cause of some of the impairment of hemodynamic outcome. This is due to inadequate sympathoexcitation and resultant vasoconstriction, and the inadequate sympathoexcitation appears to be due primarily to impaired baroreflex gain and not to SNA operating at a ceiling in most patients.

Clinical Implications

Sustained VT or VP results in an initial decrease in arterial pressure followed by gradual recovery toward baseline. The extent of this recovery greatly affects the severity of symptoms and tolerance of patients with sustained tachycardia. In the present study, we demonstrated a correlation between baroreflex gain and BP recovery during simulated VT. Knowledge of this gain in patients with tachycardia can be helpful in the management of these patients. Patients with VT and impaired baroreflex gain should probably receive aggressive therapy because they are not likely to tolerate tachycardia. In the era of implantable cardioverter-defibrillators, this would translate to less emphasis on antitachycardia pacing and earlier defibrillation therapy. Likewise, patients with supraventricular tachycardia and poor baroreflex gain should be strongly offered catheter ablation instead of drug therapy because they are more likely to have poor hemodynamic responses during tachycardia. A poor hemodynamic response to a rapid supraventricular tachycardia may also be a risk for deterioration of the rhythm to a polymorphic VT if ischemia develops. This is supported by observations of Bardy and Olson18 in which arterial pressure and electrograms were recorded during spontaneous tachyarrhythmias that deteriorated to ventricular fibrillation. Although their findings suggested that sustained hypotension may contribute in some way to this deterioration, they also pointed out that the reasons for deterioration of an arrhythmia to ventricular fibrillation are very complex. Nevertheless, efforts to improve baroreflex gain, such as exercise,19 should also be offered to patients with low baroreflex gain because they may improve their symptoms during sustained tachycardia.
Study Limitations
This study has several limitations. First, the number of patients enrolled is small. A larger number of subjects may have improved the correlational results. Second, we recognize that the baroreflex gain represents a continuous, not a dichotomous, variable (greater or less than 2.5%/mm Hg). Because baroreflex gain estimates are variable, the predictive power of a correlation analysis with a small subject number would not be expected to be strong. Although the correlation of baroreflex gain to MAP recovery was significant, the separation of subjects into 2 groups on the basis of baroreflex gain allowed the use of a t test comparison of groups to further test our hypothesis. We believe that the results of this analysis lend important support to the conclusion that baroreflex gain contributes to hemodynamic outcome. Third, several variables, such as left ventricular function and cardiac filling pressures, play a role in the recovery of MAP during sustained VP and were not controlled in this study. Our hypothesis is that baroreflex gain is an important predictor of hemodynamic response during pacing regardless of the effect of other contributing factors.

Conclusions
Baroreflex gain correlates with the BP recovery during simulated VT, suggesting that cardiovascular reflexes play an important role in the hemodynamic response during VT. Knowledge of the baroreflex gain not only is helpful for risk stratification in post–myocardial infarction patients but also could be used in the management of patients with sustained tachycardias.

References
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