Reflex Control of Sympathetic Activity During Simulated Ventricular Tachycardia in Humans

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Background—Ventricular tachyarrhythmias present a unique set of stimuli to arterial and cardiopulmonary baroreceptors by increasing cardiac filling pressures and decreasing arterial pressure. The net effect on the control of sympathetic nerve activity (SNA) in humans is unknown. The purpose of this study was to determine the relative roles of cardiopulmonary and arterial baroreceptors in controlling SNA and arterial pressure during ventricular pacing in humans.

Methods and Results—Two experiments were performed in which SNA and hemodynamic responses to ventricular pacing were compared with nitroprusside infusion (NTP) in 12 patients and studied with and without head-up tilt or phenylephrine to normalize the stimuli to either the arterial or cardiopulmonary baroreceptors in 9 patients. In experiment 1, the slope of the relation between SNA and mean arterial pressure was greater during NTP (−4.7±1.4 U/mm Hg) than during ventricular pacing (−3.4±1.1 U/mm Hg). Comparison of NTP doses and ventricular pacing rates that produced comparable hypotension showed that SNA increased more during NTP (P=0.03). In experiment 2, normalization of arterial pressure during pacing resulted in SNA decreasing below baseline (P<0.05), whereas normalization of cardiac filling pressure resulted in a greater increase in SNA than pacing alone (212±35% versus 189±37%, P=0.04).

Conclusions—These data demonstrate that in humans arterial baroreflex control predominates in mediating sympathoexcitation during ventricular tachyarrhythmias and that cardiopulmonary baroreceptors contribute significant inhibitory modulation. (Circulation. 1999;100:628-634.)

Key Words: nervous system, autonomic ■ death, sudden ■ arrhythmia ■ pressure ■ pacing

Rapid tachyarrhythmias (>250 bpm) result in hemodynamic collapse, are poorly tolerated, and often deteriorate to ventricular fibrillation. In some patients, slower ventricular tachycardia (VT) is also poorly tolerated for reasons that remain unclear. Previously, it was shown that VT or its surrogate, rapid ventricular pacing, provokes increases in sympathetic nerve activity (SNA) related to the degree of hypotension it causes. The baroreflex-mediated responses to VT are complex and unique because the brainstem receives conflicting rather than parallel inputs from the 2 major baroreceptor populations: Arterial baroreceptors are unloaded by hypotension, whereas cardiopulmonary baroreceptors are loaded by increased cardiac filling pressures. In the previous human study, the degree of maintenance of arterial pressure during sustained VT was related to the magnitude of sympathoexcitation: thus, the net control of SNA by the conflicting inputs to the arterial and cardiopulmonary baroreceptors appears to be important to hemodynamic outcome during VT.

We determined the relative roles of cardiopulmonary and arterial baroreceptors in controlling SNA and arterial pressure during VT simulated by rapid ventricular pacing in humans by comparing the response to hypotension caused by ventricular pacing with that produced by nitroprusside infusion (NTP). In addition, the effect of isolated changes in the stimuli to arterial and cardiopulmonary baroreceptors was evaluated by manipulating either the arterial pressure (with phenylephrine infusion) or central venous pressure (CVP; head-up tilt) during concurrent ventricular pacing.

Methods

Two experiments were performed to examine the relative roles of the cardiopulmonary and arterial baroreceptors in the sympathetic neural and hemodynamic responses to VT simulated by rapid ventricular pacing. In experiment 1, the sympathetic neural and hemodynamic responses to 3 rates of rapid ventricular pacing were compared with 3 doses of NTP in 12 patients referred for diagnostic electrophysiological testing (mean age, 38±3 years). Eight patients were referred for diagnosis and treatment of supraventricular tachycardia; the other 4 were studied for suspected VT. Five patients had known left ventricular dysfunction with ejection fractions <40%. In experiment 2, the sympathetic neural and hemodynamic responses to rapid
ventricular pacing with and without either head-up tilt or phenylephrine were studied in 9 patients referred for diagnostic electrophysiological testing (mean age, 45±4 years). Five patients were referred for diagnosis and treatment of supraventricular tachycardia, and 4 were studied for suspected VT. The latter 4 patients had documented left ventricular dysfunction with ejection fractions <40%. Five patients were treated with an ACE inhibitor, and 2 were treated with a diuretic. Three other patients were treated for mild hypertension with a calcium channel blocker, an ACE inhibitor, or combination therapy, including a diuretic. Each patient gave written informed consent for this study, which was approved by the Institutional Review boards of The University of Texas–Southwestern Medical Center, (Dallas, Tex) and University Hospitals of Cleveland (Cleveland, Ohio).

Experimental Design

Experiment 1
We measured SNA, mean arterial pressure (MAP), and CVP responses during ventricular pacing at 3 pacing cycle lengths ranging from 300 to 500 ms. Pacing rates were determined by the patient’s hemodynamic tolerance of the pacing so that a full minute of pacing data could be acquired for each pacing rate without excessive sustained hypotension. Mean±SEM pacing rates for all patients were 406±8, 357±6, and 328±7 ms. The responses to pacing were compared with the responses to 3 doses of NTP (0.2 to 1.0 μg·kg⁻¹·min⁻¹) that produced similar decreases in MAP. NTP was given to simulate the unloading of arterial baroreceptors without the significant loading (increased CVP) of cardiopulmonary baroreceptors produced by ventricular pacing. Although SNA is usually thought to be inversely related to diastolic pressure during sinus rhythm, this does not appear to hold true during rapid tachyarrhythmias. The SNA and diastolic pressure responses to VT vary considerably and often do not correlate significantly during tachyarrhythmias. Therefore, MAP was used as the primary stimulus for the arterial baroreceptors in this study.

Experiment 2
We measured SNA, MAP, cardiac filling pressure (as either pulmonary artery pressure [PAP] or pulmonary capillary wedge pressure), and cardiac output responses during ventricular pacing at a cycle length of 400 ms under 3 conditions: pacing alone, pacing plus head-up tilt (20° to 30°) to a level that returned cardiac filling pressure to prepacing baseline levels, and pacing plus phenylephrine infusion sufficient to reduce MAP to prepacing baseline levels. Pacing was sustained for 4 to 5 minutes. The role of cardiopulmonary baroreceptors was evaluated by comparing SNA and hemodynamic data during pacing with and without head-up tilt in which the cardiac filling pressure was normalized. Similarly, the role of arterial baroreceptors was assessed by comparing the responses to pacing with and without phenylephrine infusion so that the stimulus to the arterial baroreceptors (arterial pressure) was normalized.

Measurements
Arterial pressure was measured by use of an in-dwelling catheter inserted through the femoral artery in all but 3 patients (experiment 2). In those 3 patients, beat-to-beat arterial pressure was measured noninvasively with a photoplethysmographic device, and automated cuff pressures were obtained to corroborate the average beat-to-beat measures from the photoplethysmographic device. Cardiac filling pressures were measured in experiment 1 by placing a pigtail catheter in the right atrium advanced from the femoral vein and in experiment 2 by advancing a Swan-Ganz thermodilution catheter from the jugular vein to a pulmonary artery or wedge position. MAP was measured continuously, and pulmonary capillary wedge pressure was obtained briefly during each perturbation. Changes in PAP correlated strongly with the pulmonary capillary wedge pressure (r=0.98, P<0.0001); therefore, PAPs measured for the duration of the protocol were used for all analyses. In experiment 2, cardiac outputs were measured in triplicate by thermodilution during each condition.

Sympathetic Nerve Recordings

Muscle SNA was measured by a microelectrode inserted into a branch of the peroneal nerve near the fibular head by standard microneurographic techniques. SNA was identified by its association with cardiac activity, respiratory activity, and response to single extra electrical stimuli to the heart. SNA was averaged over 30- to 60-second data segments and quantified from the area under the curve of sympathetic bursts. Data were normalized for each control period by determining the average area per burst and assigning that area a value of 100. Burst areas during the subsequent pacing were normalized to this standard. Burst area was used because ventricular pacing often produces broad arterial pressure oscillations that provoke broad bursts of sympathetic activity. Under these conditions, burst amplitude alone does not correlate well with burst area and does not account for the prolonged activation of sympathetic nerve traffic associated with periods of protracted hypotension.

Electrophysiological Techniques

Two or 3 multipolar catheters were introduced percutaneously into the femoral vein and positioned in the right atrium and right ventricular apex as a site for pacing. Ventricular pacing was performed at a pulse width of 2 ms and an amplitude twice the diastolic threshold from the right ventricular apex. A surface ECG was recorded continuously.

All data were recorded online to a personal computer and were analyzed post hoc by custom programs. Student’s t test was used for comparisons between pacing and NTP. ANOVA with a repeated-measures design was used to compare responses during pacing with head-up tilt or phenylephrine infusion. Statistical significance was defined by α=0.05. All data are presented as mean±SEM.

Results

The responses to simulated VT were generally consistent among all patients. The pacing rates varied among patients on the basis of individual hemodynamic and symptomatic tolerance of the pacing. Typical responses to VT or its surrogate, ventricular pacing, include an initial decrease in arterial pressure and increase in CVP, which is usually accompanied by an increase in SNA, as shown in Figure 1. Broad, sustained bursts of SNA occurred at the onset of pacing when arterial pressure fell precipitously and was free of noticeable pulsatility. When pacing was sustained for ≥1 minute, arterial pressure usually returned toward baseline, whereas cardiac filling pressure remained elevated at a relatively constant level. Sympathetic activity usually achieved a steady state and then varied with fluctuations in arterial pressure. In all but 2 patients, SNA increased above baseline during sustained ventricular pacing; in those 2 patients, SNA actually decreased modestly (between 4% and 12%) from baseline values that were very high (865 and 981 U/10 s, respectively, versus 539±97 U/10 s for all patients).

Experiment 1
The responses to 3 rates of ventricular pacing were compared in each patient with the responses to 3 NTP rates to produce similar decreases in arterial pressure. Figure 2 illustrates the average increase in SNA for a given decrease in MAP caused by 3 pacing rates and 3 NTP rates. The slope of this relationship was determined for each patient; the mean slope was greater during NTP (~4.68±1.37) than during ventricular pacing (~3.36±1.14, P<0.01). The profile of the baroreceptor stimuli differed between pacing and NTP, as shown in Figure 3; Figure 3A shows the responses during graded NTP infusion rates, and Figure 3B shows the re-
Responses during graded rates of ventricular pacing. The decrease in arterial pressure was uniform during NTP for systolic and diastolic pressures and MAP, whereas diastolic pressure tended to be slightly increased during ventricular pacing. Pulse pressure decreased more during pacing than during NTP (\(238.6_{\pm}14.6_{\pm}3\) mm Hg for the middle NTP dose versus middle pacing rate, \(P<0.01\)). CVP increased during pacing at all pacing rates (\(P<0.0001\)) and decreased slightly during the higher NTP doses (\(P<0.05\)).

SNA and CVP data also were compared between a pacing rate (which produced a mean decrease in MAP of \(13.6_{\pm}2.7\) mm Hg) and a 1-minute time segment during NTP in which MAPs were similar, as shown in the Table (\(13.2_{\pm}1.8\) mm Hg, \(P=0.82\)). Despite similar decreases in MAP, CVP increased during ventricular pacing (\(4.8_{\pm}0.4\) mm Hg) and decreased during NTP (\(-1.8_{\pm}0.5\) mm Hg); the difference was significant (\(P<0.01\)). In addition, the SNA increase was greater (\(P=0.029\)) during NTP than during pacing (Figure 4).

**Experiment 2**

Responses to ventricular pacing were compared with pacing and either concomitant infusion of phenylephrine to normalize MAP or concomitant head-up tilt to normalize cardiac filling pressure. Figure 5 illustrates the data for pacing with and without phenylephrine infusion and head-up tilt. The responses of all variables to pacing in each repetition (with and without head-up tilt or phenylephrine) were not different (\(P>0.47\)). MAP decreased during pacing and returned to near baseline levels during phenylephrine infusion (\(P=0.23\)). PAP increased during pacing (\(16.8_{\pm}1.1\) to \(21.2_{\pm}2.3\) mm Hg, \(P<0.01\)) and increased insignificantly more when phenylephrine was infused (to \(22.4_{\pm}2.5\) mm Hg, \(P=0.17\)). SNA increased significantly during ventricular pacing (to \(189_{\pm}37\)% of baseline) and decreased to below baseline (\(81_{\pm}6\)% of baseline, \(P<0.05\)) during phenylephrine infusion. During pacing and head-up tilt, PAP was returned to pre-pacing baseline values by head-up tilt (\(17.1_{\pm}0.9\) mm Hg, \(P>0.05\)), and SNA increased further to \(212_{\pm}35\) of baseline (\(P<0.05\)). MAP decreased slightly more during head-up tilt.
Cardiac output decreased significantly during pacing \((P<0.05; \text{Figure 6})\). Cardiac output did not change during head-up tilt \((3.7 \pm 0.7 \text{ versus } 3.4 \pm 0.8 \text{ L/min})\) and tended to decrease during phenylephrine infusion \((3.1 \pm 0.8 \text{ L/min})\), although this difference was not significant from pacing alone \((P>0.05)\). The estimated total peripheral resistance increase was predictably greater during phenylephrine infusion (because of the direct effect of the vasoactive drug) and was slightly greater during head-up tilt (Figure 6).

**Figure 3.** Mean \(\pm\) SEM arterial blood pressure and CVP responses to graded NTP (A) and ventricular pacing (B). Pacing cycle lengths of 406, 357, and 318 ms correspond to heart rates of 148, 168, and 189 bpm, respectively. SAP indicates systolic arterial pressure and DAP, diastolic arterial pressure. *Significant difference from baseline \((P<0.05)\).

**Figure 4.** Mean \(\pm\) SEM responses to pacing and NTP that produced comparable decreases in MAP \((13.6 \pm 2.7 \text{ versus } 13.2 \pm 1.8 \text{ mm Hg}; \text{see the Table})\). *Significant difference between pacing and NTP \((P<0.05)\).

**Figure 5.** Summary data for MAP, PAP, and SNA responses to ventricular (V) pacing (VP) and ventricular pacing with phenylephrine infusion (PE, open symbols) or head-up tilt (HUT, closed symbols). Data are mean \(\pm\) SEM. *Significant difference from baseline \((P<0.05)\). †Significant difference from ventricular pacing alone \((P<0.05)\).
Discussion

VT or pacing is followed by a decrease in arterial pressure and an increase in cardiac filling pressures. This presents a unique set of stimuli to the pressure-sensitive baroreceptors: unloading of the arterial baroreceptors to stimulate SNA and loading of the cardiopulmonary baroreceptors to inhibit SNA. In a dog model of VT with previous myocardial infarction and inductive VT, selective denervation of arterial or cardiopulmonary baroreceptors suggested that the arterial baroreceptors play the predominant role in increasing SNA and maintenance of arterial blood pressure, whereas cardiopulmonary baroreceptors appeared to play a modulatory role in these responses.5 Results of the present studies suggest that in patients referred for evaluation of VT or pacing alone.

Ventricular Pacing as a Model of VT

Ventricular pacing is not a perfect surrogate for the electrophysiological profile of a particular VT; the site of origin and the conducting pathways determine this profile. Although pacing from other sites may produce somewhat varied hemodynamic outcomes,5,7 these differences are subtle. Although differences (albeit small) in cardiac index have been observed, there were no differences in MAP. We have found that standard pacing from the right ventricular apex reproduces the hemodynamic and sympathetic neural responses of septal or anterior wall tachycardias very consistently in both humans and dogs.1,5 These previous studies clearly demonstrate that right ventricular apical pacing is a physiological model of VT and thus can be used as a clinically relevant surrogate for VT.

Reflex Control of Sympathetic Activity During VT

Under most physiological stressors, arterial pressure and cardiac filling pressure change in parallel and thus evoke complementary responses from the arterial and cardiopulmonary baroreceptors. VT represents a unique and complex physiological stressor in that arterial pressure decreases, often profoundly, while cardiac filling pressures increase. Thus, the afferent inputs to the brainstem have conflicting effects on efferent SNA, the principal mediator of reflex control of circulatory function. Therefore, during VT, 2 fundamental questions arise: What is the nature of the interaction of these conflicting inputs, and which reflex mechanism predominates? Two previous studies addressed this question in dogs using similar paradigms to evaluate the sympathetic neural responses to rapid ventricular pacing.5,8 However, the results are not consistent and may be due to 2 key differences in experimental design. Halliwill et al8 found that during rapid pacing at 214 bpm, there was a tendency for a net reduction of SNA, whereas Smith et al5 showed that SNA increased during ventricular pacing or tachycardia at 220 to 280 bpm and that this response was eliminated by arterial baroreceptor denervation. Halliwill and colleagues studied healthy dogs in an open-chest preparation, whereas Smith et al studied dogs in a closed-chest preparation. Thoracic surgery produces a significant stress to the animal that is known to produce large increases in basal sympathetic activity; thus, a likely explanation for the differing responses of these 2 studies was that basal activity was extremely high in the Halliwill et al study, thereby favoring a sympathoinhibitory response.

Although the same reflex mechanisms are operational in humans, there is evidence that cardiopulmonary baroreflex mechanisms operate somewhat differently in humans, probably because of the predominant upright posture of humans. For example, the Bainbridge reflex (observed in several species), which produces significant cardiac acceleration with increased atrial pressure in many animal species, appears to be negligible in humans.5,10 The present study was designed to address similar questions regarding arterial versus cardiopulmonary control of SNA and arterial pressure during ventricular pacing in humans. In this study, ventricular pacing at 120 to 200 bpm usually resulted in elevations in SNA, although the magnitude of this response varied widely. Two patients with very high basal SNA demonstrated a symp-
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Inhibitory response during ventricular pacing. This is consistent with our interpretation of the results of Halliwill et al. A high basal sympathetic activity favors an inhibitory response. Nevertheless, these data are consistent with a previous study that showed that ventricular pacing or VT usually produces a significant sympathoinhibitory response in humans.1

In the present study, we addressed the question of how SNA is controlled in humans under these conditions of conflicting inputs. In experiment 1, we found that a comparable decrease in arterial pressure, without an increase in CVP, produced a greater sympathoexcitatory response. These data also suggest that cardiopulmonary baroreceptors may impart an inhibitory effect because the increase in SNA was greater when CVP was not increased. However, this is a guarded conclusion because CVP tended to decrease slightly during NTP. This decreased CVP would be expected to unload the cardiopulmonary baroreceptors and potentially increase SNA.11 In experiment 2, we used 2 conditions to normalize the stimulus to either arterial baroreceptors (by returning arterial pressure to prepacing baseline with infusion of phenylephrine) or cardiopulmonary baroreceptors (by decreasing cardiac filling pressure back to prepacing baseline with head-up tilt). Normalizing arterial pressure resulted in SNA decreasing below baseline. These support the conclusion that the cardiopulmonary baroreceptors contribute a significant inhibitory modulation of SNA. Furthermore, when cardiac filling pressure was normalized by head-up tilt, SNA increased ≈20% more. This occurred without a significant change in arterial pressure; thus, these data provide the most compelling evidence that cardiopulmonary baroreceptors impart a modest modulatory effect during simulated VT. In each experimental paradigm, we were unable to control the stimuli to the 2 baroreceptor populations perfectly, but the responses were consistent among the different conditions and strongly support the conclusion of our previous study in dogs that arterial baroreceptors play the primary role in mediating sympathetic neural responses to ventricular tachyarrhythmias and are modulated importantly by cardiopulmonary baroreceptors.5

Why does the net effect usually favor arterial baroreflex–mediated sympathoexcitation rather than cardiopulmonary baroreflex–mediated sympathoinhibition? During orthostatic stress, cardiopulmonary baroreceptors clearly play an important role in increasing SNA11,12 and producing vasoconstriction.13 Cardiopulmonary baroreceptor loading also produces sympathoinhibition14 and peripheral vasodilation.13,15 The magnitude of increased cardiac filling pressures is often greater during VT than that usually imposed by volume loading or leg raising used in previous studies; thus, it would be expected that the cardiopulmonary baroreflex would impart significant sympathoinhibition. In addition, cardiopulmonary unloading has been shown to enhance arterial baroreflex gain in the control of heart rate and vascular resistance, and these studies implied that cardiopulmonary loading would inhibit arterial baroreflex gain.16–18 In the face of these inhibitory effects, it appears that the balance of the stimuli during VT, unloading of arterial baroreceptors and loading of cardiopulmonary baroreceptors, is weighted toward the effects of the arterial baroreflex. The initial hypotension at the onset of VT is very profound and typically remains much greater than the elevation of cardiac filling pressures. Therefore, our data suggest that this hypotension produces a much greater sympathoexcitation than the sympathoinhibition produced by the increase in CVP. Despite the predominance of the arterial baroreflex to produce sympathoexcitation, our data also show that cardiopulmonary baroreflex inhibition does occur and can play a significant modulatory role. One reason that a greater effect was not observed could be that many patients had impaired cardiopulmonary baroreflex function. Several studies have shown that cardiopulmonary baroreflex function is impaired in patients or animals after myocardial infarction with left ventricular dysfunction or congestive heart failure.19–21

Clinical Implications

Several factors contribute to the hemodynamic outcome of a VT, including ventricular rate, left ventricular pump function, and reflex sympathetic activation. Each plays a role, yet it remains unclear how important each is in determining the net outcome. Previously, we developed a predictive model based on data from 16 patients that suggested that each factor plays an important role.1 The present study, together with our previous studies,1,5 suggests that normal reflex-mediated sympathetic activation is beneficial during VT by helping to maintain stable hemodynamic status. We predict that in patients with significantly impaired arterial baroreflex function, the prognosis for stable hemodynamic responses to VT is poor. Impaired arterial baroreflex function has been shown to correlate with increased risk of ventricular arrhythmias and mortality.22–24 Is this a causal relation? If so, what is the mechanism? The answers to these questions are unknown; however, we speculate that a mechanism for this increased risk involves impaired reflex support of arterial pressure during VT, a common precursor to ventricular fibrillation. It is clear that poor hemodynamic tolerance of VT is often accompanied by a downward spiral to polymorphic VT and ventricular fibrillation. This is consistent with the observation that patients with heart failure do not tolerate VT well and often die from sudden cardiac death when VT occurs.25

Conclusions

In conclusion, these data are generally consistent with the findings in the previous dog study that arterial baroreflex control predominates in mediating sympathoexcitation during VT. Cardiopulmonary modulation during VT functions to inhibit SNA and appears to play a greater role in humans. The net importance of these reflex mechanisms in determining hemodynamic stability during VT is still not clear; however, preliminary results from our laboratory suggest that arterial baroreflex gain is predictive of hemodynamic outcome.

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References


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