Enhancement of Sympathetic Nerve Activity by Single Premature Ventricular Beats in Humans

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This is the first systematic study of the effects of ventricular premature beats on sympathetic nerve activity in humans. Microneurographic techniques were used to record efferent sympathetic activity from the peroneal nerve, and an intracardiac electrode catheter was used to introduce ventricular premature beats after every 6 to 10 sinus heartbeats. Studies were performed in eight patients, aged 22 to 74 years (mean 57), undergoing cardiac electrophysiologic studies. Three patients did not have apparent heart disease and five had coronary artery disease.

During sinus rhythm, 19 to 93% (mean 42%) of heartbeats were followed by a pulse-synchronous burst of sympathetic activity. Provoked ventricular premature beats had obvious effects on this activity. Premature beats with coupling intervals ~80% of sinus cycle length were consistently followed by a burst of sympathetic activity, and this activity was greater in amplitude, duration and area (all p < 0.05) than were bursts of such activity during sinus rhythm. The magnitude of this burst of activity increased as the coupling interval of the ventricular premature beat decreased (p < 0.0001). In contrast, postextrasystolic beats were followed by nearly complete neural silence. These effects were seen in all patients regardless of baseline burst incidence and the presence or absence of heart disease. Total nerve activity per 10 heartbeats was 6,520 ± 770 U during ventricular extrastimulation and 5,720 ± 440 U during normal sinus rhythm (difference not significant).

It is concluded that single ventricular premature beats provoke fluxes of muscle sympathetic nerve activity in humans, comprising surges of sympathetic activity larger than those occurring during sinus rhythm, followed by neural silence.
failure or unstable angina pectoris, 3) absence of recent myocardial infarction (within 3 weeks), 4) age ≥ 21 years, and 5) willingness to give informed written consent for participation.

Seven men and one woman, aged 22 to 74 years (mean 57), were studied. Indications for clinical electrophysiologic studies were ventricular tachycardia (five patients) or unexplained syncope (three patients). Three patients had no evidence of structural heart disease. The other five patients had angiographically documented coronary artery disease; four of these had a prior myocardial infarction. Two had undergone coronary artery bypass grafting (one with aneu-

rysctomy and subendocardial resection) 10 and 11 days before study. Left ventricular ejection fraction of the patients with coronary artery disease ranged from 28 to 65% (mean 42%). Three patients were receiving no medications at the time of study. Medications for the remaining five patients included propranolol (two patients), nifedipine (two pa-

tients), digoxin (two patients), procainamide (one patient) and quinidine (one patient).

Electrophysiologic techniques. Clinical cardiac electrophysiologic studies were performed by standard techniques (11) with patients in the postabsorptive, nonsedated state. No hemodynamically important arrhythmias were induced on the day of the research study. For the research study, a quadripolar electrode catheter was located at the right ventricular apex; this catheter was inserted ≥ 1 day before the research study in three patients and on the same day as the research study in five patients. Ventricular stimulation was performed with a programmable digital stimulator (model DTU-101, Bloom Associates) through the distal two poles of the catheter. A right ventricular electrogram from the proximal two poles was sensed. A single ventricular premature electrical stimulus with a duration of 2 ms and a current of twice diastolic threshold was delivered after every 6 to 10 conducted sinus beats. The coupling interval of the extrastimulus was increased or decreased by 20 to 100 ms until the electrically excitatory diastolic period had been scanned at least 10 times.

Sympathetic nerve recordings. Postganglionic muscle sympathetic nerve activity was recorded from the peroneal nerve at the fibular head with the patient supine (10). Skin surface stimulation (10 to 60 V; duration 0.1 ms) was used to map the course of the nerve. An insulated tungsten micro-

 electrode with an uninsulated tip (diameter 1 to 4 μm) was inserted through unanesthetized skin in the region of the mapped nerve. Subcutaneous stimulation (1 to 4 V; duration 0.01 ms) was used to guide this recording electrode into the nerve. Muscle nerve fascicles were identified by muscle twitches without skin paresthesias during low voltage stimuli delivered through this microelectrode. A reference electrode was inserted subcutaneously approximately 2 cm from the recording electrode. Nerve signals were passed through a Nerve Traffic Analyzer (model 662C 3, University of Iowa Bioengineering Department). The signals were fed through a two-stage amplifier (total gain 70,000), a bandpass filter (bandwidth 700 to 2,000 Hz) and an amplitude discriminator to reduce remaining noise. Neural activity was monitored with an oscilloscope and a loudspeaker. A resistance-capacitance integrating network with a time constant of 0.1 s was used to display the mean voltage neurogram (integrated nerve activity).

Procedures for identifying muscle sympathetic nerve activity have been described previously by Vallbo et al. (12). In short, muscle nerve fascicles have characteristic afferent mechanoreceptive discharges that can be evoked by tapping or stretching the supplied muscle. Minor electrode adjustment are made until spontaneously occurring efferent muscle sympathetic nerve activity is recorded. This activity is easily recognized by its characteristic grouping into brief pulse-synchronous bursts. Muscle sympathetic activity is differentiated from skin sympathetic activity on several bases: skin sympathetic bursts are more irregular, are not related to cardiac activity and last longer. Furthermore, arousal stimuli provoke bursts of sympathetic activity in skin but not in muscle.

Recordings of the surface electrocardiogram (ECG), filtered raw nerve signal and integrated nerve activity were made on photographic paper and frequency-modulated (FM) magnetic tape in seven subjects and on photographic paper alone in one subject. Two patients had simultaneous arterial pressure recording from a femoral artery catheter connected to a strain gauge pressure transducer (Gould Instruments, model P 231D). Periods of sympathetic nerve activity without ventricular stimulation were recorded before and intermittently during the study to serve as control.

Data analysis. All bursts of sympathetic nerve activity occurring during a 3-min control period of sinus rhythm were analyzed. We ascribed a burst of sympathetic nerve activity to a QRS complex when it followed the R wave by approximately 1.3 s to account for the latency of the reflex arc (13). Burst incidence was defined as the percent of sinus beats that were followed by bursts of sympathetic activity. The mean amplitude and area of spontaneous bursts for each subject were set at 1,000 arbitrary units. Bursts associated with induced ventricular premature beats were compared with these standards. A Kolmogorov D statistic (14) was calculated to evaluate the distribution of data. Because all data sets were distributed normally, parametric statistical tests were used. One-way analysis of variance was used to test for significant differences among serial sympathetic burst areas and among serial arterial pressures. Least squares regression analysis was performed to determine the best fit for a relation between burst amplitude and premature beat coupling interval, between burst area and burst amplitude, between arterial diastolic pressure and premature beat
coupling intervals and between burst amplitude and arterial diastolic pressure. Total nerve activity was the total area contained by all nerve bursts in a given period of time. A Student's $t$ test was used to compare the mean values of total nerve activity. An alpha level of 0.05 was considered significant.

Results

Sinus rhythm. During normal sinus rhythm, heart rates ranged from 55 to 103 beats/min (mean 70). All subjects had spontaneous, pulse-synchronous bursts of muscle sympathetic nerve activity (Fig. 1A and 2A) associated with conducted sinus beats. Baseline burst incidence ranged from 19 to 93% (mean 42%). Spontaneous ventricular premature beats were rare or absent in seven subjects and frequent in one subject.

Ventricular premature beats. Provoked ventricular premature beats had obvious effects on muscle sympathetic nerve activity. All but the most late-coupled premature beats were almost always followed by a burst of sympathetic activity (Fig. 1B and 2B). Furthermore, these provoked bursts had greater amplitude, duration and area than did those that occurred during sinus rhythm. These effects were seen in all subjects regardless of the presence or absence of heart disease and of baseline burst incidence. Spontaneous (nonprovoked) premature ventricular beats were also followed by unusually large bursts of sympathetic nerve activity.

There was a relation between the coupling interval of a provoked ventricular premature beat and the amplitude of the subsequent burst of sympathetic nerve activity (Fig. 3). Sympathetic bursts occurring after late-coupled premature beats (coupling intervals >80% of baseline RR interval) were similar to those occurring during sinus rhythm. As coupling interval was shortened from 80 to 40% of the RR interval, sympathetic burst amplitude progressively increased. However, as coupling interval was shortened to <40% of baseline RR interval, burst amplitude appeared to plateau. The relation between coupling interval and burst amplitude was described slightly better by a second order regression represented by the curvilinear solid line ($r = 0.74, p < 0.0001$, SEE = 33.7 units) than by a linear regression ($r = 0.70, p < 0.0001$).

Simultaneous arterial pressure recordings were made in two subjects. As expected, there was a direct relation between the coupling interval of provoked premature beats and subsequent diastolic pressure: that is, earlier premature beats were followed by lower diastolic pressure ($r = 0.89, p < 0.001$). Furthermore, there was an inverse relation between diastolic pressure and burst amplitude: that is, premature beats with a lower diastolic pressure were followed by sympathetic nerve bursts of higher amplitude ($r = -0.65, p < 0.01$).

In six subjects we were able to calculate the area enclosed by the integrated nerve tracing. (Inadequate FM tape
Figure 4. Relation between area and amplitude of bursts of sympathetic nerve activity in six patients. The hatched area represents the absolute range of values of sympathetic bursts during sinus rhythm. Solid circles are values of sympathetic bursts for 15 consecutive provoked ventricular premature beats in each patient. The relation was best described by a first-order regression (area = 1.94 x amplitude - 380, r = 0.68, p < 0.0001, SEE = 243 units) represented by the solid line. Note that many of the circles were above the range for sinus rhythm, suggesting that ventricular premature beats increased burst area out of proportion to burst amplitude.

Figure 5. Beat to beat changes in systolic arterial pressure in two patients. Systolic pressure was decreased after a provoked ventricular premature beat (PVC) and slightly increased after the postextrasystolic beat.

though mean total nerve activity tended to be greater during periods of ventricular stimulation (6,520 ± 770 units/10 heartbeats) than during periods of sinus rhythm (5,720 ± 400 units/10 heartbeats), this difference was not statistically significant (Fig. 7).

Discussion

Ventricular premature beats and muscle sympathetic nerve activity. This is the first systematic study of the effects of ventricular premature beats on efferent sympathetic nerve traffic in humans. We used microneurographic techniques to record muscle sympathetic nerve activity, and used intracardiac electrode catheters to introduce ventricular premature beats systematically. There are several important findings. First, our study shows that even modestly premature ventricular beats predictably trigger bursts of efferent muscle sympathetic nerve activity, and that the amplitude of these bursts varies directly with the degree of prematurity. Second, bursts of muscle sympathetic nerve activity that follow
ventricular premature beats are not only of greater amplitude but also of longer duration than are bursts that occur during sinus rhythm. Finally, these unusually large sympathetic bursts are followed by brief periods of neural silence. These changes in efferent muscle sympathetic nerve activity occurred in all subjects, regardless of the baseline level of sympathetic activity, and regardless of whether heart disease was present or absent. Five patients were receiving medications that potentially alter baroreflex function or basal sympathetic nerve activity, yet their responses were not qualitatively different from those of the other three patients.

Relation to previous studies. Our results are related closely to those of three earlier studies. Wallin et al. (15) analyzed muscle sympathetic nerve activity recorded in 11 healthy volunteers with spontaneous variations of heart period (RR interval) due to sinus arrhythmia, atrioventricular block, atrial fibrillation or premature supraventricular beats. Sympathetic nerve activity was shown to be related directly to RR intervals and inversely to diastolic blood pressure. Morrison et al. (6) measured changes of cardiac sympathetic activity after closely coupled ventricular premature beats in anesthetized cats. They found that ventricular premature beats are followed by integrated sympathetic bursts that have greater amplitude and duration than do those that follow sinus beats. Herre and Thames (7) measured changes of renal and cardiac sympathetic traffic after induced ventricular premature beats in anesthetized dogs. They found the magnitude of sympathetic bursts to be directly related to the degree of prematurity of the ventricular beats.

Physiologic mechanisms. Our results agree with earlier studies (7,15,16) that indicate that the magnitude of sympathetic bursts is related directly to the prematurity of ventricular beats. It is likely that this relation is mediated by baroreceptors. Earlier ventricular premature beats usually generate lower systolic pressures and are followed by compensatory pauses and longer diastolic runoffs (5). In fact, Herre and Thames (7) showed in dogs that baroreceptor denervation abolished the increase of sympathetic nerve activity that followed ventricular premature beats.

Our study suggests that the relation between the amplitude of a sympathetic burst and coupling interval of the ventricular premature beat may be complex. We found that ventricular beats located over about 80% of the cardiac cycle triggered unusually large bursts of sympathetic activity. As the coupling interval of the premature ventricular beats decreased, there was a corresponding increase in muscle sympathetic activity. There appeared to be a plateau in burst amplitude as the ventricular premature beats became more closely coupled (<40% of the RR interval). The relation between burst amplitude and coupling interval was well described by a second-order regression ($r = 0.74$, $p < 0.0001$), thereby supporting the presence of this plateau and suggesting a limit to burst amplitude. However, a linear regression ($r = 0.70$, $p < 0.0001$) described the data almost as well.

Burst morphology. The sympathetic bursts that followed ventricular premature beats had greater areas (amplitude $\times$ duration) than did those that occurred during sinus rhythm. The area of electronically integrated bursts reflects the number of sympathetic neurons firing and their frequency of firing. In an earlier study in which large changes of sympathetic activity were provoked by pharmacologic changes in arterial pressure, Eckberg et al. (17) found a highly significant linear relation between the area and the amplitude of muscle sympathetic bursts ($area = 1.14 \times amplitude - 13.6$, $r = 0.99$, $p < 0.001$). In the present study, this same relation was present during sinus rhythm, but it was distorted by ventricular premature beats. Burst area increased out of proportion to burst amplitude, because of a disproportionate increase of burst duration.

The pulse-synchronous pattern of muscle sympathetic bursts is thought to result from entrainment of central sympathetic oscillators by pulse by pulse afferent baroreceptor input (18). Fagius et al. (19) interrupted afferent baroreceptor input with lidocaine injections into the regions of the carotid sinuses. They found that, when baroreceptor input was blocked, muscle sympathetic bursts lost pulse synchrony and were longer in duration. In our study, lengthening of sympathetic bursts after premature ventricular beats may have occurred because, during the compensatory pause, arterial pressure was too low to inhibit and thus entrain sympathetic oscillators.

Sympathetic silence. We also found that the large sympathetic bursts induced by premature ventricular beats were followed by sympathetic silence. The simplest explanation for this finding is that, after a premature beat, increased end-diastolic volume (20) and postextrasystolic potentiation

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**Figure 7.** Total nerve activity during sinus rhythm (left) and during periods of ventricular premature electrical stimulation (PVC) (right) in six subjects. Open circles and brackets indicate mean values $\pm$ SEM. The difference was not significant.
cause increased arterial pressure, which inhibits sympathetic nerve activity. Another possible explanation (23) is that unusually large bursts of activity transiently alter generator properties of sympathetic motoneurons.

Because increased sympathetic nerve activity provoked by ventricular premature beats was followed by a period of neural silence, we did not find a significant increase in net sympathetic activity during periods of induced ventricular ectopic activity. However, the total sympathetic nerve activity was somewhat increased at the peroneal nerve because of the difference in length of the efferent fibers involved. If ventricular premature beats modify sympathetic nerve activity, then these changes could be relevant to the pathophysiology of ventricular fibrillation.

Limitations. Our study addressed the effects of only sporadic, single ventricular premature beats on sympathetic nerve activity. Therefore, we do not know what effect more frequent premature beats or more complex ventricular ectopic activity (such as ventricular couplets or triplets) might have had on this activity. However, previously published data (24) suggest that higher levels of ventricular ectopic activity tend to further increase overall sympathetic activity. Geschwind et al. (24) found that, in dogs, sympathetic nerve activity was greater during an unusually large burst of activity transiently alter generator properties of sympathetic motoneurons.

The use of programmed ventricular stimulation allowed us to introduce premature ventricular beats systematically throughout diastole; however, electrical current from the pacemaker might stimulate cardiac afferent fibers and initiate a burst of sympathetic nerve activity. This possibility is unlikely because Schwartz et al. (25) found that periods of ventricular pacing were not associated with increased coronary sinus norepinephrine concentrations. Herre and Thames (7) found that, in dogs, sympathetic nerve activity was greater during induction of ventricular couplets or triplets than during induction of single ventricular premature beats.

Clinical implications. Although ventricular fibrillation is the most common cause of death in developed countries (26), its pathophysiology is not well understood. However, at least two factors relevant to ventricular fibrillation have been identified. One of these is sympathetic nerve activity (8). Research conducted in experimental animals suggests that sympathetic stimulation is arrhythmogenic and decreases the threshold for ventricular fibrillation (27,28). Sympathetic stimulation also appears to be arrhythmogenic in humans because beta-adrenergic blocking agents decrease the incidence of sudden death in postinfarction patients (29). The other factor relevant to ventricular fibrillation is ventricular ectopic activity. It is clear that, in the presence of severe heart disease, frequent ventricular premature beats are associated with increased risk of sudden death (1-4). Furthermore, there is usually an increase in the frequency of ventricular premature beats in the period before the onset of sustained ventricular tachycardia or fibrillation (30-32). In this study, we explored a possible link between these two factors.

Our study shows that within 1.5 s after a single ventricular premature beat, an unusually large burst of efferent sympathetic activity arrives at the peroneal nerve just below the knee. Cardiac sympathetic nerve activity has not been recorded in humans; however, the sympathetic nervous system is highly integrated, and efferent traffic in one group of sympathetic fibers may be mirrored by virtually identical activity in other groups of sympathetic fibers (6,7). Thus, it is likely that, in humans as in animals, single ventricular premature beats modify sympathetic traffic to the heart. The bursts of sympathetic activity would likely occur earlier at the heart than at the peroneal nerve because of the difference in length of the efferent fibers involved. If ventricular premature beats do, in fact, modify cardiac sympathetic nerve activity, then these changes could be relevant to the pathophysiology of sudden cardiac death.

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References


