Responses of Sympathetic Nerves to Programmed Ventricular Stimulation

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Ventricular arrhythmias generally result in a decrease in arterial pressure and increases in atrial and ventricular filling pressures which would be expected to induce reflex changes in efferent sympathetic nerve activity to the heart and peripheral circulation. Experiments were performed in 14 anesthetized dogs in order to 1) determine whether programmed ventricular stimulation produces changes in renal sympathetic nerve activity; 2) quantify these changes; and 3) determine the cardiovascular reflexes that mediate these changes. Arterial and right atrial pressures and renal sympathetic nerve activity were recorded in dogs before and after administration of single and double programmed ventricular stimuli.

In a group of 10 dogs after single extrastimuli, diastolic arterial pressure decreased by 18 ± 2 mm Hg (mean ± SEM) while renal sympathetic nerve activity increased by 39 ± 15 impulses/s. These changes were directly related to degree of stimulus prematurity. After double extrastimuli, diastolic arterial pressure decreased by 22 ± 2 mm Hg whereas renal sympathetic activity increased by 55 ± 8 impulses/s. In an additional four dogs, double extrastimuli decreased arterial pressure (−34 ± 1 mm Hg) and increased cardiac (86 ± 16%) and renal (82 ± 12%) sympathetic traffic. After sinoaortic denervation, neither single nor double programmed ventricular stimuli resulted in alterations in cardiac or renal sympathetic nerve activity. It is concluded that the decreased arterial pressure caused by single and double programmed ventricular stimuli leads to increases in cardiac and renal sympathetic nerve activity that are mediated by sinoaortic baroreflexes.

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The role of the autonomic nervous system in the production and worsening of ventricular arrhythmias has been supported by studies both in humans and in animal models. Higher centers, the spinal cord (1), sympathetic ganglia (2–4) and the ventrolateral cardiac nerve (5) all appear to play important roles in the efferent limb of this interrelation between the heart and central nervous system.

Arrhythmia itself, by alterations in systemic arterial pressure and atrial and ventricular filling pressures, might be expected to produce changes in autonomic tone by altering input from baroreceptors and from cardiac mechanoreceptors. Morrison et al. (6) demonstrated increased postganglionic sympathetic nerve activity in anesthetized cats after single premature ventricular stimuli. In humans, Wallin et al. (7) observed alterations of muscle sympathetic activity during spontaneous arrhythmias including atrial fibrillation, frequent atrial premature beats and second degree atrioventricular block. These alterations were seen in association with a decrease in diastolic blood pressure during the pauses resulting from the arrhythmias. We performed experiments to quantitate the alterations in postganglionic sympathetic nerve activity resulting from single and double premature ventricular beats and to determine the afferent pathways involved. We recorded from the renal nerves in one group of dogs and made recordings simultaneously from the cardiac and renal nerves in a second group of dogs.

Methods

Fourteen mongrel dogs weighing 13 to 27 kg were anesthetized with morphine sulfate (2 to 3 mg/kg body weight, intravenously) and alpha-chloralose (80 mg/kg, intravenously) and maintained with hourly doses of alpha-chloralose (10 mg/kg). The animals were intubated and venti-
lated mechanically (Harvard respirator) with room air supplemented with oxygen. Arterial blood gases were measured at intervals and pH, Pco₂ and Po₂ were corrected as needed by adjusting tidal volume or ventilatory rate or by the administration of NaHCO₃. Body temperature was maintained by external warming.

Our experiments were performed in accordance with the animal welfare regulations of our institution and with the guiding principles of the American Physiological Society.

**Experimental preparation.** Arterial pressure was measured with a catheter in the right femoral artery connected to a pressure transducer (Century Technology). Right atrial pressure was measured in 10 dogs with a catheter passed to the right atrium from the right external jugular vein. In 10 dogs a 6F quadripolar electrode (1 cm interelectrode distance, USCI) was passed to the right ventricle from the right femoral vein. In four dogs pacing wires were sewn directly to the epicardial surface of the right ventricle after a left thoracotomy. Surface electrocardiographic lead II was displayed along with the pressures on a storage oscilloscope (Tektronix D13) and recorded on an electrostatic recorder (Gould ES1000) at paper speeds of 10 to 25 mm/s.

A midline cervical incision was made to expose the vagi and carotid arteries bilaterally. The carotid arteries were dissected free from the surrounding tissues. The carotid sinus nerves were isolated with two silk sutures bilaterally. The aortic depressor nerves were isolated from the vagosympathetic trunk with the aid of a dissecting microscope as described previously (8). Identification was confirmed by the typical appearance of the nerve and by the pulse synchronous nerve traffic recorded from the nerve. The nerves were marked for later sectioning with a single encircling silk suture. The neck was closed loosely.

A left flank incision was made so as to expose the renal artery, vein and nerves. With the aid of a dissecting microscope, a branch of the renal sympathetic nerve was identified and cut distally. The nerve was dissected free of its surrounding connective tissue and the nerve sheath was removed. Exposed nerves were bathed in mineral oil to prevent dehydration.

**Nerve recordings.** The renal sympathetic nerve was positioned on a bipolar platinum-iridium electrode connected to a probe (Grass HIP 511E), amplified by a bandpass amplifier (Grass P511) and filtered between 30 and 1,000 Hz. Amplifier output was audible over a loudspeaker, visible on the storage oscilloscope and recorded on the electrostatic recorder. The output also was led into a nerve traffic analyzer which counted spikes exceeding a preselected voltage. Each action potential that exceeded the voltage setting of the window discriminator (just above the noise) was rectified and integrated so that quantification of nerve traffic was independent of individual spike amplitude. Thus, recorded spike activity was dependent on the number and firing rate of the fibers on the recording electrodes and on the voltage level at which the window discriminator was set. Cardiac sympathetic traffic was recorded from the left ventrolateral cardiac nerve in four dogs using these same methods as described previously (8).

**Protocols.** After completion of the surgical procedure, adequate time was allowed for stabilization of heart rate, arterial pressure and nerve activity. Late diastolic pacing threshold was determined and all stimulation was carried out at a current equal to twice threshold with a programmable stimulator (Medtronic 5325).

In the first group of 10 dogs, baseline recordings of arterial and right atrial pressures, electrocardiographic lead...
II, renal sympathetic nerve activity and integrated renal sympathetic nerve activity were made. Single programmed ventricular stimuli were introduced during normal sinus rhythm beginning in late diastole and decremented in 20 to 50 ms intervals until ventricular effective refractory period was reached. Each coupling interval was repeated 5 to 20 times so that at least 50 ventricular extrastimulus sequences were available for analysis. These data were averaged and compared with averages from a comparable number of complexes during normal sinus rhythm. Six to 10 seconds were allowed between extrastimuli (Fig. 1).

After an additional baseline recording, double programmed ventricular stimuli were introduced during sinus rhythm. Coupling intervals for first and second ventricular extrastimuli were kept equal and were decremented together at 20 to 50 ms intervals until either ventricular extrastimulus failed to capture the ventricle (Fig. 2). Then both previously identified aortic depressor nerves were divided. The sutures placed around the carotid sinus nerves were tied and the nerves divided between them. After a 30 minute stabilization period, single and double programmed ventricular stimuli were introduced as before.

Finally, the blood volume was expanded by rapid infusion of 6% dextran with a total of 15 ml/kg body weight. After stabilization of sympathetic traffic, single and double programmed ventricular stimuli were introduced as before (Fig. 3). Volume expansion was performed for two reasons. First, the high level of basal renal nerve traffic after sinoaortic denervation may have made it difficult to induce further increases. Volume expansion reduced basal traffic...
to a level close to the basal level observed with the baroreflexes intact. Second, we considered it possible that the influence of cardiac receptors might be relatively small under basal conditions but might be larger after volume expansion when the discharge of these endings is augmented.

In a second group of four dogs, cardiac and renal sympathetic nerve traffic was recorded simultaneously during administration of double programmed ventricular extrastimuli. Stimulation was repeated in three of these four dogs after sinoaortic denervation.

Data analysis. Renal and cardiac sympathetic nerve activity, integrated renal and cardiac sympathetic nerve activity, right atrial and arterial pressures and electrocardiographic lead II were recorded continuously during each experiment. Baseline sympathetic traffic (impulses/s) was compared with sympathetic traffic recorded 500 to 1,500 ms after the stimulus artifact at the first extrastimulus. This interval was chosen to allow for the translation of the stimulus into an electrical event (QRS complex) and a mechanical event (ventricular contraction) and for the delay between receptor activation and alteration in renal or cardiac sympathetic traffic. In the dog, alterations in carotid sinus pressure would be expected to be reflected in the renal or cardiac sympathetic nerves after approximately 260 ms (9). Renal or cardiac sympathetic nerve traffic, or both, then was recorded 1,500 to 3,500 seconds after the stimulus artifact. This interval was chosen to evaluate the effects of the postextrasystolic potentiated beat on renal sympathetic nerve traffic.

Changes in renal and cardiac sympathetic nerve activity were evaluated by comparing traffic during the intervals defined earlier with traffic during baseline recordings using a paired t test. Systolic and diastolic blood pressure changes and pulse interval changes were evaluated with a paired t test. Pulse interval was measured from the last QRS complex to a level close to the basal level observed with the baroreflexes intact. Second, we considered it possible that the influence of cardiac receptors might be relatively small under basal conditions but might be larger after volume expansion when the discharge of these endings is augmented.

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In a second group of four dogs, cardiac and renal sympathetic nerve traffic was recorded simultaneously during administration of double programmed ventricular extrastimuli. Stimulation was repeated in three of these four dogs after sinoaortic denervation.
Volume expansion after sinoaortic denervation failed to alter these relations. Diastolic blood pressure after single programmed ventricular stimuli fell from 141 ± 7 to 117 ± 8 mm Hg (p < 0.01) as pulse interval increased from 334 ± 15 to 638 ± 41 ms (p < 0.01). Renal sympathetic nerve activity did not change (60 ± 27 to 58 ± 31 impulses/s). After double programmed ventricular stimuli, diastolic blood pressure fell from 150 ± 9 to 119 ± 8 mm Hg (p < 0.01) as pulse interval increased from 334 ± 13 to 790 ± 64 ms (p < 0.01). Renal sympathetic nerve activity did not change (65 ± 29 to 60 ± 28 impulses/s).

Alterations in renal sympathetic nerve activity 1,500 to 3,500 ms after the stimulus artifact (Fig. 5). After single programmed ventricular stimuli with arterial baroreceptors intact, systolic blood pressure of the postextra-systolic beat rose from the control value of 182 ± 8 to 203 ± 10 mm Hg (p < 0.01). Renal sympathetic nerve activity during the interval 1,500 to 3,500 ms after the stimulus artifact fell from 77 ± 5 to 59 ± 13 impulses/s (p < 0.01). After double programmed ventricular stimuli systolic blood pressure rose from 182 ± 8 to 200 ± 11 mm Hg (p < 0.01). Renal sympathetic nerve activity during the interval 1,500 to 3,500 ms after the stimulus artifact fell from 86 ± 10 to 56 ± 10 impulses/s (p < 0.01). Changes in renal sympathetic nerve activity were abolished by sinoaortic denervation. Volume expansion after sinoaortic denervation did not modify this response.

Degree of stimulus prematurity and increase in renal sympathetic nerve activity. Multiple coupling intervals were tested in each dog. The number tested depended on the difference between sinus cycle length and ventricular effective refractory period and varied from 3 to 10 per dog. Greater degrees of prematurity produced greater increases in renal sympathetic nerve activity (r = 0.40, p < 0.01) (Fig. 6).

Responses of cardiac nerve traffic 500 to 1,500 ms after the stimulus artifact (Fig. 7). After double programmed ventricular stimulation in four dogs, diastolic blood

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Figure 5. Individual and mean (± SEM) values for systolic blood pressure (SBP) and renal sympathetic nerve activity (RSNA) 1,500 to 3,500 ms after the stimulus artifact during control (C) and after single (S) and double (D) programmed ventricular stimuli before and after sinoaortic denervation (SAD).

Figure 6. Relation between coupling interval expressed as percent of sinus RR interval and change in renal sympathetic nerve activity (RSNA) after single programmed ventricular stimuli.

Figure 7. Responses (in four additional dogs) of simultaneously recorded cardiac (solid bars) and renal (open bars) sympathetic traffic to double programmed ventricular stimuli during the 500 to 1,500 ms after the stimulus artifact. Each pair of bars illustrates the results from one experiment. The associated changes in pulse interval (PI) (ms) and diastolic blood pressure (DBP) (mm Hg) are listed below each pair of bars (C = control; P = pacing during).
pressure fell by 34 ± 1 mm Hg and cardiac sympathetic traffic increased by 86 ± 16% from a control value of 78 ± 17 impulses/s. Similar increases in simultaneously recorded renal nerve traffic (82 ± 12%) were observed (from control of 91 ± 19 impulses/s). These increases in renal and cardiac nerve traffic were significant but did not differ from each other. Decreases in cardiac and renal nerve traffic were observed in the postextrasystolic beat as described for the renal nerves (Fig. 5).

**Discussion**

**Ventricular arrhythmias and sympathetic nerve activity.** Ample experimental evidence suggests an important role for the nervous system in the production of ventricular arrhythmias in both ischemic and normal myocardium (1-7). The input into the central nervous system leading to changes in sympathetic tone has been examined extensively in animal models of ischemia (1-4). Hypotension occurring as a result of myocardial ischemia causes decreased input into the central nervous system from the arterial baroreceptors which, in turn, leads to increased efferent sympathetic nervous activity (10). Activation of vagal afferents by myocardial ischemia decreases efferent sympathetic activity while increasing efferent parasympathetic activity (11). Activation of cardiac receptors with sympathetic afferents may lead to increased efferent sympathetic activity (12). The balance of these effects determines the net integrated responses of sympathetic activity to the heart.

While ventricular arrhythmias are common in the setting of acute myocardial infarction, most episodes of sudden cardiac death in humans occur as a result of ventricular fibrillation remote from myocardial infarction. Thus, other forms of afferent input may be important in the initiation of central nervous system changes leading to or worsening arrhythmia. Wallin et al. (7) in 1974 described increases in muscle sympathetic nervous activity resulting from spontaneous alterations in cardiac rhythm in humans. The bursts of sympathetic activity that they observed corresponded to prolonged diastoles resulting from pauses occurring during second degree atrioventricular block, during prolonged RR intervals in atrial fibrillation and after atrial premature beats. Greater prolongations of diastole and greater falls in diastolic blood pressure more reliably produced sympathetic bursts. Because premature ventricular beats may be predictive of subsequent sudden cardiac death in selected groups of patients (13), we examined the relation between programmed ventricular stimuli and renal and cardiac sympathetic activity. Our data provide unequivocal evidence of excitation of sympathetic outflow to the heart as well as to the kidney during periods of induced ventricular arrhythmia.

**Single versus double premature ventricular stimuli.** Single premature ventricular stimuli were delivered at varying coupling intervals during normal sinus rhythm to simulate the occurrence of single, uniform ventricular premature beats at varying coupling intervals. Renal sympathetic nerve activity was measured during a baseline period and during two periods of interest after the stimulus artifact. Consistent increases in renal sympathetic nerve activity were observed during the pause after single premature ventricular stimuli. The magnitude of the increase was inversely related to the coupling interval.

*Increases in renal sympathetic nerve activity were greater after double premature ventricular stimuli despite similar decreases in diastolic blood pressure.* The pauses between effective mechanical contractions were longer after double premature ventricular stimuli. These data suggest a relation between both the degree of prematurity and length of pause and the increase in renal sympathetic nerve activity and support the conclusion of Wallin et al. (7) that sinoaortic baroreceptors mediate the afferent limb of the reflex.

**Role of sinoaortic denervation and sinoaortic baroreceptors.** Sinoaortic denervation was performed to further substantiate this relation. After sinoaortic denervation, decreases in diastolic blood pressure and increases in pulse interval were observed again. However, there was no change in renal or cardiac sympathetic nerve activity after single or double programmed ventricular stimuli. Volume expansion after sinoaortic denervation decreased overall sympathetic activity, but did not lead to any changes in renal nerve activity with programmed ventricular stimuli. As sinoaortic denervation leaves intact the sympathetic and vagal afferents from the heart, the absence of any changes after sinoaortic denervation suggests that sympathetic and vagal afferents are not importantly involved in the reflex enhancement of sympathetic efferent activity following programmed ventricular stimuli observed with all afferent pathways intact. The decreases in renal (Fig. 5) and cardiac sympathetic nerve activity after the postextrasystolic beat also appear to be mediated by input from sinoaortic baroreceptors because they also were abolished by sinoaortic denervation.

**Clinical implications.** The clinical importance of these transient alterations of sympathetic activity is not entirely clear. However, they may serve to explain, in part, some observations made in humans. Ventricular arrhythmias are common in patients after myocardial infarction (13). Recent retrospective ambulatory monitoring data from patients who had ventricular fibrillation during the period of monitoring have shown periods of minutes to hours of increasingly frequent and complex ventricular ectopic activity before the onset of ventricular fibrillation (14,15). On the basis of our studies, sympathetic activity could be expected to increase after ventricular premature beats or couplets. These increases may enhance the likelihood of sustained ventricular tachycardia or fibrillation.

*In patients with the long QT syndrome and a history of sudden cardiac arrest, improvement may occur after left stelllectomy.* While this has been attributed to the resulting
shortening of the QT interval, it may be related, in part, to the blockade of sympathetic input that results from spontaneous arrhythmia. Many of these patients have frequent episodes of polymorphic nonsustained ventricular tachycardia that could be expected to increase efferent sympathetic activity (16).

The importance of the postextrasystolic decreases in efferent sympathetic activity is less clear. Experiments evaluating the effects of increased sympathetic tone on ventricular fibrillation threshold have examined the effects of longer periods of sympathetic stimulation (17). However, rapid shifts in sympathetic tone may be important in creating the milieu for arrhythmia.

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References