Sympathetic afferent nerve activity of right heart origin

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The objectives of this study were, first, to verify the existence of right heart mechanoreceptors whose afferent nerves traverse the upper thoracic white rami communicantes. These mechanoreceptors were studied by observing changes in average, maximum, and total nerve spike frequency when right atrial and right ventricular systolic and diastolic pressures were altered by means of intracardiac balloons. Receptors that responded to volume and pressure changes were found in both the right atrium and right ventricle. Nerve activity in these afferents increased with increasing right atrial and right ventricular pressures. These mechanoreceptors were more responsive in the upper physiological ranges of right heart pressures. In most nerve fibers studied, maximum activity occurred during right atrial and right ventricular diastole.

METHODS

Six mongrel dogs, 20–28 kg, were anesthetized with sodium pentobarbital (Nembutal: Abbott Laboratories), 35 mg/kg, injected intravenously. The animals were intubated with auffed endotracheal tube and placed on positive-pressure ventilation with a Bird Mark I respirator. Arterial Po2, Pco2, and pH were measured.
ured at 30-min intervals using a Radiometer multiple-electrode blood gas and pH analyzer. The Pco₂ was maintained between 35 and 40 mmHg, and the Po₂ greater than 200 mmHg. The pH was regulated between 7.35 and 7.44 with additions of sodium bicarbonate as required. The bubble oxygenator was equipped with a heat exchanger, which was regulated to maintain the esophageal temperature between 37 and 38°C. A Sarns roller pump was used to return the oxygenated blood to the animal's circulation through cannulas placed in each femoral artery. The pump speed was adjusted to maintain mean systemic perfusion pressure between 65 and 90 mmHg. In the six experimental animals the mean systemic pressure was 80 mmHg.

With the animals on bypass, polyethylene tubes with latex balloons fixed at the ends were inserted into the right ventricle and right atrium through an incision in the right atrial appendage. The polyethylene tubes were attached to Statham pressure transducers to record intraluminal pressures. All pressures were referenced to heart level in these open-chested animals by placing the manometers at the level of the heart. Saline was injected into the balloons through a three-way stopcock to increase ventricular and atrial volumes and pressures. The compliance characteristics of the balloons were determined from pressure-volume curves for each balloon. In most instances, the injected fluid volume was less than the volume required to produce a measurable contribution to balloon wall tension. The pressures shown in subsequent figures and tables are expressed as corrected peak and pulsatile pressures.

Nerve recording. The sympathetic chain on the right side was dissected from the surrounding connective tissue. The first and second thoracic white rami communicantes were isolated and cut to eliminate efferent activity. The peripheral end of the nerve was divided into several longitudinal, small multifiber sections under a Bausch & Lomb dissecting microscope and laid across a pair of bipolar tungsten carbide electrodes under mineral oil warmed to 37°C. The electrodes were connected to a high-input impedance preamplifier in series with another amplifier equipped with high-pass and low-pass filters. The signal was visually displayed on a Tektronix type 564B oscilloscope and audibly monitored with a loudspeaker.

In order to measure nerve conduction velocities, the right cardiac stellate nerve or the nerve connections between the right stellate ganglion and the right cardiac cervical ganglion were stimulated with a constant-current stimulator using the following stimulation parameters: a current of 6 mA, a pulse width of 0.5 ms, and a frequency of 1.5 Hz. The evoked action potentials were recorded in the right second or third thoracic white rami in single-fiber preparations. The distance between stimulating and recording electrodes was carefully measured using a wet thread laid adjacent to the nerve pathway. Prior to stimulation, nerve fiber preparations were selected for study if they exhibited cyclic activity with events of the cardiac cycle and changes in activity with changes in either right atrial or right ventricular pressure. The range of conduction velocities for the fast component of the evoked potentials in four different nerve preparations was 15–30 m/s.

Data storage and analysis. Right atrial pressure, right ventricular pressure, electrocardiogram, and nerve activity were recorded using a Tandberg four-channel tape recorder. Systemic blood pressure was monitored during the experiment on a General Electric digital monitor and recorded on a Grass polygraph along with EKG and the right heart pressures. Data analysis consisted of frequency histograms of spike discharge patterns. The upstroke of the R wave of the EKG signal was used to initiate the histogram analysis. Nerve activity was conditioned by an electronic window discriminator that allowed only spike activity of a predetermined amplitude to be counted by an Ortec histogram computer. An accumulation of nerve activity occurring over 64 cardiac cycles was stored in the computer memory and printed out with an X-Y recorder. Atrial and ventricular pressure curves were superimposed on the nerve activity using a procedure similar to that described above.

The resonant frequency of the hydraulic pressure-measuring system, determined using sinusoidal pressure oscillations, was 32 Hz. This system permits accurate measurement of dP/dt up to 6,000 mmHg/s. The lag time of the system, as determined from ramp input to a second order underdamped system, was 5–7 ms. With conduction velocities of 15–30 m/s and a distance of 10 cm from the right heart to the white rami, nerve recording lag time was 3–7 ms. Therefore, the difference in the time delays between the hydraulic system and the nerve recording system was within the limits of one 10-ms interval used for histogram analysis of nerve activity and intracardiac pressures.

The nerve spike frequency accumulated in 10-ms bins was counted during atrial and ventricular systole and diastole at each of the controlled pressure levels. Mechanical systole and diastole of the right atrium and right ventricle were measured from pressure tracings. The nerve activity was expressed with reference to mechanical systole and diastole. Three indices of nerve activity were considered in the analysis of the data: a) the average discharge frequency during systole and diastole, b) the maximum discharge frequency during systole and diastole, and c) the total number of spikes during systole and diastole. The average discharge frequency was obtained by taking the number of spikes during systole (diastole) and dividing by the time of systole (diastole). The maximum discharge frequency was based on the maximum number of spikes that occurred in any of the 10-ms intervals. Each of these indices was computed from histograms which were based on 64 cardiac cycles.

Within a single nerve preparation, each of the indices was normalized with respect to its largest value in diastole and in systole and expressed as a percentage of maximum for each controlled pressure level. These normalized indices allowed the data from several preparations to be expressed as the calculated mean with standard deviation and standard error. This method of normalization was used for nerve activity at controlled pressure levels within the same animal and was also used for comparisons between animals. The variability of maximum values for the six experimental animals ranged from 8 to 110 spikes/10-ms bin for right ventricular pressure changes and 8–77 spikes/10-ms bin for right atrial pressure changes.
RESULTS

The results are based on nerve activity recorded from a total of 13 different single-fiber or small multifiber nerve preparations in 6 experimental animals. Examples of the response of nerve spike frequency to changes in right atrial systolic and right ventricular systolic pressures are shown in Figs. 1 and 2. Figure 1 shows changes in afferent nerve spike frequency that occurred when right ventricular systolic pressure was maintained at 20 mmHg and right atrial systolic pressure was varied from 0 to 20 mmHg. Nerve activity occurred predominantly during ventricular diastole and at the onset of atrial systole and increased with an increase in right atrial systolic pressure.

Figure 2 shows changes in afferent nerve spike frequency that occurred when right atrial peak systolic pressure was maintained at 10 mmHg and right ventricular systolic pressure was varied from 0 to 40 mmHg. Right ventricular systolic pressure was varied by systematically increasing right ventricular balloon volume. The pressure tracings are distorted at low ventricular volumes and pressures as a result of the balloon catheter system used to change ventricular volume and to record pressure. Afferent nerve activity increased in this preparation with an increase in right ventricular systolic pressure and volume. This increase in nerve activity occurred principally in late systole and early diastole.

Figure 3 shows the output of the histogram computer. This data display is representative of changes in nerve spike frequency as a result of changes in right atrial and right ventricular pressure. Maximum activity occurs during that portion of the cardiac cycle when both the atrium and ventricle are in diastole. The time interval of this maximum spike frequency is approximately 20 ms.

The data in Table 1 were obtained from six small multi-fiber nerve preparations in three experimental animals. The table depicts nerve activity as a function of increasing right atrial systolic pressure with peak right ventricular systolic pressure held at 20 mmHg. Signal-to-noise ratio was enhanced electronically. Spike amplitudes are approximately 50 μV. EKG belongs to bottom 2 traces.

The data in Table 2 were obtained from seven small multifiber nerve preparations in four experimental animals. This table depicts nerve activity as a function of increasing right ventricular systolic pressure with right atrial systolic pressure held at 10 mmHg. Similar results were obtained when maximum discharge frequency and total nerve activity were analyzed with respect to changes in right atrial pressure.
A representative spike frequency histogram of 64 cardiac cycles when right atrial systolic pressure was varied between 0 and 20 mmHg and right ventricular systolic pressure was held constant at 20 mmHg. (RAP = right atrial pressure; RVP = right ventricular pressure; VS = ventricular systole; VD = ventricular diastole; AS = atrial systole; AD = atrial diastole.)

There were significant increases in nerve activity during right ventricular systole and diastole. In most preparations, the maximum value for average discharge frequency occurred in both systole and diastole when right ventricular systolic pressure was 40 mmHg. Significant increases in nerve activity during right ventricular systole and diastole occurred between 0 and 30 mmHg and between 30 and 40 mmHg (P < .05). The nerve activity at 0, 10, 20, and 30 mmHg were all significantly less than the nerve activity at 40 mmHg right ventricular systolic pressure for both systole and diastole (P < .05). Similar results were obtained when maximum discharge frequency and total nerve activity were analyzed with respect to changes in right ventricular pressure. Verification of the right heart origin of these mechanoreceptors was demonstrated by probing the right atrium and right ventricle. Nerve fibers which responded only to changes in right atrial pressure were located specifically in the right atrium by probing. Nerve fibers which responded only to changes in right ventricular pressure were located in the right ventricle.

**DISCUSSION**

An increase in sympathetic afferent discharge recorded from the right upper thoracic white rami occurred as a function of incremental increases in isovolumic right atrial and right ventricular pressures. Average, maximum, and total spike activity increased significantly. This response was consistent over 64 cardiac cycles at each pressure increment.

It has not been shown previously that incremental increases in right heart intraluminal pressure can effect an increase in sympathetic afferent discharge. Uchida et al. (14) and Ueda et al. (15) demonstrated increases in sympathetic discharge produced by blunt probing of the right heart. Both authors recorded this activity from the upper right, second thoracic white ramus. Armour (1) observed an alteration in spike activity in the right stellate cardiac nerve in response to displacement of the right atrium.

When right atrial systolic pressure was increased, differences were noted between the response of the nerve activity during atrial systole and atrial diastole. During systole, there was no significant increase in activity between 0 and 5 mmHg; however, during diastole, there was a significant increase between 0 and 5 mmHg. Displacement of the right atrium by 10.220.33.3 on April 30, 2017 http://ajplegacy.physiology.org/ Downloaded from

### TABLE 1. Response of afferent nerve activity to changes in right atrial systolic pressure

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<th>Changes in Right Atrial Systolic Pressure With Right Ventricular Systolic Pressure Held at 20 mmHg</th>
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<td>Nerve activity, % max</td>
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<td>Right atrial systole, average frequency</td>
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<td>Right atrial diastole, average frequency</td>
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<td>Values are means ± SE.</td>
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### TABLE 2. Response of afferent nerve activity to changes in right ventricular systolic pressure

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<th>Changes in Right Ventricular Systolic Pressure With Right Atrial Systolic Pressure Held at 10 mmHg</th>
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<tr>
<td>Nerve activity, % max</td>
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<td></td>
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<tr>
<td>Right ventricular systole, average frequency</td>
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<tr>
<td>Right ventricular diastole, average frequency</td>
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Cardiac sympathetic afferent activity was probably adequate at 5 mmHg to produce an increased firing; whereas, during systole at the same level of right atrial pressure, the contracting atrium might not allow the mechanoreceptor to be displaced sufficiently to produce an increase in nerve activity.

Increases in right ventricular systolic pressure also elicited significant increases in average and maximum spike frequency and total spike activity. These data are in agreement with increased afferent nerve activity during right ventricular diastole when the walls of the right heart are undergoing maximal displacement. These receptors appear to be displacement receptors that may rapidly adapt to a displacement stimulus as indicated by the short interval of their maximum discharge that occurs over an average time of only 20 ms.

This study has, first of all, verified the existence of right heart mechanoreceptors whose afferents traverse the right upper thoracic white rami. This is in agreement with Randall et al. (11), who stated that right heart sympathetic afferents traverse the right upper thoracic sympathetic chain and the left heart sympathetics traverse the left chain. Characterization of some mechanoreceptors of right heart origin was also accomplished. From Fig. 3 it can be clearly seen that there are displacement receptors in the right atrium and the right ventricle. Pressure receptors responsive to increases in atrial and ventricular systolic pressures were also observed.

The largest differences in nerve activity with pressure changes were noted only at the upper physiological ranges of right ventricular pressure. Because of the high right heart pressures required to elicit this increased afferent nerve activity, a reflex protective mechanism may be involved. This study may shed some light on the sympathetic afferents involved in cardiovascular and cardiopulmonary reflex mechanisms studied by some other investigators (7).

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REFERENCES