Sympathetic afferent nerve activity of right heart origin

D. R. KOSTREVA, E. J. ZUPERKU, R. V. PURTOCK, R. L. COON, AND J. P. KAMPINE
Departments of Physiology and Anesthesiology, The Medical College of Wisconsin, and Wood Veterans Administration Hospital, Milwaukee, Wisconsin 53226

KOSTREVA, D. R., E. J. ZUPERKU, R. V. PURTOCK, R. L. COON, AND J. P. KAMPINE. Sympathetic afferent nerve activity of right heart origin. Am. J. Physiol. 229(4): 911-915. 1975.—Six mongrel dogs anesthetized with sodium pentobarbital and paralyzed with gallamine triethiodide were studied on total cardiopulmonary bypass. This study verified 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 both 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. The second through fifth ribs were removed on the right side. A thoracotomy was performed at the left fourth intercostal space, and the sternum was cut transversely. The procedure provided adequate exposure for the placement of cannulas and permitted unimpeded access to the sympathetic chain and white rami. All studies were conducted with the heart suspended in an open pericardial cradle which allowed the location of the mechanoreceptors to be confirmed by probing the right heart with a blunt insulated plastic probe.

The right heart origin of the mechanoreceptors was verified by systematically changing either right atrial or right ventricular pressure while recording afferent nerve activity in a nonejecting heart preparation. Right atrial or right ventricular pressure was changed by altering the volume of saline contained in balloon-tip catheters placed in the right atrium or right ventricle. The location of the receptors was further verified by systematically probing the surfaces of the heart while recording afferent nerve activity. Bursts of activity were associated with probing specific sites and were absent when all other areas of the heart were probed.

A polyethylene cannula was inserted into the right axillary artery and positioned in the aortic arch. The cannula was connected to a Statham P23Db pressure transducer and Grass polygraph to measure the systemic perfusion pressure. The electrocardiogram was monitored continuously using pin electrodes placed around the thoracotomy in a configuration that produced a maximal R wave.

Five minutes prior to bypass, the animals were heparinized with sodium heparin (The Upjohn Company) 500 U/kg; this was followed by 200 U/kg at hourly intervals. Nervomuscular blockade was produced using gallamine triethiodide (Flaxedil: Davis and Geck) 2 mg/kg injected intravenously. The animals were observed for depth of anesthesia, and supplemental doses of anesthetic (one-fifth the initial dose) were given as needed, followed by 1 mg/kg of gallamine triethiodide.

Systemic heart-lung bypass. The animals were placed on total heart lung bypass. Bardic cannulas were inserted into the superior and inferior venae cavae to collect venous return. Another cannula was inserted into the right ventricle through the right atrial appendage to collect venous blood from the coronary sinus, thebesian, and cardiac veins. Venous blood was returned to a bubble oxygenator where systemic blood gas concentrations could be controlled by adjusting the inflow gas mixture of carbon dioxide and oxygen. Arterial PO2, PCO2, and pH were measured.
ured at 30-min intervals using a Radiometer multipletrode blood gas and pH analyzer. The $P_{O_2}$ was maintained between 35 and 40 mmHg, and the $P_{O_2}$ 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 ballons 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 adjacent to the nerve pathway. Prior to stimulation, recording electrodes was carefully measured using a wet thread laid adjacent to the nerve pathway. Pathway 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 52 Hz. This system permits accurate measurement of $\frac{dP}{dt}$ 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: 1) the average discharge frequency during systole and diastole, 2) the maximum discharge frequency during systole and diastole, and 3) 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 multifiber nerve preparations in three experimental animals. The table depicts nerve activity as a function of increasing right atrial systolic pressure with right ventricular systolic pressure held at 20 mmHg. The data represent nerve activity expressed as the percent of the maximum value for average spike activity during right atrial systole and diastole. In most preparations, the maximum value for average discharge frequency occurred in both systole and diastole when right atrial systolic pressure was 20 mmHg. Significant increases in nerve activity during right atrial systole were observed between 0 and 15 mmHg and 5 and 20 mmHg \((P < .05)\). The nerve activity at all lower pressures was significantly less than at 20 mmHg right atrial systolic pressure. Significant increases in nerve activity occurred during right atrial diastole between 0 and 5 mmHg, between 5 and 10 mmHg, and between 15 and 20 mmHg \((P < .05)\). Similar results were obtained when maximum discharge frequency and total nerve activity were analyzed with respect to changes in right atrial pressure.

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. These data represent nerve ac
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.)

Activity expressed as the percent of the maximum value for average spike activity during 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.

Other fibers which responded only to changes in right ventricular pressure were located in the right ventricle by probing. The receptive fields were as follows: the epicardial surface of the right atrium, the junction of the right atrium and superior and inferior venae cavae, the epicardial surface of the right ventricle, the area near the anterior and posterior descending coronary arteries, and the main pulmonary artery.

**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 and right ventricle

| TABLE 1. Response of afferent nerve activity to changes in right atrial systolic pressure |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Changes in Right Atrial Systolic Pressure With Right Ventricular Systolic Pressure Held at 20 mmHg |
| Nerve activity, % max          | 0 mmHg | 5 mmHg | 10 mmHg | 15 mmHg | 20 mmHg         |
| (n = 6 in 3 dogs)               | 0      | 2      | 3      | 3      | 2               |
| Right atrial systole, average frequency | 51 ± 11 | 57 ± 10 | 73 ± 9 | 83 ± 7 | 92 ± 7         |
| Right atrial diastole, average frequency | 45 ± 4  | 60 ± 7  | 77 ± 7 | 80 ± 6 | 99 ± 1         |
| Values are means ± SE.         |        |        |        |        |                 |

| TABLE 2. Response of afferent nerve activity to changes in right ventricular systolic pressure |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Changes in Right Ventricular Systolic Pressure With Right Atrial Systolic Pressure Held at 10 mmHg |
| Nerve activity, % max          | 0 mmHg | 10 mmHg | 20 mmHg | 30 mmHg | 40 mmHg         |
| (n = 7 in 4 dogs)               | 0      | 1      | 2      | 2      | 2               |
| Right ventricular systole, average frequency | 30 ± 10 | 33 ± 8  | 41 ± 9  | 32 ± 15 | 40 ± 0         |
| Right ventricular diastole, average frequency | 30 ± 9  | 36 ± 7  | 46 ± 0  | 50 ± 16 | 99 ± 1         |
| Values are means ± SE.         |        |        |        |        |                 |
CARDIAC SYMPATHETIC AFFERENT ACTIVITY

Receptor occurring during diastole 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 probing observed by Armour (1) and Ueda et al. (15). Similar results were obtained in studies of the left ventricle described by Coleridge et al. (2).

As seen in Fig. 3, the maximal nerve discharge occurred during atrial and 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).

This study was supported by the General Electric Company and the Wisconsin Heart Association.

Received for publication 23 May 1974.

REFERENCES