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Receptors in the Canine Lung Which Respond to Vascular Pressure Changes (39985)

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Vagal afferent nerve activity from the lungs is involved in the dyspnea of heart failure. Constantine (1) found that pulmonary congestion increased the discharge frequency of slowly adapting stretch receptors. In addition, vagal afferent nerve activity from receptors located in the main branches of the pulmonary artery (2), pulmonary veins (3), and walls of intrapulmonary vessels (4, 5) which respond to vascular pressure changes were also reported. The functional relationships between vascular pressure and neural discharge frequency from intrapulmonary mechanoreceptors, however, have not been determined. The objective of the present study, therefore, was to determine the relationships between neural discharge frequency and pulmonary vascular pressures of receptors located within the lung.

Materials and methods. Afferent nerve activity was studied in four single and six small multifiber nerve preparations in five mongrel dogs (18-28 kg) anesthetized with 30 mg/kg of sodium pentobarbital (Nembutal, Abbott Laboratories). Ventilation and pulmonary arterial perfusion of the left lower lobe (LLL) were isolated from that of the animal, *in situ,* to permit optimum control of pulmonary hemodynamics and airway pressure. The LLL was exposed by removing ribs 2 through 8 on the left side. Left middle and upper lobes were ligated and removed. The airways of the LLL and right lung were separated by using a tube-within-a-tube system which allowed cannulation of the left bronchus.

Separate ventilation of the right lung and LLL was accomplished by a square-flow, solinoid respirator which enabled measurement of LLL static compliance and resistance as previously described (6). There were no appreciable differences in these measurements between the autoperfused LLL and the pump-perfused LLL during experimental manipulations. Systemic and LLL blood-gas tensions were maintained at a P_{O_2} of 100-300 mm Hg and a P_{CO_2} of 34-44 mm Hg at a pH of 7.35-7.44.

Two methods, described below, were used to systematically alter pulmonary vascular pressures.

Ramp changes in lobar vascular pressures (Method I). The LLL pulmonary artery and femoral vein were cannulated. Blood from the femoral vein was pumped through the lobe using a Sarns nonocclusive roller pump and returned to the animal via the intact lobar vein. Ramp changes in LLL vascular pressures were produced by either increasing pump speed or by tightening a snare placed around the lobar vein to increase outflow resistance.

Sinusoidal and step changes in LLL vascular pressures (Method II). Figure 1 shows the method used to produce sinusoidal and step alterations in LLL vascular pressures. The LLL vein, LLL branch of the pulmonary artery, and femoral vein were cannulated. Blood from a Mariotte bottle reservoir placed in a water bath (36-38°) was used to perfuse the LLL. Outflow blood was collected in a reservoir which could be raised or lowered to produce step changes in vascular pressures. Retrograde (vein to artery) and forward (artery to vein) perfusion of the LLL were used to produce differential alterations of venous and arterial pressures. Sinusoidal pulsations of desired amplitude and frequency were superimposed on a mean vascular pressure by using a Harvard respirator (Fig. 1). Sinuso-

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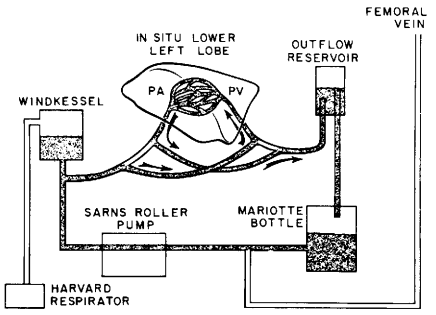

FIG. 1. Schematic diagram of the *in situ* LLL perfusion system. The stippled tubes show the retrograde perfusion circuit. Arrows show the direction of blood flow. Sinusoidal oscillations of vascular pressure were produced by changing the air pressure within the windkessel using a Harvard respirator.

idal manipulations enabled evaluation of receptor discharge pattern over a wide range of vascular pressures and determination of the relative intrapulmonary location (arterial or venous) of the receptor (see Results). Statham pressure transducers were used to monitor LLL airway and vascular pressures. Manipulations of pulmonary vascular pressures were performed when the LLL was apneic.

Nerve recording. Nerve activity was obtained from slips of nerve dissected from the left vagosympathetic trunk and placed across tungsten carbide bipolar electrodes contained in a chamber filled with warmed mineral oil. Nerve fibers selected for study were those responding to LLL vascular pressure changes. Both single and small multifiber nerve activity responded to vascular pressure alterations. Nerve activity was amplified, filtered, and then, together with LLL arterial, venous, and airway pressures, recorded on magnetic tape and displayed on a Honeywell 1912 Visicorder.

Data analysis. The tape-recorded nerve activity was fed into a window discriminator which selected action potentials on the basis of amplitude. An upper voltage threshold was selected to exclude action potentials above a desired amplitude, and a lower voltage threshold excluded action potentials below a desired spike amplitude. A standard output pulse was generated for each nerve spike falling between these voltage thresholds. Thus, with small multifiber nerve preparations a single active nerve fiber could be selected for analysis.

For sinusoidal variations of vascular pressures, the discriminator output was accumulated in 50-msec time intervals and averaged for eight pressure cycles using an Ortec Model 4620 histogram computer. The upstroke of the sinusoidal waveform was used to initiate the analysis of nerve activity, and LLL arterial and venous pressures. The resulting poststimulus time histograms and ensemble averages of LLL vascular pressures were plotted using a Honeywell 530 X-Y plotter (Fig. 3). The relationships between ramp changes of pulmonary vascular pressures and nerve activity were analyzed in a similar fashion, but the Ortec analyzer was triggered to begin the analysis manually.

Results. Ramp changes (Method I) of pulmonary vascular pressures were performed in five nerve preparations in four animals. Three fibers showed an increase in frequency of discharge when LLL venous pressure was increased by lobar vein constriction but not when pump speed was increased. Increasing pump speed increased LLL arterial pressure, but only small changes in LLL venous pressure occurred. One receptor was located within the lung close to the hilum by gently stroking the surface of the lung with an insulated probe. Inflating the lungs increased nerve discharge frequency. These receptors, therefore, were probably Hering-Breuer stretch receptors. The slopes of the linear regression lines (sensitivity) for nerve discharge frequency on venous pressure were 1.15 ($F = 7.63$, $N = 34$), 1.72 ($F = 126$, $N = 168$), and 0.510 impulses (imp)/sec/mm Hg ($F = 57$, $N = 51$) for these three nerve preparations. All regressions were significant ($P \leq 0.05$) indicating that impulse frequency was linearly related to pulmonary venous pressure. Venous pressure ranged from 0 to 40 mm Hg and impulse frequency from 0 to 90 imp/sec.

In two additional nerve preparations impulse frequency increased both when LLL vein was constricted and when pump speed was increased. These receptors did not significantly respond to inflation of the LLL. No adaptation of receptor discharge occurred when vascular pressures were held

constant for 1 min. The slopes of the regression lines of nerve activity on arterial pressure when pressure was increased by venous constriction were 2.98 (F = 188, N = 111) and 1.9 imp/sec/mm Hg (F = 155, N = 47); the slopes of the regression lines calculated when arterial pressure was increased by increasing perfusion pump speed were 1.45 (F = 92, N = 61) and 0.59 imp/sec/mmHg (F = 32, N = 45), respectively. The location of these receptors as either arterial or venous could not be firmly established using this method of perfusion.

Sinusoidal variations of LLL vascular pressures were used to define the stimulus-response characteristics and location of three pulmonary receptors in three animals. A representative response of nerve activity during pulsatile perfusion is shown in Fig. 2. Two frequencies of sinusoidal oscillation are depicted. Note that no significant change in airway pressure occurred. Poststimulus time histograms of data from this same nerve preparation are depicted in Fig. 3. It should be noted that as the pressure wave frequency increased, the venous pressure oscillation lagged the arterial. Examination, particularly of the highest frequency (56 cpm), indicates that cyclic nerve activity

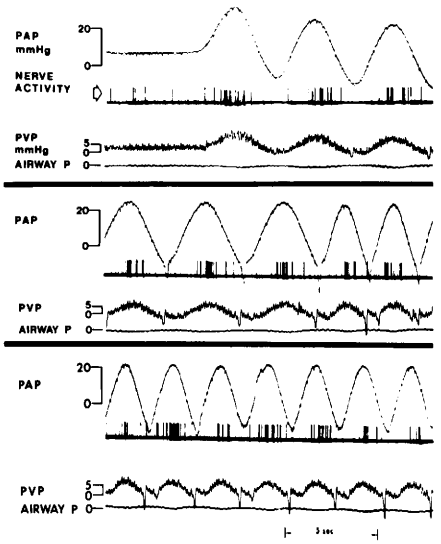

FIG. 2. Representative changes in nerve activity resulting from pulmonary vascular sinusoidal pulsation. The top trace is pulmonary arterial pressure (PAP); second from the top, nerve activity; third from the top, pulmonary venous pressure (PVP); fourth from the top, airway pressure.

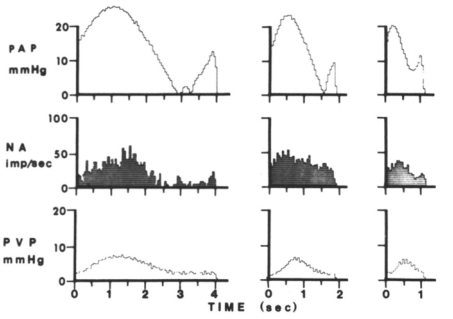

FIG. 3. Poststimulus time histograms of nerve activity and lobar vascular pressures at three pressure wave frequencies. The LLL was apneic and perfused in the forward direction. Top traces are histograms of pulmonary arterial pressure (PAP); middle, nerve activity (NA); and bottom, pulmonary venous pressure (PVP).

was more closely related to the arterial pressure wave than the venous pressure wave. This was confirmed by comparing correlation coefficients calculated for each pressure wave frequency studied. Correlations between LLL arterial pressure and nerve activity were r = 0.85 (N = 76) for 16 cpm, r = 0.80 (N = 38) for 42 cpm, and r = 0.84 (N = 22) for 56 cpm (all correlations were significant, $P \leq 0.05$). Correlations between venous pressure and nerve activity were r = 0.85 for 16 cpm, r = 0.49 for 42 cpm, and r = 0.43 for 56 cpm. The correlation between arterial pressure and nerve activity remained essentially the same as the pressure wave frequency increased but, the correlation between venous pressure and nerve activity progressively decreased. This receptor, therefore, was probably located in or near an intrapulmonary arterial vessel. Another receptor had similar response characteristics. Both did not respond to inflations of the LLL and slowly adapted to a constant elevated arterial pressure. There was a significant linear regression at the pressure wave frequencies studied with average slopes of 0.24 (F = 3.8, N = 136) and 2.44 imp/sec/mm Hg (F = 126, N = 161) for these two nerve preparations. Pulmonary arterial pressure ranged from 0 to 45 mm Hg, and impulse frequency ranged from 0 to 48 imp/sec.

Figure 4 is an example of poststimulus time histograms obtained from another

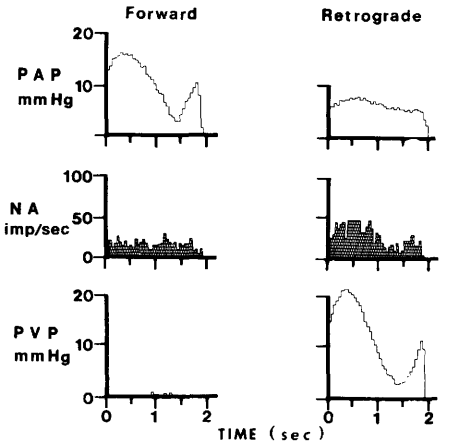

FIG. 4. Representative poststimulus time histograms of lobar arterial pressure (PAP), nerve activity (NA), and lobar venous pressure (PVP) during forward pulsatile perfusion (left) and retrograde pulsatile perfusion (right). Records of nerve activity were from the same nerve preparation. The LLL was apneic during these pressure manipulations.

nerve preparation. Cyclic nerve activity occurred with retrograde pulsatile perfusion but not forward pulsatile perfusion. This receptor, therefore, was located in or near a LLL intrapulmonary venous vessel. Results similar to those presented in Fig. 4 were obtained at three additional pressure wave frequencies (i.e., 15, 23, and 34 cpm). There were significant linear regressions ($P \leq 0.05$) of nerve activity on venous pressure at all pressure wave frequencies studied. The average slope of these regression lines was 2.0 imp/sec/mm Hg ($F = 42$, $N = 168$). This receptor did not significantly respond to lung inflation.

Discussion. Three types of intrapulmonary receptors have been extensively studied: irritant, Hering–Breuer stretch, and juxtupulmonary capillary (type J) receptors (7). In the present study several Hering–Breuer stretch receptors, identified by their response to lung inflation, responded to alterations in pulmonary venous pressure. Previous studies have shown that pulmonary congestion (1) and the cardiac pressure pulse (5, 8) can alter the discharge pattern of Hering–Breuer stretch receptors. The relationships between pulmonary vascular pressure and impulse frequency, however, were not determined. From results of the present study it appears that the relationship between pulmonary venous pressure and impulse frequency was linear over a wide range of vascular pressure for those receptors responsive to pulmonary vascular pressure changes.

Five receptors which did not respond to inflation of the LLL but did respond to elevated pulmonary vascular pressure were also identified. Because these receptors did not show significant adaptation to constant elevated vascular pressures, it is unlikely that these receptors were irritant receptors (7). In addition, because there was an immediate increase in nerve activity upon elevation of lobar vascular pressure and the maximum impulse frequency of these receptors was greater than 20 imp/sec, it is unlikely that these receptors are type J receptors (7, 9). Three of these receptors were studied using sinusoidal oscillations of pulmonary vascular pressures. This method took advantage of the "low-pass filter" properties of the pulmonary vasculature (10). With this system it was possible to produce, at higher oscillation frequencies, arterial and venous pressure waves which were out of phase with one another. This permitted the approximate intrapulmonary localization (i.e., arterial side or venous side) of these receptors. Two of these receptors responded to arterial pressure changes.

Histologically, afferent nerve endings were located in the walls of the intrapulmonary arterial branches (11, 12) and venous vessels (11). In the present study receptors responding in a linear fashion to elevation of pulmonary arterial pressure were identified. A receptor which responded to venous pressure elevation was also found. It appears that receptors exist within the lung which may be similar to pulmonary arterial baroreceptors (2). These findings confirm several earlier studies (4, 5, 13) which identified intrapulmonary vascular receptors responsive to arterial and venous pressure pulsations. Further studies are needed to determine the role that these receptors may play during physiological and pathological alterations of pulmonary vascular pressures.

Summary. Intrapulmonary neural receptors responding to pulmonary vascular pressure changes were studied. Intrapulmonary receptors which could not be classified as

irritant, Hering-Breuer, or Type J were identified electrophysiologically. These receptors increased impulse frequency in a linear fashion with elevations of pulmonary vascular pressure. Receptors which responded to elevation of pulmonary arterial pressure and receptors responding to elevation of pulmonary venous pressure were identified. In addition, several Hering-Breuer stretch receptors which responded in a linear fashion to elevated pulmonary venous pressure were found. We conclude that elevation of pulmonary pressure can increase nerve impulse frequency from Hering-Breuer stretch receptors and from baroreceptors located in the intrapulmonary vasculature. Stimulation of these receptors may play a role in the reflex alterations of respiration during cardiac failure.

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