Effects of Sympathetic Nerve Stimulation on the Pulmonary Arterial Tree of the Isolated Lobe Perfused in Situ

By Roland H. Ingram, J. Peter Szidon, Richard Skalak, and Alfred P. Fishman

ABSTRACT

The hemodynamic response to sympathetic nerve stimulation (SNS) was studied in canine lung lobes isolated in situ and perfused with a pulsatile pump. For the same input pulse, both the rate of rise and the rate of fall of pulmonary arterial pressure increased during SNS; the peak systolic pressure was also higher during SNS, whereas diastolic pressure levels were either at, or below, control levels. The increase in pulse pressure produced little or no change in mean pulmonary artery pressure and resistance. During SNS, compliance per unit length in large arteries fell, pulse wave velocity increased, and elastic modulus increased. Phenoxybenzamine produced opposite changes. Norepinephrine injections increased resistance and produced smaller compliance changes than SNS.

Flow loads imposed by short bursts of rapid pump rate at constant stroke volume caused increments of vascular volume which returned to control levels after return to the slower rate. Volume increments were smaller and restoration rates faster during SNS than during control. After phenoxybenzamine, volume increments were larger and restoration rates slower than control.

The results indicate that the distensibility of the large pulmonary arteries and the precapillary bed is decreased during sympathetic stimulation, while calculated resistance is not changed.

ADDITIONAL KEY WORDS

pulmonary circulation
alpha-receptor mechanisms
sympathetic stimulation
isolated perfused lung
pulmonary vascular compliance
pulmonary innervation

In 1896, François-Franck showed in intact dogs that stimulation of the sympathetic nerves supplying the thoracic viscera results in an increase in pulmonary arterial pressure as well as in heart rate (1). However, the experiments were too incomplete to be more than suggestive of pulmonary vasoconstriction. In 1904, Plumier (2) and more recently I. deB. Daly and associates (3, 4) performed a series of experiments which took into account many of the cardiac and respiratory changes on the pulmonary vascular bed during sympathetic nerve stimulation (SNS) which François-Franck did not measure. These workers used nonpulsatile perfusion of the isolated lung and demonstrated a modest but definite vasoconstriction and thus established that stimulation of the sympathetic nerves could produce a direct pulmonary vaso-motor response.
The present study examines in greater detail the hemodynamic response of the pulmonary circulation to SNS using canine lung lobes isolated in situ and perfused with a pulsatile pump. The pulmonary circulatory responses to SNS during pulsatile perfusion provided insights into the behavior of the pulmonary circulation that previous studies could not supply.

Methods

Experiments were performed on 30 mongrel dogs weighing 11 to 15 kg, anesthetized with pentobarbital, 30 mg/kg of body weight, iv. The preparation is shown schematically in Figure 1 and has been described elsewhere (5). A pulsatile blood pump (Harvard Apparatus Co.) was used to perfuse the left lower lobe in situ with autologous blood. The total volume of blood contained in the circuit was approximately 250 ml. A tracheal divider (no. 37 Carlens tube) separated the airway to the left lower lobe from the other airways; the completeness of separation was established by inflating the lungs separately. The two sides were ventilated separately by constant-volume pumps (Harvard Apparatus Co.). Inflation pressure on the left side was monitored throughout, using a lateral pressure tap connected to a Statham P23AA strain gauge.

The left pulmonary artery and left lobar pulmonary vein were cannulated with rigid L-shaped polyethylene tubing (6 mm i.d.). Needles (20 gauge, 15 cm) were passed through the walls of the cannulas and extended 1 cm beyond the tips. The needles had three side holes near the extremity and their distal holes had been obliterated; they were connected directly to Statham P23Db strain gauges. The dynamic response of the manometer system was flat ±5% to 30 cps. The 90% response time was 10 msec. Instantaneous blood flow was measured with a gated sine-wave electromagnetic flowmeter (Biotronex) using cannulating transducers (12 mm i.d.) which were connected in series with the cannulas. The flow transducers were calibrated in vitro with continuous flow of blood. The probes gave a linear output for the range of flow used in these experiments. The frequency response was electronically limited to 20 cps. The possible distorting effect of the L-shaped cannula on the instantaneous flow pattern was tested by comparing recordings of two flow transducers connected in series by an L-shaped cannula identical to those used in the preparation (5). The flow patterns thus obtained were identical. The level of zero flow was repeatedly determined throughout each experiment by stopping pump action; it was consistently reproducible. The venous cannula was connected to a water-jacketed, siliconized lucite reservoir which was kept at 37 to 38 °C by a thermostatic water bath and circulating pump. Tygon tubing (3/8 inch, i.d.) connected the cannulas to the pump and reservoir. The level of the reservoir was monitored as hydrostatic pressure by a tap near the bottom connected to a Statham P23A strain gauge and calibrated for volume. All data were recorded on a multichannel oscillographic recorder (Electronics for Medicine), and some experiments were also recorded on magnetic tape.

The isolated lobe was ventilated with a mixture of 5% CO₂ in air. The outflow of the air pump passed through a cannula submerged under 3 cm H₂O. The resulting values for blood Pco₂ were 38 to 42 mm Hg. The pH throughout the experiment remained at 7.39 to 7.42 after adding 1 to 3 mEq of sodium bicarbonate to the blood at the start of the perfusion. The right lung, which was perfused by the dog's own pulmonary circulation, was ventilated with air.

Pulmonary edema, evidenced by outpouring of fluid from the cut surface of the lobe at autopsy, invariably occurred if perfusion was prolonged beyond 4 hours, even though perfusion pressures were kept at normal levels throughout the experiments. On the other hand, if the experiments lasted for less than 2 hours, overt pulmonary edema would not occur and the water contents of the lungs, determined by drying, were normal (6).

The perfusion pump was set at a rate of 60 cycles/min, and at a systole-cycle ratio of 1:3;
Representative record showing the effects of a flow load produced by suddenly increasing pump rate from 60 cycles/min to 150 cycles/min with a fixed stroke volume. Res. \( \Delta = \) change in reservoir level. \( P_{PA} \) = pulmonary arterial pressure; \( Q_{PA} \) = pulmonary arterial flow; \( P_{PV} \) = pulmonary venous pressure; \( Q_{PV} \) = pulmonary venous flow; \( Pao \) = airway opening pressure.

its stroke output was 5 ml and its peak flow rate was 19 to 22 ml/sec. At these settings, with the mean pulmonary venous pressure set at approximately 10 mm Hg by adjusting the level of the reservoir, the average pulmonary arterial pressure was 25/12 mm Hg with a mean pressure of 17 mm Hg.

To avoid the influence of positive-pressure inflation and lung volume changes on hemodynamics (7, 8), all measurements were made while both respiratory pumps were stopped in expiration. Since airway pressure was maintained at 3 cm H\(_2\)O during the measurements and the blood reservoir level was always well above the level of the lobe, recruitment of parallel vascular channels would not be expected during increases in arterial pressure (9).

Flow loading was accomplished by increasing the pump rate to 150-180 cycles/min, while stroke volume was held constant, with a systole:cycle ratio of 1:2. This change in rate regularly resulted in an increase in the blood volume of the lobe, which was measured by the fall in the level of the reservoir as shown in Figure 2.

The left stellate ganglion was carefully dissected from the parietal pleura. A bipolar electrode (C. F. Palmer, Ltd.) was positioned at the junction of the ganglion and the sympathetic chain. No attempt was made to separate the possible effects of stimulation of afferent and of efferent fibers by decentralization of the ganglion. Stimulation was accomplished with rectangular pulses, 3 to 5 msec in duration at a frequency of 15 to 20 cps for periods of 10 to 30 seconds, using a square-wave stimulator (S4 Grass). In preliminary studies, these characteristics of the stimulus...
had been shown to give supramaximal stimulation.

Norepinephrine (Levophed) was added to the circuit as a bolus injection through the pulmonary arterial needle in doses varying from 10 to 200 μg, dissolved in 0.5 ml of saline solution. The following drugs were given by the routes specified in Results: phenoxybenzamine hydrochloride (Dibenzyline),\(^1\) 10 to 15 mg; propranolol (Inderal),\(^2\) 10 mg; atropine sulfate, 2 mg; isoproterenol hydrochloride (Isuprel), 400 μg.

**Results**

I. PRESSURE PULSE CHANGES WITH CONSTANT INFLOW PULSE

A. Stimulation of Sympathetic Nerves.—In 25 of 30 dogs successful SNS, evidenced by an increase in the heart rate and systemic blood pressure of the animal, produced an increase in the systolic pulmonary arterial pressure in the isolated lobe (range, 3 to 12; average, 5 mm Hg) and either no change or a slight decrease in diastolic pressure (range, +1 to −2; average, −0.25 mm Hg); the corresponding changes in mean pulmonary arterial pressure were −1 to +2, with an average of +0.25 mm Hg. The systolic pressure in the pulmonary artery increased within 3 to 6 seconds after the start of SNS and returned to control levels within 8 to 10 seconds after it was stopped (Fig. 3). There was no appreciable change in mean pressure after stimulation, and since stroke volume, flow profile, and pump rate were also constant, there was no change in calculated pulmonary vascular resistance. Both the amplitude of the pressure and the contour of the pressure pulse changed. Thus, during SNS, the rate of fall in diastolic pressure beyond the dicrotic notch increased. The mean pressure level in the pulmonary artery thus remained unchanged, as shown by the superimposed pressure pulses in Figure 4.

Neither the changes in the blood volume of the lobe nor increased bronchial arterial inflow was responsible for the changes in pulmonary arterial systolic pressure. Thus, during SNS, the reservoir level did not change, indicating that the blood volume of the lobe had not changed acutely. Bronchial arterial blood inflow was steady but small, requiring the withdrawal of approximately 5 ml every 10 minutes from the reservoir; this rate did not change during SNS. Additional evidence that bronchial blood flow did not contribute to the increase in pressure was obtained in two dogs which developed irreversible ventricular fibrillation during SNS; in both dogs, SNS within 10 minutes after the start of the fibrillation produced an increase in systolic pressure identical to that observed during the previous stimulation.

In the nine experiments in which 10 to 15 mg of phenoxybenzamine was injected into the closed circuit, the response of the isolated lobe to SNS was completely abolished even though tachycardia and systemic hypertension

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\(^1\)Courtesy of Smith, Kline & French Laboratory.

\(^2\)Courtesy of Ayerst Laboratory.
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10 and 200 μg. An increase in diastolic pressure invariably accompanied the increase in systolic pressure. A typical response to norepinephrine is shown in Figure 5. The increase in pressure persisted for several minutes before it gradually returned to control levels.

C. Phenoxybenzamine.—As indicated above, 10 to 15 mg of phenoxybenzamine was given to the perfusion circuit in nine dogs. The alpha-receptor block produced by this drug was complete since it abolished the effects of injecting 400 μg of norepinephrine directly into the cannula; this was at least twice the dose required for maximal response in all of the lobes. In addition, a previously effective SNS produced no change in the pressure pulse after phenoxybenzamine. As shown in Figure 6, within 15 to 20 minutes after phenoxybenzamine had been added to the circuit the pressure pulse was characterized by a lower systolic and higher diastolic pressure. Since the mean pressure was unchanged, the calculated pulmonary vascular resistance remained unchanged.

II. MECHANICAL PROPERTIES OF THE LOBAR ARTERY

Both sympathetic nerve stimulation and phenoxybenzamine strikingly altered the
pressure pulse, even though the inflow pulse was fixed and the values for resistance (calculated as the ratio of mean pressure drop to mean flow) were largely unchanged from the control state. This suggested that mainly the physical properties of the large arteries had been changed by the procedures. Therefore, the pulse wave velocity, compliance, and elastic modulus of the lobar artery were calculated according to the methods outlined in the appendix. Computations were based on data from 12 lobes, initially recorded either at paper speeds of 100 mm/sec or on magnetic tape which allowed playbacks at rapid paper speeds.

Table 1 contains the results of these computations. There was a consistent decrease in compliance and an increase in both the elastic modulus and the pulse wave velocity during SNS. Phenoxybenzamine was given to 7 of the 12 lobes. It consistently produced a decrease in the elastic modulus and in pulse wave velocity and an increase in compliance of the lobar artery. Norepinephrine produced changes similar to SNS but with a higher diastolic pressure. The higher diastolic pressures after phenoxybenzamine and norepinephrine complicate comparison with control values since they would themselves tend to increase the elastic modulus and the pulse wave velocity and to decrease the compliance even if there were no active change in the tone of the vascular smooth muscle. But, since the changes in these indices after phenoxybenzamine are opposite to those expected on the basis of an increased diastolic pressure, they clearly indicate a change in vasomotor activity. Also, the fact that the elastic modulus and pulse wave velocity were generally less after norepinephrine than after SNS, despite higher diastolic pressures, suggests a quantitative difference in the response of the lobar arteries to these two interventions.

### III. Compliance Changes in the Precapillary Bed

The observations on the changes in the distensibility characteristics of the lobar arteries after sympathetic nerve stimulation were extended by investigating the behavior of the entire precapillary bed. Since the methods used for determining compliance applied only to a short segment of the lobar arteries, the method of Engleberg and Dubois (10) was used to calculate compliance for the entire precapillary bed. The method is based on a Windkessel analogy which is a fair approximation during diastole (11). The results are shown in Table 2. The control arterial compliance averaged 0.24 ml/mm Hg (range 0.13 to 0.36); it decreased to an average of 0.15 ml/mm Hg (range 0.07 to 0.25) during

<table>
<thead>
<tr>
<th>Lobe no.</th>
<th>Control</th>
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<th>Norepinephrine</th>
<th>Phenoxybenzamine</th>
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<tr>
<td></td>
<td>C</td>
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</table>

C = compliance of the lobar artery per unit length, cm$^4 \times$ dyn$^{-1} \times 10^{-6}$; E = elastic modulus of the lobar artery, dyn$e \times cm^{-2} \times 10^6$; a = pulse wave velocity in the lobar artery, cm$ \times sec^{-1}$.
SNS as shown in Table 2. After norepinephrine, the average arterial compliance was 0.18 ml/mm Hg (range 0.15 to 0.27) and after phenoxybenzamine the average was 0.29 ml/mm Hg (range 0.22 to 0.45). In each instance, the arterial compliance decreased during SNS and after norepinephrine and increased after phenoxybenzamine. Table 2 also shows that calculated vascular resistance is nearly unchanged by SNS but increases after norepinephrine, while the compliance decreases less after norepinephrine than during SNS.

IV. CHANGES IN PULSE TRANSMISSION ACROSS THE ENTIRE VASCULAR BED

The transmission time was measured as the interval between the start of the upstrokes in pulmonary arterial systolic pressure and flow to the start of the rapid upstrokes in pulmonary venous pressure and flow. Shown in Table 2 are the transmission times during the control period, which averaged 0.12 seconds (range 0.10 to 0.18); during SNS, which averaged 0.09 seconds (range 0.07 to 0.13); after norepinephrine, which averaged 0.12 seconds (range 0.10 to 0.17); and after phenoxybenzamine, which averaged 0.17 seconds (range 0.14 to 0.19). The differences in transmission times are in qualitative agreement with the values to be expected on the basis of the changes in wave velocity shown in Table 1.

V. PRESSURE-VOLUME CHANGES WITH FLOW LOADING

To relate the compliance changes in the lobar artery and precapillary bed to the behavior of the total pulmonary vascular bed, four lobes were subjected to bursts of rapid pump rate from a rate of 60 cycles/minute to 150-180 cycles/minute; the stroke volume was fixed at 5 ml. The resulting flow load was associated with an increase in blood volume of the lobe and an increase in intravascular pressure, as shown in Figure 2. The increase in blood volume during flow loading was consistently less during SNS, and more after phenoxybenzamine, than during the control state. The results after norepinephrine were inconsistent in terms of changes in volume, but pressures were always much higher.

The pressure-volume relationships were examined in two other ways. First, the changes in blood volume and pressure during flow loading were compared in two lobes in which

<table>
<thead>
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<th>TABLE 2</th>
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<tr>
<td>Hemodynamic Changes in the Entire Lobar Precapillary Bed in Response to Sympathetic Nerve Stimulation, Norepinephrine, and Phenoxybenzamine</td>
</tr>
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<td>30</td>
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</tbody>
</table>

R = resistance, mm Hg/cm<sup>2</sup>/sec; C<sub>T</sub> = total arterial compliance, cm<sup>3</sup>/mm Hg [according to the method of Engleberg and DuBois (10)]; T<sub>T</sub> = transmission time, seconds.

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the average intravascular pressures, \((\frac{P_{Pa} - P_{Pv}}{2})\), during the control period, during SNS and after phenoxybenzamine were the same at the slower rate. As shown in Figure 7, in each of the two lobes there was a greater change in volume with a smaller change in pressure from control after phenoxybenzamine; during SNS there was a smaller change in volume with a greater change in pressure from control.

As the second approach to pressure-volume relationships, the data from one experiment were digitized from the magnetic tape and were computer-programmed for continuous integration of arterial and venous flow signals. End-diastolic changes in volume were obtained by subtracting the venous from the arterial stroke volume. The average of the end-diastolic arterial and venous pressures was computed for comparison with the simultaneous changes in volume. In Figure 8, results of flow loading are shown for the control state, during SNS, and after injections of norepinephrine and of phenoxybenzamine. During the control periods, and after norepinephrine and phenoxybenzamine, the volume increased steadily after the end-diastolic pressure had reached a plateau. On the other hand, during SNS, the change in volume was less and reached a plateau as the pressure reached a steady level. In addition, there was a more rapid return of the volume to initial levels after flow loading during SNS, including an overshoot in the first few beats.

VI. MECHANICAL ALTERATIONS OF THE LOBAR ARTERY AFTER FLOW LOADING

As shown in Figure 9, the pressure pulses of the first complete slow cycle immediately after the flow load had a lower systolic pressure, a slower rate of rise and a higher diastolic pressure than the pressure cycles which preceded the flow load. The differences between the pressure pulse immediately before and after flow loading were prominent during the control period and after norepinephrine, but were minimal during SNS and absent after phenoxybenzamine. In three lobes in which sufficient records were taken following the return to control rate after flow loading to demonstrate the return of the original configuration of the pressure pulses, compliance per unit length and the elastic modulus were calculated. The slow cycle immediately preceding flow loading, the first complete slow cycle after, and the fifth to sixth subsequent slow cycles were used for the calculations. Figure 10 shows the results. The largest changes, i.e., a decrease in the elastic modulus and an increase in compliance, occurred during the control state and after norepinephrine, whereas the differences were smaller during SNS and absent after phenoxybenzamine.
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FIGURE 8
Beat-by-beat volume change versus average end-diastolic intravascular pressure with flow loading during control state, sympathetic nerve stimulation and after norepinephrine and phenoxybenzamine. For complete description see text.

FIGURE 9
Pulmonary arterial pressures $P_{PA}$ and flows ($Q_{PA}$) during flow loading. Note the gradual decline in peak systolic pressures with rapid rates in the control state and after norepinephrine, as compared with the periodicity of peak systolic pressures during sympathetic nerve stimulation and the steady peak systolic pressures after phenoxybenzamine. Note also the difference in the pressure pulse of the slow beat immediately preceding flow loading (arrow) as compared with the slow ones following flow loading (arrow) in control and after norepinephrine. Differences are not apparent after sympathetic nerve stimulation and after phenoxybenzamine.

In Table 3 is shown the behavior of certain variables during short periods of increased pump rate. By this approach, properties of the large arteries (lobar) can be distinguished from those of the entire vascular bed of the lobe since the changes in arterial wall compliance and elastic modulus in the cycles immediately following flow loading, and the
Compliance (C) per unit length calculated for cycles immediately preceding, immediately following, and for the fifth to sixth cycle after flow loading. Note the quite small changes with sympathetic nerve stimulation and after phenoxybenzamine. E = elastic modulus for the same cycles. Again, the smallest changes are seen with sympathetic nerve stimulation and after phenoxybenzamine.

Behavior of the peak systolic pressure level during the period of rapid flow rate, reflect properties of large arteries, whereas the changes in end-diastolic volume with respect to average end-diastolic pressure reflect properties of the entire vasculature. In the control, non-stimulated state, the spontaneous sympathetic nervous tone of the large arteries of the isolated lobe—presumably reflecting the general level of activity of the sympathetic nervous system of the dog—is insufficient to prevent mechanical alterations in the properties of the vascular walls as volume inflow increases. On the other hand, the heightened sympathetic activity evoked by electrical stimulation of the sympathetic nerves maintains mechanical properties of the vascular walls virtually constant. Blockade of alpha-adrenergic receptors by phenoxybenzamine, which reduces smooth muscle tone to a minimum so that the

TABLE 3

<table>
<thead>
<tr>
<th>Condition</th>
<th>Factors reflecting response of large arteries</th>
<th>Factors reflecting response of entire vascular bed (increase in EDV after EDP became steady)</th>
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</thead>
<tbody>
<tr>
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<td>+</td>
</tr>
<tr>
<td>Symp. nerve stim.</td>
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</tr>
<tr>
<td>Norepinephrine</td>
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<td>+</td>
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<tr>
<td>Phenoxybenzamine</td>
<td>0</td>
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E = elastic modulus of the lobar artery; C = compliance of the lobar artery; EDV = end-diastolic volume; EDP = average end-diastolic pressure.
mechanical behavior of the arterial wall is due mainly to elastic fibers, also eliminates changes in the mechanical properties of the vessels induced by flow loading. After a bolus injection of norepinephrine, flow loading is associated with changes in the compliance and elastic modulus of large vessels. These changes, most apparent in the cycles immediately following return to control rate (Fig. 10), are due to greater systolic pressures after norepinephrine than exist in the other three situations.

**Discussion**

The present experiments showed that stimulation of the sympathetic nerve supply to the lungs consistently produces changes in the pulmonary arterial pressure pulse even though there may be no change in calculated resistance. The response after the use of pharmacologic blocking agents (phenoxybenzamine, propranolol, atropine) indicated that the effects of sympathetic stimulation were due largely to stimulation of alpha-adrenergic receptors. The nature of the hemodynamic responses is consistent with the idea that the major effects of sympathetic stimulation are exerted on the large pulmonary arteries rather than on the small pulmonary vessels. This view is supported by the decrease in pulmonary arterial compliance, the increase in pulse wave velocity and the increase in elastic modulus without change in calculated pulmonary vascular resistance, during SNS.

The anatomical observations of others lend support to the physiological evidence that the major effects of sympathetic nerve stimulation are exerted on the larger, rather than on the smaller, pulmonary arteries. Thus, the large pulmonary arteries (more than 2 mm in diameter) have a greater supply of nerves (12, 13) and contain more norepinephrine in their walls (14) than do the small muscular arteries. Also, the sparse smooth muscle in the large pulmonary arteries is intimately associated with abundant elastic fibers, an arrangement which could effect considerable changes in distensibility without appreciably narrowing the large vascular lumens (15, 16). The plentiful supply of nerves and elastic fibers in the large pulmonary arteries suggests that their function is capacitance; the concentric organization of smooth muscle in the smaller pulmonary vessels suggests that their function is resistance. The present experiments have displayed only the predominant effects of sympathetic stimulation on the pulmonary arterial tree and do not indicate the relative contributions of the consecutive segments to the overall response.

In contrast to the present experiments, previous studies have found modest but definite increases in pulmonary vascular resistance during stimulation of comparable parts of the upper sympathetic chain (2-4). But these earlier experiments were performed using nonpulsatile and low flows. Because of the nonlinear behavior of blood at low shear rates, such studies would be expected to exaggerate the effects of viscosity on the pulmonary vascular bed. In contrast, such viscosity effects would be expected to be negligible at physiological rates of flow (17). In addition, in some experiments in which a constant perfusion pressure was used, a fall in inflow would tend to exaggerate the increase in calculated resistance by decreasing pulmonary blood volume and, consequently, the cross-sectional area of the bed.

**Norepinephrine.**—In the present experiments, the injection of norepinephrine increased the calculated resistance and decreased the compliance of both the precapillary bed and lobar arteries. This combination is consistent with vasomotion of both the large and small pulmonary arteries. The response to both norepinephrine and to SNS was abolished by phenoxybenzamine in keeping with the idea that both effects are mediated by way of stimulation of alpha-receptor sites in pulmonary vascular smooth muscle. The predominant involvement of the small arteries (less than 0.1 mm in diameter) after norepinephrine injection was also observed anatomically by Patel and Burton (18). The difference between the effects of injected norepinephrine and the effects of SNS (endogenous norepinephrine released from nerve endings)
probably reflects the discrepancy between the number and distribution of alpha-receptor sites and the distribution of adrenergic nerve endings in the vascular wall. Stimulation of the sympathetic nerves would be expected to release norepinephrine in the vicinity of nerve endings, whereas a bolus of norepinephrine injected in the pulmonary artery would be expected to be distributed uniformly to capillaries, to diffuse across their walls, and to stimulate receptor sites in vascular smooth muscle not only near nerve endings but elsewhere as well. One would anticipate a more generalized vasoconstrictive response in which both large and small vessels participate.

Effect of Sympathetic Nerve Stimulation in Adjusting Vascular Tone to Increased Inflow. —During sympathetic stimulation, the pattern of response of the pulmonary artery pressure to brief periods of increased pump rate differed strikingly from control. Instead of a steady decline in peak systolic pressure and an unchanged diastolic pressure observed during control experiments (Fig. 9), systolic and diastolic pressures during SNS remained practically unchanged throughout the flow loading period. Also, SNS was associated with smaller changes of the contour of pressures in the cycles immediately following the return to control rate after flow loading. Thus, the increase in vascular compliance and end-diastolic volume were considerably smaller after flow loading for SNS than for control experiments. These observations suggest that for the control experiments, the increased pump rate was delivering into a continually enlarging system, whereas during sympathetic stimulation the tendency of the vascular bed to enlarge was being opposed by the effects of alpha-receptor mechanisms on vascular smooth muscle. In effect, sympathetic stimulation seemed to bring about a smaller, less distensible pulmonary arterial tree than that without such stimulation.

Although smooth muscle fibers cannot be regarded as perfect elastic structures, the net behavior of major pulmonary arterial walls up to transmural pressures of approximately 40 mm Hg is that of a perfect elastic structure (19). It seems reasonable to conclude that the acute reversible changes in volume-distensibility characteristics of pulmonary vessels during the brief changes in pump rate would be due to changes in smooth muscle behavior. Therefore, the variations observed in the present experiments during flow loading (Table 3) seem to reflect alterations in smooth muscle, and the magnitude of the changes may represent the degree of sympathetic innervation and the activity of the pulmonary vasomotor nerves.

Continually enlarging end-diastolic vascular volume after average end-diastolic pressure reaches a plateau reflects a change in properties of the vascular bed which cannot be localized from the present measurements. Since SNS was the only procedure which prevented changes in compliance and the elastic modulus during flow loading, volume distensibility characteristics of portions of the vasculature other than the lobar artery must have been affected. Since alpha-receptor blockade would be expected to diminish smooth muscle tone only in those portions of the vascular bed where tone is maintained largely by alpha-receptor mechanisms, it is possible that the continual increase in volume occurred in parts of the vasculature where tone, in the absence of direct stimulation, is not maintained by alpha-receptor mechanisms.

We have pointed out that recruitment of parallel vascular channels as pulmonary arterial pressure increased would not be expected to occur in our isolated lobe because of the high level of the venous reservoir with respect to alveolar pressure. However, the remote possibility remains that the pulmonary vessels have an unexpectedly high critical closing pressure, higher than the 5 to 7 mm Hg which would represent the pressure difference between pulmonary venous and alveolar pressure in the upper portion of our isolated lobe. Indeed, Burton has suggested a critical closing pressure of at least 10 mm Hg for pulmonary vessels (20). However, recent attempts to demonstrate such a pressure, using a preparation designed to explore the interplay between hydrostatic and alveolar pressures, have
been entirely unsuccessful (21). Consequently, there is no reason at present to consider seriously the recruitment of parallel vessels through the mechanism of critical closing pressure as an alternate explanation for the observed pressure-volume relationships during flow loading.

Possible Physiological Meaning of the Effects of Heightened Sympathetic Activity on the Pulmonary Circulation.—The stiffening of large arteries in response to sympathetic nerve stimulation in our experiments cannot be described as physiological since both the stimulus and the circumstances were artificial. Nonetheless, the present experiments do suggest some physiological implications for the intact animal. A low resistance to blood flow is important for the normal operation of the pulmonary circulation in its location between the low-pressure right ventricle and the high-pressure left ventricle (22). The present experiments suggest that pulmonary vascular resistance is kept low in physiological situations characterized by increased sympathetic activity. In addition, the changes in mechanical characteristics of the large pulmonary arteries also seem to be important with respect to hemodynamic behavior of the strategically placed pulmonary circulation. For example, Franklin et al. have shown in dogs that the outputs of the two ventricles are in such precise phasic balance during quiet respiration at rest that an increase in right ventricular stroke volume increases the stroke volume of the subsequent left ventricular beat (22). Morkin et al. (23) demonstrated that the flow pulse generated by the right ventricle is transmitted across the pulmonary circulation in approximately 0.1 seconds and is propelled into the left atrium at the precise moment of rapid ventricular filling. This temporal sequence in the transmission of the pulsatile flow allows the pulmonary circulation to maintain a precise adjustment between the two ventricular outputs. Without some type of automatic adjustment, the increase in heart rate and cardiac output during exercise or excitement would alter this synchrony and upset the balance in ventricular outputs; an increase in rate of pulse wave transmission should occur to maintain the orderly sequence. In the studies of Franklin et al. on dogs (22), an abrupt onset of exercise (treadmill) without previous warning as well as an abrupt acceleration of venous return to the right ventricle (intravenous infusion) produced an increase in right ventricular stroke volume which preceded corresponding left ventricular stroke volume changes by several beats. Under these circumstances pulmonary blood volume must increase and the vascular bed become distended. However, when the onset of exercise was anticipated by the dog and sympathetic nerve activity was presumably heightened, the ventricular outputs changed exactly in phase. Human studies have shown relatively constant pulmonary blood volume during exercise (24). An increase in stiffness of large pulmonary arteries as found in our studies, if it occurred in the intact organism, would increase the rate of pulse wave transmission needed to maintain ventricular balance and minimize changes in pulmonary blood volume.

If one assumes that the distensibility of the precapillary vasculature decreases during exercise in association with a heightened sympathetic activity, it is conceivable that it could influence the amplitude of the pressure pulse in the consecutive segments of the vascular tree. A greater amplitude of pulsations at the level of the small vessels where the "waterfall" effect takes place (9) might be the mechanism by which recruitment of parallel vessels at the top of the lung could take place in exercise (25), resulting in a more homogeneous distribution of blood flow, a greater capillary surface available for gas exchange and a fall in calculated resistance (26, 27).

Appendix

Compliance per unit length was calculated according to the following formula which may be derived from transmission line equations (28) assuming there are no reflected waves present and neglecting viscous effects:
\[ C = \frac{\rho}{A} \times \frac{(dQ/dt)^2}{(dP/dt)^2}, \]

where \( Q = \text{flow (ml/sec)} \)

\( P = \text{pressure (dyne/cm}^2\) \)

\( \rho = \text{density of blood (1.06 g/ml)} \)

\( A = \text{area of flow (cm}^2\), taken as 0.283 cm}^2\) based on the 6-mm internal diameter of the arterial cannula which matched closely the internal diameter of lobar arteries of the dogs used in these experiments.

\( t = \text{time (sec)} \)

\( C = \text{compliance (cm}^4\times\text{dyne}^{-1}) \).

Assuming that the first bifurcation would be the closest reflection site, the calculated pulse wave velocity and the 2.0 to 2.5 cm distance of the first bifurcation (measured from arterial casts made in this laboratory), indicate that the initial 15 to 20 msec would be free from reflected waves. The first time derivatives of pressure and flow were taken during the initial 10 msec of systole to insure absence of reflected waves. Flow was assumed to be nonviscous, and the radial displacement was assumed to be small with respect to the initial diameter in deriving the inertial term.

Characteristic impedance (\( Z_0 \)) in dyne-sec/cm}^4\) was calculated as

\[ Z_0 = \sqrt{\rho/AC}. \]

From \( Z_0 \) and \( C \) the pulse wave velocity \( (a) \) in cm/second was calculated as

\[ a = \frac{1}{Z_0 \times C}. \]

Elastic modulus \( (E) \) in dynes/cm}^2\) was calculated as

\[ E = \frac{2 \times (1 - \sigma^2) \times 2\pi r^3}{Ch}, \]

where \( r = \text{radius (cm)} \), taken as 0.3 cm (see area notation above)

\( \sigma = \text{Poisson's ratio, taken as 0.5 (27)} \)

\( h = \text{wall thickness (cm), taken as 10\% of radius (29)} \).

The possibility of a nonlinear stress-strain relation of vascular wall requires that measurements start from or near the same diastolic pressure level in order for a change in computed properties to be strictly interpreted in terms of alteration in the mechanical properties of the arterial wall.

References


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