Sympathetic Control of Pulmonary Vascular Impedance in Anesthetized Dogs

By John B. Pace

ABSTRACT

The effects of left stellate ganglion stimulation on pulmonary hydraulic input impedance was evaluated in 21 experiments on open-chest dogs anesthetized with chloralose. The stellate ganglion was stimulated at 1, 2, 5, 10, and 20 cps, and impedance spectra were generated at each frequency. Control spectra were characterized by frequency-dependent oscillations in impedance magnitude. Generally, impedance minimums occurred between 2 and 3 cps and maximums between 4 and 6 cps. Stellate ganglion stimulation caused elevations in impedance magnitude and shifted the impedance curve upward. The average control impedance magnitude at the minimum was 4780 dyne sec cm⁻² kg ± 262 SE and was increased to 8280 ± 452 during stimulation at 20 cps, while the frequency of the first harmonic in the control averaged 2.50 ± 0.08 SE cps and was 3.10 ± 0.08 during stimulation at 20 cps. Maximum activation of sympathetic outflows (10—20 cps) caused the impedance curve to flatten, attenuating frequency dependent oscillations characteristic of control spectra. The administration of propranolol attenuated cardiogenic increases in pulmonary pressure and flow during stellate ganglion stimulation, but elevations in pulmonary vascular impedance still occurred, indicating that this was not dependent on changes in harmonic content of the flow pulse that attended changes in heart rate and stroke volume. Frequency dependent oscillations in impedance magnitude were usually enhanced during left stellate ganglion stimulation following propranolol. The results indicate that sympathetic nerve stimulation increases the opposition to pulsatile flow; since pulmonary vascular resistance was relatively less affected, the input impedance becomes a greater fraction of the total opposition that must be overcome in moving blood through the lungs.

KEY WORDS

propranolol
Fourier analysis
right ventricular function
stellate ganglion stimulation
pulmonary arteries

The pioneer studies of I. deB. Daly et al. demonstrated that sympathetic nerve stimulation increased the opposition to steady flow through artificially perfused lungs, thus establishing the existence of a sympathetic innervation to pulmonary vessels which could produce a direct vasomotor response (1). Recently, Ingram et al. showed that the primary hemodynamic alteration associated with stellate ganglion stimulation in isolated lung lobes perfused with pulsatile flow was an increase in arterial pulse pressure with an insignificant effect on the level of mean pressure (2). This resulted from generalized stiffening of large pulmonary arteries rather than from constriction of smaller muscular arterioles. Further studies showed that stellate ganglion stimulation reduced the volume distensibility of the main pulmonary artery and increased the elastic modulus of the arterial wall; thus these studies established a physical basis for the observed increases in pulsatile pressure (3).

Since stiffening of conduit vessels tends to augment pressure pulsations, a major hemodynamic consequence of activation of sympathetic pathways to the pulmonary vasculature...
may be an increase in the opposition to pulsatile flow. Experiments by Bergel and Milnor showed that normally the opposition to pulsatile flow in the lung is 20–50% of the resistance to steady flow (4) and that oscillations can account for a highly significant fraction of the total hydraulic power generated by the right ventricle (5). Consequently, studies concerned with evaluating the role of the sympathetic nerves in controlling pulmonary hemodynamics require an analysis of the pulsatile character of flow. The relation of pulsatile pressure to flow in the lung can be expressed in terms of fluid impedance by resolving the pressure and flow pulses into a Fourier series and expressing the opposition to pulsatile flow as the ratio of the pressure modulus to the flow modulus for each of an integral number of harmonics (4–7). Input impedance, with which the present report is concerned, describes the ratio of oscillatory pressure to oscillatory flow at the origin of the system, in this case the main pulmonary artery.

The experiments reported in this paper were intended: (1) to evaluate the influence of sympathetic nerve stimulation on pulmonary vascular input impedance in the anesthetized dog, (2) to determine the effects of beta-receptor blockade on pressure-flow relations in the lung before and during sympathetic nerve stimulation, and (3) to reexamine in the intact preparation existing reports which indicate that the major effects of sympathetic stimulation are exerted on the large pulmonary arteries rather than on small pulmonary vessels.

Methods
Experiments were performed on 21 mongrel dogs weighing 10.2–33.0 kg (mean 19.8 kg). The animals were anesthetized with chloralose, 80 mg/kg, after premedication with 1- (1-phenylethyl)cyclohexyl piperidine hydrochloride, 2 mg/kg, which has central dissociative effects. A tracheostomy tube was inserted, and a bilateral thoracotomy with sternal transection was performed through the third interspace. Respiration was maintained by positive pressure with an Emerson respirator delivering a tidal volume of 300–400 ml at a frequency of 16 cps. The respirator was supplied with pure oxygen. The animals exhaled against a pressure of 2.0 cm H2O.

In ten experiments, the heart was suspended in a pericardial cradle, and right ventricular pressure was recorded with a plastic cannula inserted through the free wall. The physical dimensions and frequency response characteristics of this device have been described (8). The main pulmonary artery was prepared to receive an electromagnetic flow probe by dissecting off the fat pads surrounding the vessel and freeing the vessel from connective tissue for a length of 1.5 cm. Special care was taken to avoid interrupting sympathetic nerves passing between the ascending aorta and pulmonary artery. A large polyethylene cannula was tied into the left atrial appendage. Two methods were employed to record pressure in the main pulmonary artery. In the first 14 experiments of the series, the right anterior lobar pulmonary artery was cannulated with 7 cm of PE90 polyethylene tubing and the tip was advanced into the main pulmonary artery until it was midway between the pulmonic valve ring and the bifurcation. This placement ensured that the orifice of the cannula was perpendicular to the flow stream and therefore that the recorded pressure included the kinetic energy of the blood. During positive inotropic stimulation, flow velocity increases, and kinetic energy represents a greater fraction of the total pressure energy in the flowing blood. Hence, measurements of static or lateral pressure would tend to give lower values for input impedance than those derived from measurements of end-on or impact pressure. In the last seven experiments, pulmonary arterial pressure was measured through a 19-gauge needle inserted through the wall of the main pulmonary artery. The needle was turned so that the bevel faced perpendicular to the flow stream.

Pressures were measured with Statham P23Gb gauges. The hydrostatic base line for all gauges corresponded to the level of the right atrium. The manometers were calibrated with a mercury column at the conclusion of each experiment, and the domes were filled with freshly boiled distilled water prior to each experiment. The frequency response characteristics of the catheter-manometer system used to record pulmonary arterial pressure were tested using the step-pressure technique. The natural frequency was 150 cps and the damping ratio calculated from the response was 0.70.

Volume flow rates in the main pulmonary artery were measured with a Statham gated sine-wave electromagnetic flowmeter (model M-4001). Application of the flow probe (Medicon, type Q) to the main pulmonary artery reduced the cross section by about 10–20%. The average diameter of the probe was 12.7 mm. In the
experiments in which pulmonary arterial pressure was recorded through a needle catheter, the needle was inserted 2—3 mm above the flow probe. Inserting the needle did not distort the flow signal. The flow probes were statically calibrated on blood vessels with whole blood and a pressurized reservoir system which could deliver up to 10 liters/min. A battery voltage was impressed across the input terminals of the flowmeter immediately following the calibrations procedure; hence each probe used in this study had a reference voltage which could be translated into flow units. In ten experiments, the flow calibrations were determined from reference voltages. Upon repeated calibrations, the reference voltage for a given probe varied between 10 and 15% of the mean. The dynamic response of the flowmeter was tested (9); phase shift was 5°/cycle, and the amplitude ratio decreased 5% at 10 cycles. All blood flow data were corrected for this phase and amplitude distortion prior to computations of vascular impedance. Mechanical zero flow signal was determined by assuming that net flow through the probe during diastole was zero (4).

Pulmonary arterial pressure, pulmonary arterial flow, left atrial pressure, and femoral arterial pressure were simultaneously recorded on analog tape (Ampex model, FR 100). Upon completion of the experiment, the analog tape was played back and recorded on paper (Brush, Mark 200) along with a binary decimal sequential number code. The code was placed on an empty channel of the analog tape prior to the experiment with a code generator (Hyperion, model H1-150). For the pressure and flow pulses selected for analysis, the period was constant for 2 cycles before and 2 cycles after the pulse being analyzed and the peak systolic and end diastolic levels of the curves were identical on both sides of the selected curve. The selected cardiac cycles were then converted to digital form using an analog-to-digital converter and recorded on digital tape. The converter usually operated at a sampling rate of 1000/sec with resolution of about 1 mv. The digital tape was used as input to a computer program (IBM 360/75) which defined cycle length, calibrated the data points, and performed a Fourier analysis on the calibrated data for the first nine harmonics. The impedance magnitude was calculated for each harmonic by dividing pressure amplitude by flow amplitude, and the impedance phase by subtracting the flow phase angle from the pressure phase angle. Pulmonary vascular resistance was defined as the difference between mean pulmonary arterial pressure and mean left atrial pressure divided by mean pulmonary flow and was considered to represent the impedance at zero frequency. Resistance and impedance values were adjusted for the size of the animal by using blood flow/kg body weight in all computations.

Sympathetic outflows to the heart and lungs were activated by stimulating the left stellate ganglion (1, 2). The ganglion was decentralized by cutting the rami from T1 through T3, and the caudal pole was crushed. Stimulation was performed with bipolar wire electrodes fixed to the body of the ganglion. The ganglion was stimulated with square-wave pulses having a duration of 5 msec and an intensity of 8—10 v. This voltage range ensured supramaximal activation. Stimulation parameters were continuously monitored on a cathode-ray oscilloscope. The stimulus was applied to the ganglion for 15—20 seconds. A steady state was usually attained after 15 seconds of stimulation. Pressure and flow pulses were selected for analysis in the control and at stellate ganglion stimulation rates of 1, 2, 5, 10, and 20 cps.

Figure 1 shows a record of the alterations in pulmonary arterial pressure and flow induced by sequential increases in the frequency of left stellate ganglion stimulation (LSS). Pulmonary arterial pressure was increased from 28/8 mm Hg in the control to 70/9 mm Hg during stimulation at 20 cps, while peak flow was increased from 4200 ml/min to 8200 ml/min. Mean flow rates for each condition are shown above the flow pulses. The augmentations in pulmonary arterial pressure greatly exceeded concomitant increases in peak pulmonary flow.

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less than 1 ml/sec were not used in computations of vascular impedance. To prevent changes in myocardial contractility of vessels, propranolol (10 mg/kg iv) was administered.

### Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>LSS 1 cpm</th>
<th>LSS 2 cpm</th>
<th>LSS 3 cpm</th>
<th>LSS 10 cpm</th>
<th>LSS 20 cpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary flow (ml/min kg⁻¹)</td>
<td>84.9 ± 6.8</td>
<td>95.9 ± 6.5*</td>
<td>99.8 ± 6.7*</td>
<td>105 ± 8.0*</td>
<td>110 ± 7.6*</td>
<td>116 ± 7.8*</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>14.6 ± 0.8</td>
<td>17.7 ± 0.7*</td>
<td>18.6 ± 0.8*</td>
<td>19.5 ± 0.8*</td>
<td>21.2 ± 0.8*</td>
<td>22.4 ± 0.9*</td>
</tr>
<tr>
<td>LAP (mm Hg)</td>
<td>5.7 ± 0.3</td>
<td>5.1 ± 0.3†</td>
<td>4.8 ± 0.2†</td>
<td>4.4 ± 0.5†</td>
<td>4.5 ± 0.5†</td>
<td>4.5 ± 0.5†</td>
</tr>
<tr>
<td>HR (beats/sec)</td>
<td>2.50 ± 0.08</td>
<td>2.60 ± 0.09</td>
<td>2.65 ± 0.08†</td>
<td>2.77 ± 0.08*</td>
<td>2.97 ± 0.08*</td>
<td>3.10 ± 0.08*</td>
</tr>
<tr>
<td>PVR (dyne sec cm⁻⁵ kg⁻¹)</td>
<td>11,920 ± 1037</td>
<td>12,163 ± 1181</td>
<td>13,486 ± 585</td>
<td>13,982 ± 1289</td>
<td>15,558 ± 1211†</td>
<td>15,982 ± 1249†</td>
</tr>
</tbody>
</table>

All parameters except pulmonary vascular resistance (PVR) and heart rate (HR) changed significantly from the control at each frequency of sympathetic nerve stimulation. The increase in resistance became significant at stimulus frequencies of 10 and 20 cpm. The increase in heart rate was not significant at 1 cpm, but became significant at all higher frequencies. All values are means ± SE.

* = P < 0.001; † = P < 0.05; ‡ = P < 0.01. LSS = left stellate ganglion stimulation; PAP = pulmonary arterial pressure; LAP = left atrial pressure.
Figure 2 shows average (± SE) pulsatile pressure-flow relations plotted as vascular pressure-flow relations plotted as vascular

and they imply a graded response of the resistance at each level of stimulation.

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impedance derived from the same 21 experiments for which nonpulsatile parameters are shown in Table 1. Magnitude and phase relations of the hydraulic impedance were derived for the control and at each of five levels of left stellate ganglion stimulation. The average values, plotted as the composite impedance spectra, were obtained from the first five harmonics of the fundamental for each condition, and no attempt was made to select and group points representing maximums and minimums from individual experiments. The standard errors indicated in Figure 2 show the variability in position of these points along the frequency scale as well as the variability of their magnitude and phase. In the control shown in Figure 2 the impedance magnitude fell from the value at zero frequency to a minimum at 2.50 ± 0.08 cps followed by a maximum at 5 ± 0.17 cps. Control observations were characterized by impedance minimums between 2 and 3 cps and maximums between 4 and 8 cps. The impedance phase was slightly negative at the control fundamental frequency, changed to positive between 5 and 8 cps, and remained positive at higher frequencies, although tending to move back toward zero. In general, left stellate ganglion stimulation tended to shift the impedance phase to less positive angles between 5 and 8 cps. This change was not significant in the grouped data.

Stimulation of the left stellate ganglion at 1 cps significantly increased the magnitude of the first harmonic \( (P < 0.001) \) without significantly altering its frequency. Vascular resistance and the frequency and magnitude of the remaining harmonics were not significantly altered \( (P > 0.05) \). Stimulation at 2 cps caused a significant increase in the magnitude of the second harmonic \( (P < 0.001) \) without significantly altering its frequency from the control. Similarly, the magnitude of the fifth harmonic generated at 2 cps was significantly increased from control independent of frequency. Stimulation at 5 cps increased heart rate to the extent that the frequency of each harmonic was significantly different from corresponding control values, thus it was impossible to compare real data points at a specific frequency. However, a statistical comparison could be made for the first harmonic, since the discrepancies in frequency between control and the various levels of left stellate ganglion stimulation, although significant, were relatively small (Table 1). In this connection, Bergel and Milnor have shown that in the frequency interval under consideration (2.50–3.10 cps) normal pulmonary vascular impedance is declining smoothly \( (4) \); hence, even slight undulations in impedance magnitude would not be expected to occur within this interval. The impedance magnitude of the first harmonic in the control was 4780 ± 262 sec dyne sec cm\(^{-5}\) kg and was increased to 8280 ± 452 dyne sec cm\(^{-5}\) kg at a stimulation frequency of 20 cps. Stimulation at 5, 10, and 20 cps tended to flatten the impedance curve after the first minimum so that a definite impedance maximum was no longer discernible.

Augmentations of the first harmonic occurred together with a marked elevation of the impedance curve at the higher frequencies. The characteristic impedance was derived by averaging the impedance magnitudes for the last three harmonics in each condition; this covered a frequency range between 7 and 16 cps. Values for characteristic impedance were as follows: control, 5840 ± 479 dyne sec cm\(^{-5}\) kg; 1 cps, 6395 ± 512; 2 cps, 7400 ± 541; 5 cps, 8220 ± 656; 10 cps, 9560 ± 718; and 20 cps, 10,260 ± 803. In contrast, pulmonary vascular resistance was not significantly increased from control during stimulation at frequencies of 1, 2, and 5 cps, but was significantly increased at 10 and 20 cps, indicating that sympathetic nerve stimulation at low frequencies may alter the relations of pulsatile pressure to pulsatile flow without affecting the interaction between steady pressure and flow. In addition, the results shown in Figure 2 indicate that left stellate ganglion stimulation can cause marked increases in the opposition to pulsatile flow in the main pulmonary artery.

To examine the effects of stellate ganglion stimulation on pulmonary hemodynamics
Record shows alterations in pulmonary hemodynamics during stimulation of the left stellate ganglion before and after propranolol. Prior to propranolol, stellate ganglion stimulation induced increases in peak pulmonary arterial pressure and flow, while heart rate increased 60 beats/min. The administration of propranolol caused a 30 beats/min reduction in heart rate, while pulmonary arterial pressure was unchanged and peak flow increased slightly. Stimulation following propranolol produced a marked increase in pulmonary arterial pressure with a slight increase in diastolic pressure, while peak flow was reduced. The elevation in right ventricular systolic pressure was accompanied by 2.0 mm Hg increase in ventricular diastolic pressure. This change together with reduced pulmonary flow reflects a substantial increase in vascular impedance.

without concomitant alterations in stroke volume, flow acceleration, and pressure of cardiac origin, the chronotropic and inotropic effects of nerve stimulation were blocked with propranolol. Figure 3 shows a record illustrating the effects of left stellate stimulation on pulmonary hemodynamics before and after propranolol. Before propranolol, stellate stimulation increased right ventricular systolic pressure and pulmonary and femoral arterial pulse pressures. Augmentations in systolic pressures were accompanied by an increase in pulmonary flow and a reduction in right ventricular diastolic pressure. Propranolol caused a reduction in heart rate. Pulmonary arterial mean pressure and pulse pressure were unchanged. Stellate stimulation following propranolol caused a marked increase in pulmonary arterial pulse pressure without affecting the diastolic level. Right ventricular systolic and diastolic pressures were increased, reflecting a passive response to the marked elevation in pulmonary vascular impedance.

Femoral arterial pressure was essentially unaffected during stimulation after propranolol. These results indicate that left stellate ganglion stimulation may exert substantial control over pulsatile hemodynamics in the lung independent of concomitant increases in pressure and flow arising from enhanced right ventricular contractility.

The harmonic content of pressure and flow wave forms recorded during left stellate ganglion stimulation before and after propranolol are shown in Figure 4 for a typical experiment. The control pressure and flow moduli decrease rapidly with harmonic number, and little significant information can be obtained beyond 12 cycles/sec (7). Left stellate ganglion stimulation increased both mean pressure and mean flow and markedly
increased the pressure and flow moduli. The increase in pressure moduli relative to control was considerably greater than corresponding increases in the flow moduli. This disproportionate increase in the amplitudes of pressure moduli compared to flow moduli corresponds to the elevation in impedance magnitude obtained during stellate ganglion stimulation. The administration of propranolol reduced the heart rate and decreased the amplitudes of pressure and flow moduli. Following propranolol, stellate ganglion stimulation caused an increase in mean pressure and in the moduli of the first and second pressure harmonics. On the other hand, mean flow and the harmonic content of the flow wave form was essentially unaltered from control levels. The invariance of the harmonic content of the flow wave indicates that the inotropic response was completely blocked by propranolol, since even slight increases in contractility would be expected to increase the amplitude of the flow pulse. Hence the input signal to the pulmonary bed was unaltered during left stellate ganglion stimulation after propranolol, and therefore the observed alterations in the harmonic content of the pulmonary arterial pressure wave could be attributed solely to changes in the physical characteristics of the pulmonary vasculature induced by sympathetic vasomotor nerves. Figure 4 shows that the effect of heightened right ventricular contractility was to increase the harmonic content of the pressure and flow waves in the main pulmonary artery by elevating the amplitude of pressure and flow moduli derived from both
TABLE 2

Effects of Stimulation of the Left Stellate Ganglion on Pulmonary Mean Pressures and Flow before and after Propranolol

<table>
<thead>
<tr>
<th>Dog</th>
<th>Control</th>
<th>LSS 20 cps</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MPAP (mm Hg)</td>
<td>MLAP (mm Hg)</td>
</tr>
<tr>
<td>1</td>
<td>13.2</td>
<td>6.1</td>
</tr>
<tr>
<td>2</td>
<td>16.0</td>
<td>2.1</td>
</tr>
<tr>
<td>3</td>
<td>19.0</td>
<td>3.8</td>
</tr>
<tr>
<td>4</td>
<td>17.9</td>
<td>3.8</td>
</tr>
<tr>
<td>5</td>
<td>20.0</td>
<td>5.8</td>
</tr>
<tr>
<td>6</td>
<td>16.2</td>
<td>3.7</td>
</tr>
<tr>
<td>7</td>
<td>14.4</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Before Propranolol

After Propranolol

MPAP = mean pulmonary arterial pressure; MLAP = mean left atrial pressure; CO = cardiac output; PVR = pulmonary vascular resistance; LSS = left stellate ganglion stimulation.

The influence of left stellate ganglion stimulation exclusive of enhanced right ventricular contractility was primarily to augment pressure moduli at the lower frequency harmonics.

The administration of propranolol caused pulmonary vascular resistance to increase, but this alteration was not statistically significant in the grouped data (Table 2). Left stellate ganglion stimulation after propranolol produced an elevation in pulmonary mean pressure with little change in peak flow (Fig. 5). The impedance magnitudes of the first three harmonics increased with each successive increase in stimulus frequency, and stimulation at 20 cps caused an elevation in the impedance magnitude of each harmonic above corresponding control values.

Table 2 shows the results of seven experiments in which the effects of left stellate ganglion stimulation on pulmonary vascular resistance were determined before and after propranolol. Left stellate ganglion stimulation before propranolol produced a significant increase in pulmonary mean pressure (P < 0.025) with a slight increase in mean left atrial pressure. Augmentation in nonpulsatile parameters during stimulation was associated with a marked increase in impedance moduli (Table 3). The administration of propranolol (1.0 mg/kg) caused reductions in pulmonary mean flow and mean pressure, but pulmonary vascular resistance was not significantly affected. This dose of propranolol effectively blocks the chronotropic and inotropic effects of 0.5 μg/kg isoproterenol. Left stellate ganglion stimulation following propranolol increased flow in two of seven dogs, decreased it in three, and had essentially no effect on it in the other two (Table 2). The failure of propranolol to completely block the inotropic response to nerve stimulation accounts for the
flow increases. The flow decreases were most likely the result of the elevation in hydraulic impedance which suppressed right ventricular flow (Fig. 3). A marked reduction in pulmonary flow occurred in only two experiments; hence this change should not be considered as a characteristic hemodynamic response associated with left stellate ganglion stimulation after propranolol. Table 3 shows average (± SE) values of impedance magnitudes associated with left stellate ganglion stimulation before and after propranolol for the five harmonics for the same dogs as in Table 2. The magnitude of the first harmonic increased 60% during stimulation before propranolol and 81% after drug administration. In comparison to impedance spectra generated before propranolol, the impedance magnitudes of higher frequency harmonics (8-12 cps) were only slightly elevated during left stellate ganglion stimulation after propranolol.

### Discussion

The general features of the control input impedance pattern in experiments of this study were similar to those reported by Bergel and Milnor in open-chest dogs (4). They found that impedance magnitude fell from relatively high values at frequencies below 2 cps to a minimum between 2 and 4 cps, followed by a maximum around 6 cps. Their interpretation of oscillations in impedance magnitude was based on the transmission line model proposed by Taylor (12), in which impedance minimums and maximums are explained on the basis of reflected pressure waves originating from a theoretical termination where vessel discontinuities and points of branching occur. The transmission line concept provides for a coherent interpretation of pressure-flow data, and the experimental results from the present study are analyzed within the framework of this model.

The effects of left stellate ganglion stimulation on pulmonary vascular impedance spectra were primarily to increase the impedance magnitude and decrease impedance phase. These results are consistent with observations made by Ingram et al. showing that sympathetic nerve stimulation decreased the volume distensibility of the main pulmonary artery and generated a 59% increase in dynamic elastic modulus (3). In the present experiments, the upward shift in the curves of impedance magnitude could logically be attributed to arterial stiffening. The average characteristic impedance was increased 76% from control during stimulation at a frequency of 20 cps. The positive phase angles between pressure and flow were progressively reduced as the frequency of nerve stimulation was increased, and during stimulation at 20 cps the phase lag was essentially reduced to zero degrees. Similarly, O'Rourke demonstrated that when lucite ferrules were applied to the brachiocephalic artery and descending thoracic aorta, arterial distensibility was reduced and ascending aortic input impedance moduli

### Table 3

Effects of Stimulation of the Left Stellate Ganglion on Impedance Magnitude and Heart Rate before and after Propranolol

<table>
<thead>
<tr>
<th></th>
<th>Before propranolol</th>
<th>After propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>LSS 20 cps</td>
</tr>
<tr>
<td>Impedance magnitude (dyne sec cm⁻⁵ kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Z₁</td>
<td>5588 ± 780</td>
<td>8949 ± 654</td>
</tr>
<tr>
<td>Z₂</td>
<td>7121 ± 960</td>
<td>10439 ± 915</td>
</tr>
<tr>
<td>Z₃</td>
<td>5282 ± 795</td>
<td>13901 ± 2244</td>
</tr>
<tr>
<td>Z₄</td>
<td>7495 ± 880</td>
<td>9500 ± 792</td>
</tr>
<tr>
<td>Z₅</td>
<td>6725 ± 241</td>
<td>11323 ± 1527</td>
</tr>
<tr>
<td>Heart rate (beats/sec)</td>
<td>2.4 ± 0.09</td>
<td>3.1 ± 0.1</td>
</tr>
</tbody>
</table>

Values represent mean (± SE) for the seven experiments shown in Table 2. Impedance magnitudes (Z) are shown for the first five harmonics. The frequency of the first harmonic corresponds to the heart rate. LSS = left stellate ganglion stimulation.

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were greater than under control conditions, while impedance phase was decreased (13). It appears that in both the systemic and pulmonary circulations arterial stiffening increases the hydraulic load presented to the ventricles. This effect may be of considerable importance in the pulmonary circulation, since during physiological adjustments involving heightened sympathetic activity, the opposition to pulsatile flow may be expected to increase as much as 40% without a significant change in resistance (Fig. 2, 5 cps). This means that under the influence of the sympathetic nerves, pulmonary vascular input impedance becomes a greater fraction of the total opposition that must be overcome in moving blood through the lungs.

As the frequency of left stellate ganglion stimulation was progressively increased, the frequency-dependent oscillations in the impedance were attenuated so that at 5 cps the impedance spectrum tended to flatten out after the initial minimum (Fig. 2). Attenuation of impedance oscillations suggests the loss of “effective” sites for wave reflection (14). This might result from an increase in the radii of small pulmonary arteries (0.5-2.0 mm diameter) due to elevated mean arterial pressure arising from augmented right ventricular contractility. In this connection, several studies have demonstrated that the physical effects of augmented intra-arterial pressure can markedly influence pressure-flow relations in the lung (15-17). Rudolph and Auld showed, in perfused lungs, that calculated pulmonary vascular resistance was rapidly decreased as pulmonary arterial mean pressure was raised to 20 mm Hg, but further increases in pressure were not associated with a fall in resistance (18). Presumably this reduction in pulmonary vascular resistance reflects a passive distention of resistance vessels resulting from increased transmural pressure. In the present study, average mean pulmonary arterial pressures were 21.2 and 22.4 mm Hg at left stellate ganglion stimulation rates of 10 and 20 cps, respectively; hence pressure was at a level sufficient to cause radial distention of small arteries. The experiments of Rudolph and Auld also demonstrated that small pulmonary arteries constricted by serotonin were strongly influenced by alterations in transmural pressure. They showed that serotonin caused a great increase in calculated resistance at a mean pressure of 30 mm Hg, but when pulmonary arterial mean pressure was increased to 75 mm Hg, pulmonary resistance was reduced to a level within the normal range. Pulmonary arteries influenced by serotonin also appear to represent the major sites for reflection in the pulmonary circulation, and this lends support to the contention that increased pressure and flow during left stellate ganglion stimulation may act to distend these small arteries thereby attenuating their capacity to act as sites for wave reflection.

On the other hand, left stellate ganglion stimulation following propranolol often produced impedance patterns indicative of augmented wave reflection. In general, stellate ganglion stimulation following propranolol tended to elevate impedance magnitude primarily between 2 and 6 cps, with comparatively less of an effect on the magnitudes derived from higher frequency harmonics (Fig. 5, Table 3). Similar alterations in impedance pattern were reported by O'Rourke and Taylor in the femoral bed following close arterial injections of norepinephrine (19). They demonstrated that elevation of the impedance curve at the lower frequencies was the result of drug-induced vasoconstriction which tended to increase wave reflection. This phenomenon was also shown to occur in the pulmonary bed during serotonin infusion (4). Conceivably, in the present experiments, vasoconstriction of small arteries (about 1.0-2.0 mm diameter) during stellate ganglion stimulation after propranolol may have generated more optimal conditions for wave reflection. This is supported by the fact that increases in resistance were usually greater during stimulation after propranolol (Table 2). However, in the presence of concomitant augmentation of cardiac activity, the increased transmural pressure may have countered the vasomotor effects of left stellate
ganglion stimulation and prevented vasoconstriction (15). Indeed, the attenuation of oscillations in the impedance curves generated before propranolol (Fig. 2) suggests that these vessels may have been slightly dilated.

It is important to consider possible direct effects of propranolol on the pulmonary vasculature. Burks and Cooper (20) demonstrated that propranolol enhanced the pressor response to sympathetic nerve stimulation in isolated mesenteric arteries, and they concluded that alpha-receptor stimulants combine with both alpha and beta receptors and that blockade of the peripheral beta receptors makes more stimulant available for alpha-receptor stimulation. This mechanism may have contributed to the enhanced elevation in pulmonary vascular resistance observed during nerve stimulation after propranolol. On the other hand, Oskoui and Aviado demonstrated that in the heart-lung preparation propranolol caused calculated pulmonary vascular resistance to increase but concluded that this was the result of a local action producing either spasm of bronchial muscle or vasodilation of blood vessels in the bronchial mucosa. The effects on resistance were not attributed to an action on pulmonary vessels (21).

Furthermore, in the experiments of Ingram et al., propranolol did not appear to alter the physical characteristics of the main pulmonary artery in vivo or its responsiveness to sympathetic nerve stimulation (3). In the present study, the administration of propranolol did not significantly change calculated pulmonary vascular resistance or impedance magnitude as a function of frequency (Tables 2 and 3). It is therefore doubtful that the observed differences in impedance curves generated during nerve stimulation before and after propranolol can be attributed to a direct action on the lung vasculature. These differences are most likely the result of the beta-receptor-blocking effects of propranolol, which attenuated the pressure and flow increases associated with the cardiac sympathetic response and thus allowed the vasomotor nerves to effect a greater reduction in vessel radius.

The increases in calculated resistance during nerve stimulation before propranolol occurred with elevated mean arterial pressure and little alteration in mean left atrial pressure. The latter effect is of importance since wide fluctuations in left atrial pressure can strongly influence calculated pulmonary resistance independent of neural effects on vessel caliber (17, 22, 23). However, enhanced vascular resistance together with elevated mean arterial pressure and essentially unchanged mean left atrial pressure during left stellate ganglion stimulation is a strong indication of vasoconstriction. Anderson and Brown have shown that strong activation of sympathetic outflows by stimulation of the hypothalamic integrative area elicited marked increases in pressure and flow together with intense pulmonary vasoconstriction in the cat (24). Similarly, the results of the present experiments indicate that with maximal activation of sympathetic outflows (left stellate ganglion stimulation, 10-20 cps) vasoconstriction probably occurred, causing an increase in calculated resistance. Judging from the comparative flatness of the impedance curves generated at these frequencies, it may be inferred that pulmonary arteries less than 0.5 mm in diameter were involved in the vasomotor response, since constriction of larger vessels would be expected to enhance reflection and produce oscillations in the impedance curve as was often the case after propranolol. Caro and Saffman have shown that pulmonary arteries less than 0.5 mm in diameter are essentially unaffected by intravascular pressures ranging from 0 to 25 cm H$_2$O (25); hence these vessels would not be expected to undergo distention as a consequence of increased intravascular pressure during left stellate ganglion stimulation, but they may participate in the vasomotor response because of their close association with sympathetic nerve endings (26). In vessels of such small internal diameter even minute reductions in radius resulting from a weak sympathetic effect would be expected to produce significant increases in vascular resistance.

On the other hand, the possibility also exists that postcapillary venoconstriction may have
played a role in the elevation of resistance. Extensive pulmonary venoconstriction has been reported by Stern and Braun, who showed that during reflex sympathetic nerve activation approximately 25–60% of the increase in total pulmonary resistance may develop across the venous system (27, 28). In the present experiments, postcapillary venoconstriction may have played a part in producing the elevation in resistance observed during high frequency left stellate ganglion stimulation.

It could be argued that the elevations in impedance magnitude observed during stellate ganglion stimulation were attributable, in large part, to reduced volume distensibility of the arterial system arising from increased intravascular pressure (29), rather than from a direct neural effect on the arterial wall. Stimulation at 10 cps caused an increase of 7.8 mm Hg in mean pulmonary pressure in the experiments before propranolol (Table 1) and an increase of 5.3 mm Hg after propranolol (Table 2). Based on measurements of phase velocity in the main pulmonary artery during serotonin infusion, Bargainer calculated that an elevation of 17.2 mm Hg in mean pulmonary arterial pressure with serotonin would cause a 50% increase in characteristic impedance (30). In the present experiments, much smaller increases in mean pressure produced a substantially larger increase in the average impedance between 7 and 16 cps. Furthermore, Bergel and Milnor found that impedance spectra obtained during serotonin infusion showed no perceptible increase in characteristic impedance, although mean pressure was elevated 18.7 mm Hg (4). It is therefore doubtful that elevated mean pressure is entirely responsible for the increases in impedance magnitude at the lower frequencies.

The effect of left stellate ganglion stimulation on pulmonary hemodynamics in the absence of increases in cardiac function was primarily an increase in the opposition to low-frequency flow pulsations. Physiologically, these results mean that excitation of pulmonary vasmotor nerves will increase the hydraulic load presented to the right ventricle. Since the major effect of nerve activation is to reduce the distensibility of large arteries, the increase in hydraulic energy would most likely be expended in oscillations. Normally, approximately 30% of the total hydraulic energy generated by the right ventricle is given to pulsations (5). This value would be expected to increase during sympathetic nerve stimulation because of the augmented arterial pulse pressure characteristic of reduced vessel distensibility. Indeed, preliminary studies along these lines have shown that during left stellate ganglion stimulation the energy associated with oscillations can represent close to 50% of the total.

References


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