Pulmonary vascular impedance in the Dog

By Derek H. Bergel, M.B., B.S., Ph.D., and William R. Milnor, M.D.

Pulmonary vascular resistance, defined as the ratio of mean pressure drop across the pulmonary bed to mean blood flow through it, has proved a useful concept in the study of the pulmonary circulation, but fails to take into account the pulsatile nature of blood flow. Pulmonary vascular impedance, which describes the ratio of oscillatory pressure to oscillatory flow, is a more comprehensive expression, and a logical one to use in studying the characteristics of the pulmonary bed that influence the relation between pressure and flow.

Vascular impedance, like its electrical analogue, is a function of frequency, and must be expressed as a spectrum in which the magnitude and phase of the impedance are specified for various frequencies. An impedance spectrum can be computed from experimental data by transforming pressure and flow into Fourier series and using the terms representing each harmonic in the series to calculate impedance for each particular frequency. Input impedance, with which the present work is concerned, describes the ratio of oscillatory pressure to oscillatory flow at the origin of the system, in this case the main pulmonary artery. All that part of the vascular bed between the origin and the region where oscillations are no longer present constitutes the input impedance. The principles governing the application of the impedance concept to a vascular bed, and methods of measuring impedance experimentally, have been described in detail by McDonald.1 2

The usefulness of the concept of vascular impedance rests on the assumption that the vascular bed is a linear system. The pulmonary vascular bed is certainly not perfectly linear, but the degree of its nonlinearity, or the magnitude of the error introduced by treating it as a linear system, have not previously been evaluated in vivo. Linearity implies that impedance will be independent of the form of the applied pressure pulse so long as the dimensions of the vascular bed, the physical properties of the blood vessels, and the rheological properties of the blood flowing through them remain constant. If the pressure is doubled under these conditions, for example, the flow should also double, regardless of the absolute magnitude of pressure and flow. In a nonlinear system, the values calculated for impedance would vary with the shape and magnitude of the pressure pulse, as well as with the characteristics of the vascular channels. Since impedance is meant to summarize quantitatively those properties of the vascular bed that determine the relation between pressure and flow, the calculation of impedance in a grossly nonlinear system would be of little value.

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The experiments reported in this paper were intended: (1) to measure pulmonary vascular impedance in the anesthetized dog, using Fourier analysis of phasic pressure and flow measurements, (2) to assess the linearity of the pulmonary bed by measuring impedance while the heart rate, and hence the pulsatile input to the bed, was varied, and (3) to determine the effect of pulmonary vasoconstriction on impedance, using 5-hydroxytryptamine (serotonin) as the vasoconstrictor. We have interpreted the results by analogy with a simple model whenever possible.

Methods

The control experiments were performed on 13 mongrel dogs, weighing between 13.5 and 21.8 kg (mean 18.4 kg). They were anesthetized with intravenous sodium pentobarbital, 20 mg/kg, after premedication with intramuscular morphine sulfate, 1 mg/kg. A tracheostomy tube and a femoral venous cannula were inserted, and the animals were turned on their right sides. In five dogs a femoral artery catheter was also introduced, to provide a sampling site for determination of cardiac output by the dye dilution method. The animals expired passively against a pressure of 2.5 cm water.

The pericardium was opened, and the proximal portion of the main pulmonary artery was prepared for the probe of an electromagnetic flowmeter. The fat pads which surround the vessel were dissected off and the vessel was separated from the aortic root by blunt dissection over a length of approximately 1.5 cm. The average circumference of the pulmonary artery in this cleared area, measured by encircling it with a length of thread, was 55 mm. A large polyethylene cannula was tied into the left atrial appendage, and a pulmonary artery cannula was placed via a puncture wound in the wall of the right ventricular outflow tract, the wound being closed around the cannula with a superficial purse-string suture if necessary. Various types of cannulae were used in the pulmonary artery but the most successful version was made from 0.05 cm i. d. Teflon tubing about 15 cm long, with the end occluded by a short length of wire and two side holes cut 5 to 10 mm behind the tip. When stiffened by the insertion of a wire this cannula could be pushed through the ventricular wall with little difficulty.

Pressures were measured with Statham P23Db gauges. The hydrostatic base line for all gauges was 2.5 cm above the top of the operating table, in a position which corresponded approximately to the level of the right atrium. The manometers were calibrated frequently, and the systems were flushed with heparinized freshly-boiled saline at appropriate intervals. The frequency response of the pressure-sensing system was determined by recording the response to a square-wave pressure input produced by bursting a rubber balloon over the catheter tip. In general, the natural frequency of the gauge and catheter used in the pulmonary artery, calculated from this response, was 110 cycles/sec and the relative damping 0.3 to 0.4.

The electromagnetic flow probe was then placed around the main pulmonary artery as near as possible, and the probes used were C-shaped, with an iron core (type EMP-100, Electromagnetic Probe Company, Winston-Salem, North Carolina). Careful adjustment of the probe was necessary to avoid kinking or distortion of the vessel. Application of the probe reduced the cross section of the artery by about 10% in most cases, and less than 20% in all cases. At times the probe had to be suspended by an elastic band before a good fit was obtained. The pulmonary arterial cannula was then adjusted until its tip lay just beyond the probe.

Blood flow was measured with this probe and a square-wave electromagnetic flowmeter (model 202, Carolina Medical Electronics Inc., Winston-Salem, North Carolina). In five animals the flowmeter and probe were calibrated in vivo, after all other experimental procedures had been completed, by recording simultaneously the flowmeter signal and an indicator dilution curve for determination of cardiac output. Cardiogreen dye (Hynson, Westcott and Dunning, Inc., Baltimore, Maryland) was the indicator used, and the technique was similar to that we have described previously. To extend the range of calibration, measurements were also made after blood flow had been increased by intravenous administration of isoproterenol, 2 μg/kg min, so that calibration was carried out at flows ranging from 0.9 to 4.5 liters/min. The mean calibration constant in 14 determinations on these five dogs was 37.31 (SEM ± 1.55) ml/min per microvolt signal at the probe electrodes. Since the standard error of this determination was approximately that of the indicator dilution method itself, and since the standard error in determination of the calibration constant in a series of in vitro tests of the flowmeter was only 1.6%, we used the mean...
calibration constant for this probe in all experiments. The dynamic response of this flowmeter to known sinusoidal flows has been tested in vitro by Cessner and Bergel; phase shift is 0.87 radians at 10 cycles/sec, and amplitude sensitivity is 20% less at 10 cycles/sec than at 1 cycle/sec. These measurements of dynamic response were used to correct all flow data in subsequent computations.

In our first trials we experienced the same difficulties in determining the zero flow signal that have plagued most users of electromagnetic flowmeters. The flow base line often varied considerably with respiration despite all efforts to adjust the probe position and balance, and a satisfactory signal corresponding to zero flow could not be obtained either by switching off the probe magnet or by arresting the heart with acetylcholine. Clamping the pulmonary artery beyond the probe to stop flow temporarily was not entirely satisfactory, since it often could not be accomplished consistently without disturbing the probe. Base line stability was improved greatly by flooding the thoracic cavity with saline to a depth that submerged the pulmonary artery and probe, which had the additional advantage of reducing the temperature of the probe, and the zero flow signal was determined by assuming that net flow through the probe during diastole was zero.

In the course of the experiment the pulmonary arterial blood flow, pulmonary arterial pressure, left atrial pressure, electrocardiogram, and respiratory phase were recorded simultaneously on a multichannel recorder (model DR-8, Electronics for Medicine, White Plains, New York). A section of a typical record is shown in figure 1. Continuous records were made at a paper speed of 100 or 200 mm/sec for periods of 5 to 10 seconds, with time-lines at intervals of 0.02 sec. From these records, strips containing an integral number of cardiac cycles and covering one respiratory cycle were selected, being careful to find a sequence in which the final pressures and flows were very nearly the same as the initial ones. The pressure and flow traces were then measured at each time-line in arbitrary units, using approximately 1000 units for the 19-centimeter width of the paper. The resulting numbers, together with the necessary base line and calibration constants, were transferred to punched cards and analysed on an IBM 7094 digital computer.

The first steps in the computer program were the subtraction of zero base lines, conversion into pressure and flow units, and computation of mean values. The means were then subtracted from the original data and Fourier analysis was performed on the remaining oscillatory values. From 60 to 90 harmonics were computed, the exact number depending on the number of beats in the record; in a run containing 8 cardiac cycles, for example, the 8th harmonic corresponds to the fundamental of the cardiac cycle and the 80th to 10th. Analysis was not carried beyond the 10th heart rate harmonic as a rule, since the amplitude of higher harmonics was less than the noise level. Harmonics at frequencies of 1 cycle/sec or less were presumably influenced by the respirator, which functioned at a rate of 0.25 cycles/sec, and were discarded except in later experiments where steady inflation of the lung was maintained.

The computed Fourier coefficients were converted to modulus and phase form and then corrected in accordance with the measured frequency response of the pressure and flow-sensing systems. 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. For the first harmonic in table 1, for example, impedance magnitude = (6.20 \times 1.334)/2.65 = 3.121 dyne sec cm\(^{-5}\) kg, and impedance phase = (0 - 0.06) = -0.06 radians. Negative phase angles for impedance therefore signify that flow leads pressure. Since measurements were made at the input of the system,
these calculations give the input impedance, and the term impedance is used in this sense except where otherwise specified. All input impedances, including impedance at a "frequency" of zero, were computed without reference to left atrial pressure. Pulmonary vascular resistance, on the other hand, was calculated in accordance with the usual practice in physiology, which defines pulmonary vascular resistance as the difference between mean pulmonary arterial and mean left atrial pressures, divided by mean pulmonary blood flow. In the present report, "resistance" refers to this pulmonary vascular resistance, "impedance" to the oscillatory components of impedance, and "impedance at zero frequency" is so designated. Resistance and impedance values were adjusted for the size of the animal by using blood flow per kilogram of body weight in all computations.

Computer time for each run was about 0.03 hour.

A graphic illustration of a Fourier series derived from a single flow pulse is given in figure 2. A tracing of the experimental record of pulmonary arterial blood flow appears as a broken line at the top of this figure. By appropriate calculations, measurements of the observed flow can be transformed into a Fourier series such that:

$$Q(t) = A_0 + \sum_{n=1}^{N} (A_n \cos n\omega t + B_n \sin n\omega t)$$

where $A_0$ is the mean flow, $\omega = 2\pi/T$, and $T$ is the length of the record, or base period.

Each pair of terms in the sum following $A_0$ in this series represents a sinusoidal wave with frequency of $n\omega$ radians/sec, or $n\omega/2\pi$ cycles/sec, and can be expressed more concisely as:

$$A_n \cos n\omega t + B_n \sin n\omega t = M_n \sin (n\omega t + \phi_n)$$

where:

$$M_n^2 = A_n^2 + B_n^2$$

$$\tan \phi = A_n/B_n$$

$M_n$ is the modulus of the $n$th sinusoidal wave, or harmonic, in the series, and $\phi_n$ is its phase angle. The series cannot actually be carried to infinity, of course, since the Fourier coefficients, $A_n$ and $B_n$, are calculated from a finite number of measurements at discrete time intervals (20 msec in the present experiments). If these measurements are made at equal intervals of time such that $N$ points are measured in the base period $T$, then the greatest number of harmonics that can be calculated is $(N-1)/2$. The curve representing the Fourier series so calculated will pass through each of the points measured, but may not coincide exactly with the observations at intervening points.

Pressure and flow tracings in our experiments, however, and in those of McDonald, are very closely represented by series that include only the first six harmonics. The power represented by pressure and flow terms above the sixth harmonic in our control experiments was between 2 and 3% of the total input power.

One cardiac cycle constitutes the base period in figure 2, so the first or fundamental harmonic has the same frequency as the heart rate: 2.5 cycles/sec. The frequency of the second harmonic is twice the fundamental, and subsequent harmonics are at consecutive integral multiples of the fundamental frequency. If two cardiac cycles were included in the base period, the fundamental frequency would be half the heart rate, or 1.25 cycles/sec, provided the period $T$ were exactly two cardiac cycles in length. The greater the number of consecutive cardiac cycles analyzed, therefore, the greater the number of harmonics in the series, and the greater the number of frequencies for which impedance can be calculated. Harmonics which are not integral multiples of the heart rate will be small in amplitude, however, and experimental errors relatively large. With these considerations in mind, we used eight to ten cardiac cycles for analysis in most cases, and selected the number of cycles nearest one complete respiratory cycle in experiments where phasic respiration was maintained. All harmonics with pressure amplitude less than 0.1 mm mercury, or flow amplitude less than 1 ml/sec, were discarded, these levels being the mean +2 standard deviations of statistically random events, or "noise," in our measurements.

### TABLE 1

<table>
<thead>
<tr>
<th>Harmonic number</th>
<th>Frequency (cycles/sec)</th>
<th>Modulus (mm Hg)</th>
<th>Phase (radians)</th>
<th>Pressure</th>
<th>Modulus (ml/sec kg)</th>
<th>Phase (radians)</th>
<th>Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.55</td>
<td>0.20 (±0.07)</td>
<td>0*</td>
<td>0.65</td>
<td>(±0.21)</td>
<td>+0.06 (±0.05)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5.70</td>
<td>2.76 (±0.28)</td>
<td>-1.90 (±0.28)</td>
<td>1.06</td>
<td>(±0.14)</td>
<td>-2.00 (±0.29)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>8.55</td>
<td>0.92 (±0.19)</td>
<td>-1.58 (±0.49)</td>
<td>0.32</td>
<td>(±0.06)</td>
<td>-1.99 (±0.52)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>11.40</td>
<td>0.72 (±0.12)</td>
<td>-2.09 (±0.27)</td>
<td>0.33</td>
<td>(±0.04)</td>
<td>-2.33 (±0.23)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>14.25</td>
<td>0.35 (±0.07)</td>
<td>-3.34 (±0.47)</td>
<td>0.18</td>
<td>(±0.03)</td>
<td>-3.55 (±0.46)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>17.10</td>
<td>0.21 (±0.05)</td>
<td>-2.76 (±0.25)</td>
<td>0.13</td>
<td>(±0.02)</td>
<td>-3.27 (±0.38)</td>
<td></td>
</tr>
</tbody>
</table>

*Arbitrary reference for all phases.
Misleading results in this application of Fourier methods can arise from inexact correspondence between the base period and the length of the cardiac cycles selected for analysis. Although we made every effort to end the base period at the same point in the heart cycle that the first measurement was made, (usually the onset of the sharp rise in pulmonary arterial pressure) small discrepancies between this point and the 20-msec time lines were inevitable. To minimize this kind of error, we computed Fourier series three times from each set of data: first, with the full set of approximately 200 data points; second, with the last point removed; and third, with the last 2 points removed. Harmonics that showed marked variations in the computed impedance as the base period was thus shortened by 0.02 or 0.04 second were discarded. For the remaining harmonics, the average of the three computations was taken as the impedance. This procedure was used to sharpen the details of the average impedance pattern shown in figure 3, but in all other experiments only the conventional harmonics, at integral multiples of heart rate, were used.

In addition to the control observations, a num-
ber of other experiments were carried out. In some dogs the heart rate was increased by atrial pacing with a small bipolar electrode sewn to the epicardial surface of the right atrium. In others, the rate was slowed by cooling the region of the sinoatrial node with cold water circulated through a small hollow thermode in the form of a disc 5 mm thick and 30 mm in diameter. In order to study very slow heart rates, chronic complete atrioventricular block was produced surgically by placing sutures through the endocardial surface of the right atrium into the region of the atrioventricular node in two animals. The same experimental procedures described for the control dogs were carried out 12 days after operation in one of these animals, and 20 days after operation in the other. In these two dogs, pulmonary arterial flow was measured by a gated sine wave electromagnetic flowmeter (type K-2000, Medicon Division, Statham Instruments Inc., Los Angeles, California), and a hinged, coreless probe (series "K"). Frequency response of this flowmeter had been measured and calibration was performed in vivo as described above. Impedance was measured in both animals at the control rate established by their idioventricular rhythm (0.40 and 0.41 beat/sec), and at faster rates ranging up to 3.06 beats/sec produced by a bipolar stimulating electrode on the right ventricle. During these measurements, the lungs were kept at a steady state of inflation with intratracheal pressure of +5 cm water.

Pulmonary venous pressure was measured in a large vein, within 2 cm of the veno-atrial junction, in three dogs. In one instance the pulmonary venous catheter entered through the left atrium, in the others it was inserted into a small tributary vein and advanced downstream. Fourier series for some of these venous pressures were computed by the method already described.

Serotonin was administered by constant infusion through a catheter in the femoral vein in four dogs with normal rhythm, and two with complete heart block. All but one of these animals received 0.05 mg/kg min, while one received 0.20 mg/kg min. The volume infused was less than 1.0 ml/min. The data needed for computation of impedance were recorded two to six minutes after the start of the infusion. In the two animals with complete block, heart rate was varied by ventricular pacing during serotonin infusion as well as in the control state.

In four dogs with normal cardiac rhythm impedance was measured while the respirator was turned off and the lungs inflated by constant intratracheal pressures of 0, 5, 15, or 25 cm water. Respiration was suspended approximately six seconds for each of these runs.

Results

Average values (± SEM) for nonpulsatile parameters in the 13 sets of control observations in dogs with normal rhythm were as follows: heart rate, 2.85 ± 0.08 beats/sec; mean pulmonary arterial blood flow, 32.9 ± 2.2 ml/sec (or 1.78 ± 0.12 ml/sec kg); mean pulmonary arterial pressure, 19.0 ± 1.0 mm Hg; mean left atrial pressure, 5.3 ± 0.7 mm Hg; pulmonary vascular resistance 10,630 ± 1170 dyne sec cm⁻⁵ kg.

The harmonic content of flow and pressure pulsations in these controls (table 1) was similar to that reported by Patel, deFreitas, and Fry. No significant information could be extracted from either pressure or flow records above the sixth harmonic of the heart rate (15 to 20 cycles/sec) in most cases because the amplitude of higher harmonics fell below the noise level defined earlier.

In each of these animals, a plot of impedance magnitude versus frequency showed peaks and valleys like those reported by Caro and McDonald. The frequencies at which these maxima and minima appeared varied slightly from one animal to the next, but in each instance the impedance magnitude fell from relatively high values at frequencies below 2 cycles/sec to a minimum between 2 and 4 cycles/sec, followed by a maximum in the neighborhood of 8 cycles/sec. In 9 of the 13 dogs a second minimum between 9 and 16 cycles/sec could be identified. The average values plotted as the composite impedance spectrum in figure 3 were obtained by selecting from each control experiment the harmonics that represented the first minimum, first maximum, second minimum (where possible), points approximately midway between these inflections, and a point midway between zero frequency and the first minimum. The standard errors indicated in figure 3 show the variability in position of these points along the frequency scale, as well as the variability of their magnitude and phase. The frequency for the first impedance minimum averaged 2.93 (SEM ± 0.15) cycles/sec, and for the first maximum 6.22 (SEM ± 0.44) cycles/sec. Impedance phase changed from...
negative to positive between 3.0 and 4.5 cycles/sec, reached a positive maximum at 6 to 7 cycles/sec, and remained positive at higher frequencies, though tending toward zero. The data given in table 1, which include only harmonics that are integral multiples of the heart rate, can also be used to compute impedance, and points so calculated fit the graph in figure 3 quite closely. Impedance in the two dogs with heart block showed the same characteristics, and at the slowest heart rates the relatively large pressure and flow harmonics at low frequencies made it possible to define the contour of the impedance curve from 0 to 3 cycles/sec in considerable detail (fig. 6 below).

EFFECTS OF LUNG INFLATION

Cyclic artificial respiration apparently did not influence the impedance pattern above 1 cycle/sec in these experiments, since the pattern was unchanged when respiration was suspended and the lungs inflated at a steady pressure of +5 cm water (fig. 4). Changing intratracheal pressure from 0 to 25 cm water did not alter the frequency at which impedance minima and maxima were seen, but the magnitude of these impedance swings increased as inflation pressure increased (fig. 4).

TRANSMISSION OF PRESSURE OSCILLATIONS TO VEINS

The pressure pulsations in large pulmonary veins near their junction with the atrium were normally too small to measure accurately. When the vein was completely occluded by a ligature at its opening into the atrium, the pulsations increased so that amplitudes of the first three pressure harmonics were 10, 9, and 7%, respectively, of their counterparts in the pulmonary artery.

Pressure variations measured near the closed end of such a totally occluded vessel may be as much as twice their value in the unoccluded vein, because of reflections, and
Pulmonary vascular impedance in a dog with complete atrioventricular block, showing effects of changing heart rate and of serotonin. (A) Points represent impedance measurements at four different heart rates: i.e., control rate of 0.41 beats/sec, and artificially paced rates of 1.32, 1.94, and 2.47 beats/sec. The relative constancy of the impedance pattern with changes of heart rate is evidence that the system is approximately linear. (B) Impedance during continuous intravenous infusion of serotonin, 0.05 mg/kg min at three different heart rates: 0.46, 1.76, and 2.45 beats/sec. The impedance pattern differs from that seen in the control periods, but remains constant at different heart rates. (C) Superimposed estimates of the average impedance patterns in A and B, fitted visually to the observations. Solid line: controls; broken line: serotonin. Serotonin displaced the magnitude and phase curves toward the right, and also increased the oscillation of impedance magnitude with frequency, so that impedance was higher at low frequencies and lower at the minimum than in the controls. These changes suggest that the major reflection sites were closer to the main pulmonary artery during serotonin infusion than in the control state, and that the reflection coefficient was increased.

The proportion of the first pressure harmonic actually transmitted to this site was therefore probably about 5%. The values cited were obtained at a constant intratracheal pressure of +5 cm water; raising the intratracheal pressure decreased transmission to the veins, so that as pressure rose from +5 to +25 cm water, the first two harmonics in the vein were reduced to one-third their previous amplitude and the third harmonic became too small for reliable measurement.

EFFECTS OF VARYING HEART RATE

Artificially induced changes of heart rate were used to present the pulmonary vascular bed with a number of different input waveforms, to provide an in vivo test of the linearity of the system. The fundamental frequency, or heart rate, varied from 0.4 to 4.0 cycles/sec, while the amplitude of the pressure harmonics at any one frequency ranged from less than 0.1 up to 15 mm Hg. The impedance pattern was remarkably stable under these conditions, as would be expected in an approximately linear system. This stability was observed in the dogs with heart block (fig. 6 above) as well as in the other animals (fig. 5). Although the impedance pattern was altered by serotonin infusion, it showed no further change when heart rate was varied during serotonin administration (fig. 6).

EFFECTS OF SEROTONIN

Table 2 lists some of the effects of intravenous infusion of serotonin in four animals with normal rhythm and two with complete heart block. The general hemodynamic effects were similar to those observed in earlier experiments in this laboratory and by other investigators. In each experiment the impedance magnitude increased at frequencies below 3 cycles/sec, the first impedance minimum shifted to about 6 cycles/sec and decreased in magnitude, and the first maximum
Effects of Serotonin

<table>
<thead>
<tr>
<th>Control values</th>
<th>Change produced by serotonin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary blood flow, ml/sec kg</td>
<td>Mean (±SEM)</td>
</tr>
<tr>
<td>Pulmonary arterial pressure, mm Hg</td>
<td>2.00 (±0.28)</td>
</tr>
<tr>
<td>Left atrial pressure, mm Hg</td>
<td>18.5 (±1.3)</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, $10^3$ dyne sec cm$^{-5}$ kg</td>
<td>4.8 (±1.3)</td>
</tr>
<tr>
<td>Characteristic impedance, $10^4$ dyne sec cm$^{-5}$ kg</td>
<td>10.33 (±1.33)</td>
</tr>
</tbody>
</table>

*Average impedance between 8 and 18 cycles/sec.

appeared at about 12 cycles/sec (fig. 6). The impedance phase angles shifted toward negative values, so that phase changed from negative to positive between 5 and 6 cycles/sec. Characteristic impedance, estimated from the mean of the impedance oscillations between 8 and 18 cycles/sec, was not altered significantly by serotonin. In the experiments with serotonin, as in all other experiments, there was no significant correlation between pulmonary vascular resistance and input impedance.

Discussion

The general features of the input impedance pattern in our control experiments (fig. 3) bear a strong resemblance to those seen in simple models\textsuperscript{12, 13} and in the rabbit lung perfused in situ with sinusoidal oscillations.\textsuperscript{8} This pattern has been interpreted as the result of reflected waves,\textsuperscript{8} and it is difficult to arrive at any other reasonable explanation.

The pulmonary impedance in the closed-chest dog reported by Patel and his colleagues,\textsuperscript{8} while similar to that reported here, does differ in several respects. They found a relatively high peak in the impedance magnitude at about 8 cycles/sec, averaging 80% of the resistance, which was much higher than our values at that frequency. A more serious discrepancy appears in the impedance phase angles. They found increasingly negative phase angles with increasing frequency, reaching $-70^\circ$ ($-1.22$ radians) at 18 cycles/sec, while our data show a positive angle at all frequencies above 3 cycles/sec and a tendency to return toward zero above 6 cycles/sec. In view of the careful calibration methods that were applied, this difference is too great to attribute to errors in measurement.

The flow probes used in most of the present experiments were larger and heavier than those used by Patel and his group, but they were carefully placed to avoid marked compression of the pulmonary artery, and in any case the impedance computed from a pressure measurement just distal to the probe should not be greatly affected by slight loading or compression of the more proximal part of the vessel. In the experiments on dogs with heart block, moreover, the probe and flowmeter were similar to those used by Patel et al.,\textsuperscript{8} yet the impedance magnitude and phase showed the same pattern as in our other experiments.

There remains the possibility that the closed-chest dog differs in this respect from the open-chest animal, but this also seems unlikely. First, the harmonic content of pressure and flow waves in our experiments (table 1) was similar to that reported by Patel et al.\textsuperscript{8} Second, we have found the same impedance pattern in two unanesthetized, closed-chest animals with chronically implanted pulmonary artery flowmeters and catheters as in the open-chest dogs reported here. We are therefore unable at present to explain this difference in the phase angle of the impedance.

Since input impedance is determined by all that part of the vascular bed in which pulsations of pressure or flow are present, it is relevant to ask what portion of the pulmonary
vascular bed this includes. Oscillations persist in the pulmonary veins, although greatly attenuated by passage through the small arteries and capillaries. Other investigators have found that 50% of the pressure pulse in the pulmonary artery is transmitted through the capillaries to a "wedged" pulmonary venous catheter, which is probably considerably more than would be present in the absence of wedging, and that approximately 5% is transmitted as far as the lobar veins. These figures applied to frequencies of 2 to 4 cycles/sec, and higher harmonics were attenuated to a greater degree. The 5% transmission that we found in large pulmonary veins near their entrance to the left atrium is consistent with these reports.

If this same degree of attenuation applies to retrograde transmission, then waves reflected back from the pulmonary veins should have little influence on input impedance. Given a pressure harmonic that has been attenuated to 25% of its original size by the time it reaches the veins, for example, even total reflection would return only 0.25, or 6%, back to the main pulmonary artery. It follows that pulmonary venous impedance and reflections from the veins play a relatively small part in the total pulmonary input impedance. By the same reasoning, the influence of oscillatory pressures in the left atrium on pulmonary impedance must be negligible.

Transmission of pulsations to the large pulmonary veins was diminished when the capillaries were compressed by high intra-alveolar pressures, as might be expected. Vasoconstriction in the small pulmonary arteries presumably has a similar effect, thus decreasing still further the capillary and venous contributions to impedance.

PULMONARY BED AS A LINEAR SYSTEM

It is to be expected that the distensibility of blood vessels, the complex elasticity of their walls, and the elliptical cross section of the major pulmonary arteries, will all lead to nonlinearity. A linear model can, therefore, only approximate the behavior of the pulmonary circulation, but the error involved in this approximation has not previously been evaluated. Womersley's equations for blood flow contain nonlinear terms, and he estimated that the error introduced by neglecting them in the calculation of blood velocity is less than 5%. His equations describe a single distensible tube, however, and direct experimental evidence is needed to assess the magnitude of nonlinearity in a real vascular bed.

Our experiments with varying heart rate were designed to provide such evidence, since the changes in rate were necessarily accompanied by changes in the magnitude, phase, and frequency of the pressure harmonics. If the pulmonary bed were a linear system, such variations in input would have no effect on the calculated impedance, and in these experiments the only changes observed were within the limits of error of our methods. We conclude that the vascular bed does approximate a linear system within the limits of accuracy of our measurements and the range of waveforms tested. While rigorous proof of linearity and superposition would require the demonstration that the response to the sum of any two input signals equaled the sum of the responses to those two inputs applied separately, the range of sinusoidal pressure inputs represented by the Fourier terms in the present experiments gives strong evidence of linearity. Further support for this conclusion is provided by the similarity between the impedance pattern found in these experiments, where the input signals were the asymmetric pulses of the living animal, and in the experiments of Caro and McDonald, where the input was a pump-generated sinusoidal wave.

These experiments do not show that nonlinear relationships are absent, but only that they cannot be demonstrated unequivocally by the methods of measurement now available. They do show that consistent results may be obtained by treating the pulmonary bed as a linear system, and that Fourier analysis of pressure and flow may be used therefore to estimate impedance. They also justify comparisons between the pulmonary bed and relatively simple linear mathematical models.
PULMONARY VASCULAR IMPEDANCE

Such a model is almost essential for coherent interpretation of experimental results, in view of the complexity of the distensible branching structure of the vascular bed, and the scarcity of information about pressure and flow in the various segments. The transmission-line model proposed by Taylor\(^{12}\) is, in many ways, the most satisfactory one at present, and permits a consistent set of conclusions from our observations.

**Wave Reflection**

If we adopt the transmission-line model, and regard the variations of impedance with frequency observed in our experiments as the result of reflected pressure waves travelling back from a distal reflecting site to the point at which measurements were made, we can then estimate the distance to the site of reflection, the “characteristic” impedance of the bed apart from reflections, and the reflection coefficient or proportion of the incident wave that is reflected.\(^{2}\)

In this model the termination of the line is of the “closed” type,\(^{5}\) which means that reflected and incident pressure waves summate so as to produce increasing pressure oscillations near the termination. At a distance of one-quarter wave length from the termination, pressure oscillations are at a minimum and flow oscillations at a maximum, so that impedance is at a minimum. One-half wave length away from the termination, as at the termination itself, the situation is reversed, and impedance reaches a maximum. Since wave length equals wave velocity divided by frequency, this sequence of impedance maxima and minima can be observed either by making measurements at one site and different frequencies, as in the present experiments, or by making measurements of a single frequency at different sites, as in Taylor’s experiments with rubber tubes.\(^{12}\) In a complex branching system, such as a vascular bed, reflections arise probably from many different sites, but the obvious oscillations in impedance seen in our experiments and those of other investigators\(^{5,9}\) show that the behavior of the pulmonary bed in this respect resembles that of the simple model with a single reflecting site.

Another feature of this model is that the phase of the impedance passes through zero at the same frequency as the first minimum in impedance magnitude, which is clearly the case in our experiments (figs. 3-6). In the model, however, the phase again crosses zero at each impedance maximum or minimum,\(^{13}\) while our data show consistently positive phase angles after the first zero crossing. In this respect our results are not consistent with the transmission-line model, and we cannot account for this discrepancy at present.

To calculate the distance to the apparent reflecting site it is necessary to know the pulse wave velocity in the pulmonary artery. Attinger estimated this to be 200 cm/sec in the dog,\(^{14}\) which is higher than the 83 cm/sec velocity found by Caro and McDonald\(^{9}\) in the rabbit, but roughly the same as the value of 182 cm/sec suggested by a small number of observations in human subjects by Caro and Harrison.\(^{17}\) It is also consistent with measurements of the elasticity of the canine pulmonary artery by Patel et al.\(^{18}\)

Our average impedance minimum at 2.9 cycles/sec (fig. 3) implies that the distance from measuring site to reflecting site equals one-quarter the wavelength of oscillations at this frequency. Assuming a pulse wave velocity of 200 cm/sec, this places the reflecting site 17 cm downstream from the mid-portion of the main pulmonary artery, where our catheter and flowmeter were located. Waves at the frequency of the impedance maximum at 6.2 cycles/sec should be one-half wave length from the reflecting site, which gives an estimate of 16 cm for this same distance. In the dog lung, this corresponds to arteries 0.5 to 1.0 mm in diameter, according to data given by Attinger\(^{14}\) and according to our own measurements on a single injected specimen. This seems a reasonable average anatomic site for major reflections, and agrees with the conclusions of Caro and McDonald.\(^{9}\) Attinger\(^{14}\) found that a greater change in apparent phase velocity could be produced by clamping the major lobar arteries than by raising intra-alveolar pressure, and concluded

\(^{1}\) Circulation Research, Vol. XVI, May 1965
that the branch points of these arteries were the principal source of reflection. His data, however, are entirely compatible with our conclusion that the greatest source of reflections lies between the major arteries and the capillary bed. His results also show a peak of apparent phase velocity at approximately 6 cycles/sec, which is consistent with our impedance pattern.

The characteristic impedance of a transmission line is defined as the impedance in the absence of reflected waves, and in blood vessels is determined by the dimensions of the vessels and the elastic properties of their walls. In the presence of reflected waves, the observed impedance oscillates in the manner already described around this characteristic value. These oscillations diminish as frequency increases, because the reflected waves are increasingly attenuated as the number of wavelengths to be traversed from reflecting site to measurement site increases, and at higher frequencies the observed impedance assumes the characteristic value.

Here again our results conform to the proposed model, although the impedance tends toward a constant value after a single oscillation, indicating rather strong attenuation. In the aorta, attenuation may be as high as 50% per wavelength, and it may be equally high in the pulmonary artery, but a similar effect could arise from dispersion of reflecting sites. In our control experiments the characteristic impedance, calculated by averaging the impedances observed at 8 to 18 cycles/sec, was 167 (SEM±14) dyne sec cm⁻¹ kg, or 3,094 (SEM±270) dyne sec cm⁻¹ kg when adjusted for body weight.

The reflection coefficient \( R_f \), or ratio of reflected to incident pressure wave, at the peripheral termination, can be calculated from the characteristic impedance \( Z_0 \) and terminal impedance \( Z_t \):

\[
R_f = \frac{Z_t - Z_0}{Z_t + Z_0}
\]  

Terminal impedance in this context means the impedance of the bed beyond the reflecting site, but this can be estimated only indirectly from the measurements made in these experiments. The best estimate is probably made by assuming that impedance at very low frequencies approximates the terminal impedance, as McDonald has suggested. The dogs with complete heart block provided reliable low-frequency harmonics for this purpose, and the impedance measured at 0.4 cycle/sec in these two animals averaged 6,440 dyne sec cm⁻¹ kg. Substituting this for \( Z_t \), and their average characteristic impedance of 3,340 dyne sec cm⁻¹ kg for \( Z_0 \), \( R_f = 0.32 \). In the 13 control experiments on dogs with normal rhythm, harmonics in the neighborhood of 1.5 cycles/sec were the lowest that could be measured accurately, and the impedance at this frequency averaged 5,450 dyne sec cm⁻¹ kg. Their average characteristic impedance was 3,094 dyne sec cm⁻¹ kg, giving \( R_f = 0.28 \). These reflection coefficients are in the same range reported by McDonald for the femoral artery of the dog \( (R_f = 0.3 \) to 0.4), and by Caro and McDonald for the pulmonary bed of the rabbit \( (R_f = 0.25) \). All such estimates must be regarded as rough approximations because of the inaccuracy with which \( Z_0 \) and \( Z_t \) are determined and the errors introduced by neglecting attenuation and phase shift on reflection.

**Vasoconstriction by Serotonin**

The increased impedance at frequencies below 3 cycles/sec and decreased impedance at 5 to 6 cycles/sec seen during infusion of serotonin (fig. 6) suggest increased reflection, and are similar to the changes in the femoral bed following norepinephrine reported by McDonald. The reflection coefficient rose during serotonin to approximately 0.55. The shift of the impedance minimum towards 6 cycles/sec and the transition from negative to positive phase angle in this same part of the frequency scale indicate an apparent shift in the predominant reflecting sites. This could arise either from an alteration of the bed such that the main reflecting sites came to lie nearer the main pulmonary artery, or from an increase in wave velocity. The changes observed could be accounted for by a 50% reduction in the distance to the major reflecting site, by doubling of the wave velocity, or by appropriate mixture of the two effects. A change in the
phase angle of reflection is another mechanism that must be admitted as a logical possibility, though one that cannot be evaluated from the present data.

Two kinds of evidence suggest that increased wave velocity is not the mechanism involved. First, vasoactive agents in general appear to have relatively small effects on the physical properties of the vessel wall that determine wave velocity, although very little experimental evidence on this point is available. These properties include elastic modulus of the wall \(E\), wall thickness \(h\), vessel radius \(r\), and fluid density \(\rho\), in accordance with the Moens-Korteweg equation for wave velocity, \(c\):

\[
c = \sqrt{\frac{Eh}{2\rho}} \tag{6}
\]

To the best of our knowledge, no one has measured the effects of serotonin on the elastic modulus of vessels, but calculations from the data of Rudolph and Auld, who studied the effects of serotonin on pulmonary vascular resistance at various transmural pressures in dogs, indicate that the changes in modulus are not large. Patel et al. found that norepinephrine decreased the change of radius per unit change of pressure by 19% in the pulmonary artery of the dog, and from their data we estimate that the elastic modulus increased by about one-third. The data of Hinke and Wilson on the effects of norepinephrine on a small systemic artery in the rat also suggest very little change in elasticity, provided an estimate of changes in wall thickness is included in the calculations. Norepinephrine is less potent than serotonin in its action on the pulmonary bed, so this evidence is not entirely conclusive. A decrease of vessel radius would also tend to increase wave velocity, and doubtless the caliber of some pulmonary vessels does decrease in response to serotonin, but it seems unlikely that this amounts to the fourfold decrement in radius that would be required to produce the changes of impedance we observed.

A second, and stronger, argument against increased wave velocity is the absence of any significant change in characteristic impedance (table 2). The equation for characteristic impedance, \(Z_0\), of a strongly tethered elastic tube, derived by Womersley is:

\[
Z_0 = \frac{\rho c_0}{\sqrt{(1 - \sigma^2)}} \cdot \frac{1}{\sqrt{(M')}} \cdot e^{-\pi\alpha^2} \tag{7}
\]

where \(\rho\) = density of blood, \(\sigma\) = Poisson’s ratio, \(c_0\) = wave velocity, and \(j = \sqrt{-1}\). \(M'\) and \(\varepsilon\) are functions of Womersley’s nondimensional parameter \(\alpha\), which in turn is a function of vessel radius, frequency of pulsation, density and viscosity of the fluid. These functions have been computed for a wide range of values of \(\alpha\), and in the blood vessels under consideration here \(M'\) approaches 1.0, while \(\varepsilon\) approaches zero. Assuming \(\rho = 1.05\), \(\sigma = 0.5\), and \(c_0 = 200\) cm/sec, the characteristic impedance would be 242 dyne sec cm\(^{-3}\). This expresses impedance as pressure (dyne/cm\(^2\)) per unit velocity of blood flow (cm/sec), while the impedance in our experimental results is expressed as pressure per unit volume flow (dyne sec cm\(^{-3}\)). Dividing 242 dyne sec cm\(^{-3}\) by our average pulmonary arterial cross section of 1.6 cm\(^2\) gives a characteristic impedance of 151 dyne sec cm\(^{-6}\), to be compared with our experimentally determined value of 167 dyne sec cm\(^{-5}\). This correspondence between theoretic prediction and experimental result suggests that the relation between \(Z_0\) and \(c_0\) in equation 7 is valid for the pulmonary bed, and that the absence of any significant change in \(Z_0\) with serotonin implies a similar absence of change in wave velocity. Direct measurements of phase velocity would be the best evidence on this question, but the technical difficulties of such measurements in the presence of reflections, especially in the pulmonary bed, are formidable.

The alternative possibility that the major sites of reflection are now actually further upstream as a result of vasoconstriction by serotonin is quite consistent with our data, as well as with the theory embodied in the transmission-line model and Womersley’s equations. There is ample evidence that most of the pulmonary vasoconstriction caused by serotonin occurs in the arterial bed, and the marked drop in pulmonary blood volume...
suggests that a large part of the bed is involved. Angiographic studies in dogs by Hirschman and Boucek\(^\text{21}\) show that serotonin constricts arteries 2 mm and less in diameter, while the caliber of larger arteries increases slightly. Casts of the pulmonary vessels of the rabbit by Patel and Burton\(^\text{22}\) demonstrate that vasoconstriction by norepinephrine and Pri-\(\text{vine} (-2-(1-naphythyl-methyl) imidazoline hydrochloride)\) also affects the small vessels predominantly. Such changes of vascular dimensions would provide just the conditions needed to shift the dominant reflection sites upstream, and we believe this to be the most probable explanation of our results.

The changes of pulmonary vascular input impedance produced by serotonin appear, then, to result from displacement of the dominant reflection sites toward the larger arteries, and an increase of the reflection coefficient. Although serotonin was selected for these experiments because of its known efficacy as a pulmonary vasoconstrictor, it is entirely possible that other agents which raise pulmonary vascular resistance have quite different effects on impedance and act by other mechanisms.

One consequence of this change of impedance, it should be noted, is an increase in the pulsatile power input to the pulmonary bed, in addition to the power associated with mean pressure and flow. Calculation of input power, or work per unit time, from mean pressure and flow alone in these experiments would underestimate the increase resulting from serotonin infusion by 27%.

Comparison of the changes of impedance produced by infusing serotonin with those that result from raising intratracheal pressure demonstrates the differences between constricting small pulmonary arteries and compressing the pulmonary capillaries. Neither procedure is completely limited in action to one part of the pulmonary circulation, since serotonin also constricts pulmonary veins, and high intralveolar pressures may stretch or compress vessels other than capillaries, but the predominant effect is arterial constriction in the one case, and reduced capillary cross section in the other. Both increased the oscillations of impedance with frequency, indicating increased reflection, and with variations of intratracheal pressure this effect was roughly proportional to the pressure applied (fig. 4). Increased intratracheal pressure, unlike serotonin, did not alter the predominant reflection sites, however, which we interpret as further evidence that the changes of impedance with serotonin arise in the precapillary part of the bed.

Pulmonary vascular resistance was raised by both procedures, demonstrating that changes of impedance and of resistance can be dissociated, but this should not be regarded as evidence that impedance and resistance are normally controlled by different vessels. While the capillary bed contributes largely to the pulmonary vascular resistance, and relatively little to impedance, alterations of both resistance and impedance under physiologic conditions are probably controlled by the smaller branches of the arterial tree.

**Summary**

Pulmonary vascular hydraulic input impedance was measured in 13 anesthetized open-chest dogs with normal sinus rhythm, and 2 dogs with surgically induced atrioventricular block, by means of electromagnetic flowmeters and strain gauge manometers of known frequency response. The linearity of the pulmonary bed was evaluated by measuring impedance while the heart rate, and hence the pulsatile input to the bed, was varied.

The pulmonary bed behaved as a quasi-linear system, within the limits of accuracy of the methods employed and the range of frequencies tested. The use of input impedance, or oscillatory pressure/flow ratio, to describe some characteristics of the bed is therefore justifiable, and analogies with linear models like the simple transmission line are not unreasonable.

The characteristic input impedance averaged 3,094 dyne sec cm\(^{-5}\) kg, or about one-third the magnitude of the pulmonary vascular resistance, and was therefore a significant part of the total opposition that must be overcome in moving blood through the lungs. This
PULMONARY VASCULAR IMPEDANCE

impedance to pulsatile flow is not included in calculations of resistance from mean pressure and flow measurements.

The pattern of the impedance spectrum suggested that reflections originating from arteries 1.0 mm and less in diameter play a large role in determining input impedance and its variations with frequency. Pulmonary vasoconstriction by 5-hydroxytryptamine (serotonin) altered the impedance pattern in a manner consistent with increased wave reflection and displacement of the dominant reflecting sites to positions nearer the main pulmonary artery. Capillary compression by increased intra-alveolar pressure also increased reflection, but did not alter the sites of reflection significantly, providing further evidence that the normal impedance pattern and its modification by serotonin are both determined by the characteristics of the arterial part of the bed.

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