An Analysis of the Pulsatile Hemodynamic Responses of the Pulmonary Circulation to Acute and Chronic Pulmonary Venous Hypertension in the Awake Dog

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SUMMARY In this study we measured high fidelity pulsatile pressure and flow waveforms at the inlet to the pulmonary vascular bed to assess the differences in adaptation to acute and chronic pulmonary venous hypertension in awake dogs. Acute elevations in left atrial pressure (P\textsubscript{La}) were effected by inflation of left atrial balloons, while chronic elevations were accomplished by placement of aorta to left atrial shunts. Pulmonary artery hydraulic impedance was calculated and analysis of these data revealed marked differences between the responses to acute and chronic elevations of left atrial pressure. The acutely stressed dogs (n = 12) had significantly decreased pulmonary vascular resistance (when P\textsubscript{La} = 16.9 ± 1.0 mm Hg, PVR = 212 ± 57 dynes sec/cm\textsuperscript{5}; when P\textsubscript{La} = 28.6 ± 1.4 mm Hg, PVR = 18 ± 115 dynes sec/cm\textsuperscript{6}; control P\textsubscript{La} = 6.1 ± 1.5 mm Hg, and PVR = 355 ± 69 dynes sec/cm\textsuperscript{5}) and normal characteristic impedances (Z\textsubscript{o}) (210 ± 36, 227 ± 39, 178 ± 14 dynes sec/cm\textsuperscript{5}, respectively), indicating recruitment of arteriolar-capillary perfusion density and no change in proximal pulmonary arterial physical properties. The chronic pulmonary venous hypertension group (n = 11) retained normal PVR (496 ± 30 dynes sec/cm\textsuperscript{5}) but demonstrated a markedly higher characteristic impedance, Z\textsubscript{o} = 361 ± 11 dynes sec/cm\textsuperscript{5} (P < 0.001). This indicated a measurably different and extremely potent effect of chronic venous hypertension on the physical properties of the pulmonary vessels with an apparently increased arterial stiffness correlating with a 4-fold increase in Young's elastic modulus. These changes were not reversed by a-adrenergic blockade or acute lowering of left atrial pressures.


PULMONARY venous hypertension has been implicated repeatedly as an important factor in the development of pulmonary arterial hypertensive disease (Hutchins and Ostrow, 1976). However, the mechanisms involved have remained obscure. Disproportionate increases in pulmonary arterial pressure have been observed clinically in mitral stenosis, left ventricular failure, and pulmonary venous occlusive disease (Dexter, 1956; Gorlin, et al., 1951). Severe pulmonary vascular disease is known to occur earlier in congenital cardiac diseases associated with elevated pulmonary venous pressures, e.g., anomalous pulmonary venous return, cor triatriatum, AV canal, and transposition of the great vessels (Plauth et al., 1970; Ferencz and Dammon, 1957). Studies on animals designed to elucidate the mechanisms functioning in the development of pulmonary hypertension as a consequence of elevated pulmonary outflow pressures have revealed disparate and complex responses (Lloyd and Schneider, 1969).

Acute studies on open-chest canines with short term elevations in pulmonary venous pressures have demonstrated both decreased pulmonary vascular resistances (Borst et al., 1956; Hanlon et al., 1956) and increased resistances (Sawyer et al., 1959), and these changes usually have been attributed to neurally mediated vasomotor reflexes (Lloyd and Schneider, 1969). Because of the short duration of the stimulus and the unphysiological nature of the experimental conditions, these studies have limited applicability to the problem of chronic pulmonary venous hypertension.

Studies on animals involving chronic left atrial pressure elevations (pulmonary venous constriction, partial mitral valve obstruction, aorta-left atrial fistulas) have been primarily histological in focus (Blank et al., 1961). Hemodynamic studies have implicated both active and passive mechanisms in the arterial pressure elevations (Silove et al., 1972; Vasco et al., 1967; Von Bogaert and Tozetti, 1963).
A major limitation in virtually all clinical and animal studies that investigate the pulmonary vascular response to pulmonary venous hypertension is that of modeling the pulmonary circulation in terms of mean pressures and flow. This tends to overemphasize vascular recruitment (effective perfusing radius) and ignores changes in vascular stiffness and the relationship of vascular viscoelastic properties and geometry.

In this study, high fidelity pulsatile pressure and flow waveforms were measured in the pulmonary artery of awake dogs with either acute or chronic elevations of left atrial pressure. Hydraulic impedance parameters were calculated and used to compare the mechanisms for adaptation to acute and chronic pulmonary venous hypertension in awake dogs.

**Methods**

**Experimental Preparation**

Two different preparations were studied in which either acute or chronic elevations in left atrial pressure were made. Initial surgery to produce chronic left atrial pressure elevations was performed in fifteen 22- to 25-kg mongrel dogs by creating descending aorta-left atrial fistulas with 12-mm woven Dacron shunts, 30–35 mm in length, via left thoracotomy. Despite preoperative digitalization (0.25 mg digoxin per day), four animals died of pulmonary edema or acute ventricular distention with fibrillation. In the remaining eleven, digoxin was discontinued 5 days after surgery and they were placed in a chronic care facility and exercised daily. Patency of the shunt was assured by periodic auscultation of a continuous murmur in the left chest. After 2 months, these dogs were returned to the laboratory for placement of chronic instrumentation.

**Instrumentation**

The following procedure for instrumentation implantation was performed on 12 dogs with no prior surgery (acute animals) and on the 11 dogs in which an aorta to left atrial shunt had been created previously (chronic animals). The dogs were anesthetized with pentobarbital (30 mg/kg, iv) and ventilated with a Bennett MA-1 respirator. A thoracotomy was performed aseptically in the left 4th intercostal space. The main pulmonary artery was minimally dissected from the aorta and an electromagnetic flow probe (Howell Instruments) placed about the pulmonary artery with careful matching of size to ensure good electrical contact and minimize stenosis. In five of the chronic animals, flow probes also were placed on the shunts. Silastic introducer catheters (access for later placement of pressure transducer tipped catheters) were sutured into the right ventricular infundibulum and into the pleural space adjacent to the pulmonary artery. A bipolar pacing electrode was sutured to the right ventricle. Polyvinylchloride catheters (14-gauge; Alpha Wire Corp.) with heparinized saline were placed in the right atrium, left atrium, and in the aorta via the left subclavian artery. Acute animals also had 30-ml silastic balloon catheters sutured to the left atrium. The lead wires and catheters were tunnelled through the chest wall and placed in subcutaneous pouches. The chest was closed and the animals allowed to recover for 10–14 days. Intramuscular propracaine penicillin G (6 × 10⁶ U), dihydrostreptomycin (0.75 g), and oral digoxin (0.25 mg) were administered for 5 days postoperatively. All animals tolerated the chronic instrumentation procedure without difficulty. Digoxin was used only in the chronic dogs and was discontinued 10 days prior to study.

On the day of the study the dogs were given intramuscular morphine sulfate (0.25 mg/kg). Under local xylocaine anesthesia, the subcutaneous pouches were opened and the leads and catheters exteriorized. With fluoroscopic visualization, a 7-French high-fidelity micromanometer catheter (PC-470, Millar Instruments, Houston, Tex.) was passed through the right ventricular introducer catheter and the sensor positioned just distal to the flow probe in the main pulmonary artery. There were no pressure gradients across the flow probe site or waveform distortions in the main pulmonary artery in the animals studied. A 5-French micromanometer catheter (PC-350 A, Millar Instruments) was passed through the other introducer into the pleural space adjacent to the pulmonary artery. The left atrial catheter was connected to a Statham P23-Gb pressure transducer. The flow probe was driven by a gated sine wave flowmeter (M4001, Statham Instruments). All data were recorded on an eight-channel strip chart recorder and on an FM analog magnetic tape (Ampex FR 1300 A recorder) for subsequent computer processing.

Pulsatile pulmonary artery flow, pulmonary artery pressures, pleural pressure, left atrial pressure, and aortic pressure were recorded after the dogs had adjusted to laboratory conditions for 2 hours. Various heart rates from 60 to 180 beats/min were obtained with pacing and by recording during spontaneous sinus arrhythmia. Acute elevations in left atrial pressure were produced in twelve 22- to 25-kg mongrel dogs by inflating a previously implanted left atrial balloon. The balloon inflations were performed stepwise to approximately 15 mm Hg (step 1) and 30 mm Hg (step 2) and held for 30 minutes prior to acquisition of data. Measurements were also obtained initially, prior to the balloon inflations, with normal low left atrial pressures; these are termed control data. Transmural pulmonary artery pressure (intravascular-pleural pressure) and transmural left atrial pressure (atrial-pleural pressure) were used for data analysis.

Pressure transducers were warmed for 24 hours prior to use and calibrated statically before, during, and after each experiment with a water manometer.
in a constant temperature bath held at 38°C. Dynamic testing of the micromanometer was performed using a sinusoidal oscillating pressure wave at varying frequencies with responses consistently flat to beyond 200 Hz. Flow probes were calibrated in a constant flow device containing saline both before implantation and after the dogs had been killed; if flow calibrations deviated by 5% or more, the experiment was discarded. Dynamic electronic calibration of the flowmeter revealed an amplitude response of 100% to 9 Hz, falling linearly to 40% at 50 Hz. Phase lag was 45° at 10 Hz and linear to 50 Hz. The system phase shift between the pressure and flow waveforms was found to be negligible by a computer cross-covariance technique, and thus no phase correction was required.

Five of the animals with shunts underwent α-adrenergic blockade with phenoxybenzamine. The phenoxybenzamine was delivered as an intravenous drip over 45 to 60 minutes. Lack of response to phenylephrine, 20 μg as an intravenous bolus, was accepted as evidence for adequate blockade. Hemodynamic data were obtained when adequate blockade had been achieved. Dextran 70 in 0.9% sodium chloride then was infused to expand intravascular volume. Hemodynamic data were again recorded when left atrial pressure was equal to the pre-blockade values.

Data Analysis

The methods for data analysis have been described previously (Hopkins et al., 1979). The computations of impedance were based on Fourier analysis of the pulmonary artery pressure and flow waveforms as previously described (Attinger, 1963; Milnor et al., 1966). Ten harmonics were calculated for each heart beat. Total pulmonary flow was expressed as

\[ Q(t) = Q_m + \sum_{n=1}^{10} Q_n \sin(n \omega t + \theta_n) \]

where \( Q_m \) mean flow, \( Q_n \) = amplitude of the \( n \)th harmonic, \( \omega \) = the fundamental angular frequency, \( t \) = the length of the sequence and \( \theta_n \) = phase angle of the \( n \)th harmonic. Terms of the equation in which flow moduli were less than 6.0 ml/sec were eliminated from subsequent analysis since this flow magnitude approaches the noise level of the data recording system.

Pressure waveforms were expressed as

\[ P(t) = P_m + \sum_{n=1}^{10} P_n \sin(n \omega t + \beta_n) \]

where \( P_m \) mean pressure, \( P_n \) = amplitude of the \( n \)th harmonic, and \( \beta_n \) = the phase angle of the \( n \)th harmonic. Terms of the equation with pressure moduli less than 0.75 mm Hg were eliminated.

Division of mean terms (\( P_m/Q_m \)) yielded the input impedance to mean flow. Similarly, the division of each of the sinusoidal terms (\( P_n/Q_n \)) gave the input impedance to the \( n \)th harmonic. The corresponding phase angle \( \phi_n \) was derived from subtraction of the flow phase angle from the pressure phase angle \( \phi_m = \theta_n \). Characteristic impedance \( (Z_o) \) was defined as the average impedance modulus between 7 and 11 Hz. Differences between group means were assessed by unpaired two-tailed Student’s t-test (Zar, 1974).

Impedance, Viscoelasticity, and Geometry

Input impedance \( (Z) \) is measured at the vascular bed inlet and determines the specific amplitude and time relationship between the pressure and flow waveforms. Impedance is therefore a frequency dependent property of the system which is modulated by vascular geometry, the viscoelastic properties of the vessels, and wave reflections (Attinger, 1963). Impedance at the lower frequencies is determined partially by reflected waves as modified by the distribution of reflection sites and vessel attenuation characteristics. The characteristic impedance \( (Z_o) \) is by definition the impedance in the absence of reflected waves and, therefore, in blood vessels, is determined only by dimensions and elastic properties of the walls (McDonald, 1974).

Womersley defined the relationship between wave velocity \( (C_o) \), vessel radius \( (R) \), and the characteristic impedance \( (Z_o) \) (Womersley, 1957):

\[ Z_o = \frac{\rho C_o}{p R^2 (1 - \alpha^2)} \cdot \frac{1}{M_{10}} \cdot e^{-j\pi/2} \]

where \( \rho \) = density of blood = 1.055 g/ml, \( \alpha \) = Poisson’s ratio = 0.5, \( j = \sqrt{-1} \), \( M_{10} \) and \( \epsilon \) are Bessel functions of Womersley’s nondimensional parameter \( \alpha \). Bargainer has validated the application of Womersley’s equations with direct measurements of apparent phase velocities in the canine main pulmonary artery (Bargainer, 1967).

The classical Moens-Korteweg equation for wave velocity expresses the basic relationship of elasticity and geometry to \( C_o \):

\[ C_o = \sqrt{(Eh)/(\rho 2R)} \]

where \( h/2R = 0.03 \) and \( h \) is Young’s elastic modulus.

Measurements of the peak main pulmonary artery circumference at the time of construction of the shunt and at instrumentation revealed no significant static changes in the proximal vascular diameters. Thus, wave velocities and elastic moduli can be calculated with the Womersley and Moens-Korteweg relationships. Changes primarily reflect alterations in vessel stiffness.

Results

Standard Hemodynamics

Acute Studies

A typical analog recording of hemodynamic data obtained during control conditions and two levels
of elevated left atrial pressure are shown in Figure 1. Significant incremental increases in pulmonary artery pressures were observed in the 12 dogs in which left atrial pressures were acutely elevated (Table 1). The transpulmonary vascular mean pressure gradient ($P_{PA} - P_{PA}'$) progressively and significantly narrowed from $9.3 \pm 0.7$ mm Hg in the controls to $0.4 \pm 0.1$ mm Hg ($P < 0.005$). As there were no significant differences in the pulmonary blood flows ($Q_{pa}$) in these acute studies, the pulmonary vascular resistance progressively fell, indicating a recruitment of arteriolar-capillary perfusion density, presumably as a consequence of the increasing transmural distending pressures.

**Chronic Studies**

Typical phasic hemodynamic data obtained in a dog with chronic elevation of left atrial pressure are shown in Figure 2. The average shunt flow (aorta to left atrium) measured in five of the animals with chronic pulmonary venous hypertension was $692 \pm 98$ ml/min. Aorto-left atrial shunting for 10 weeks resulted in elevation of the transmural left atrial pressures in these 11 dogs to a mean of $11.3 \pm 0.4$ mm Hg ($P < 0.05$). The $Q_{pa}$ was decreased in these animals although the left ventricular cardiac outputs ($Q_{pa} +$ shunt flow) as measured in the five dogs was essentially the same as the control dogs. The transpulmonary vascular gradient narrowed somewhat so that, despite the depressed pulmonary blood flow, the PVR was only modestly increased to $140\%$ of control ($0.10 > P > 0.05$). This resistance approximately $15$ mm Hg (transmural). Left atrial pressure is electronically meaned for five systoles, then displayed phasically. Panel C: Left atrial pressure step 2 to a mean of approximately $30$ mm Hg. Note the distortion of the phasic left atrial pressure tracing by the balloon inflation.
TABLE 1 Standard Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>P_P (mm Hg)</th>
<th>P_max (mm Hg)</th>
<th>P_end (mm Hg)</th>
<th>HR (beats/min)</th>
<th>Q_b (l/min)</th>
<th>PVR (dynes sec/cm^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control, acute group</td>
<td>6.1 ± 1.5</td>
<td>22.6 ± 1.6</td>
<td>11.5 ± 1.0</td>
<td>102</td>
<td>2.19 ± 0.14</td>
<td>355</td>
</tr>
<tr>
<td>Acute pulmonary venous hypertension (step 1)</td>
<td>16.9** ± 1.0</td>
<td>26.2 ± 1.6</td>
<td>19.8* ± 1.6</td>
<td>173** ± 1.5</td>
<td>173 ± 0.23</td>
<td>212</td>
</tr>
<tr>
<td>Acute pulmonary venous hypertension (step 2)</td>
<td>28.6** ± 1.4</td>
<td>33.5* ± 2.3</td>
<td>26.0** ± 1.5</td>
<td>33.5 ± 1.5</td>
<td>16 ± 0.19</td>
<td>115</td>
</tr>
<tr>
<td>Chronic pulmonary venous hypertension</td>
<td>11.3* ± 0.4</td>
<td>29.9* ± 2.3</td>
<td>14.2 ± 0.2</td>
<td>95.6 ± 0.10</td>
<td>1.34** ± 0.10</td>
<td>496</td>
</tr>
</tbody>
</table>

Results are expressed as means ± SEM. P_P = mean left atrial pressure; P_max = systolic pulmonary artery pressure; P_end = pulmonary artery diastolic pressure; HR = heart rate; Q_b = pulmonary blood flow; PVR = pulmonary vascular resistance (P_max-P_end/Q_b).

* Different from control, P < 0.05, unpaired two-tailed t-test; ** P < 0.005.
† Transmural pressures.

response is markedly different from that of the acute animals in which the PVR measurably decreased to values significantly different from the chronic dogs (P < 0.005). Microscopic analysis with hematoxalin-eosin and Verhoef-Van Gieson stains revealed normal vascular histology in these animals.

Impedance

Acute Studies

In these dogs the impedance spectra were altered only by significant elevations in Z_m (control: 609 ± 59, step 1: 910 ± 94, step 2: 1376 ± 154 dynes sec/cm^5). The impedance to mean flow (Z_m) progressively increased as the pressures were acutely elevated. Whereas there was slightly altered maxima and minima in the higher frequencies, the characteristic impedances (Z_o) were not different for the control and acute pulmonary venous hypertension dogs (Fig. 3): control Z_o = 178 ± 14, step 1 Z_o = 210 ± 36, step 2 Z_o = 227 ± 39 dynes sec/cm^5. Calculated elastic moduli for the dogs with acutely elevated left atrial pressures were not significantly different from controls (Table 2).

Chronic Studies

The animals with chronically elevated left atrial pressures demonstrated dramatically altered impedance spectra with elevations at all frequencies (Fig. 4). The characteristic impedance was significantly increased to 361 ± 11 dynes sec/cm^5 (P < 0.001), indicating profound alterations in the physical properties of the pulmonary vessels. Comparison of the calculated elastic moduli (control E = 3.165 ± 0.020, chronic E = 12.998 ± 0.013 dynes/cm^2 × 10^6, p < 0.001) demonstrates a highly significant stiffening or loss of compliance of the vessel walls only in the animals exposed to chronic pulmonary venous hypertension (Table 2).

Sympathetic Blockade in Chronic Pulmonary Venous Hypertension

Alpha adrenergic blockade was induced with phenoxybenzamine in five animals in the chronic series after baseline values were obtained. The results are tabulated in Table 3.

After α-blockade, the animals consistently responded with a marked drop in left atrial pressure,
Table 2  Impedance and Elastic Properties

<table>
<thead>
<tr>
<th>Condition</th>
<th>( P_a ) (mm Hg)</th>
<th>( Z_m ) (dynes sec/cm(^3))</th>
<th>( Z_o ) (dynes sec/cm(^2))</th>
<th>( C_o ) (cm/ sec)</th>
<th>( E ) (dynes/cm(^2)) \times 10(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control, acute</td>
<td>6.1 ± 1.5</td>
<td>609 ± 59</td>
<td>178 ± 14</td>
<td>300 ± 24</td>
<td>3.165 ± 0.020</td>
</tr>
<tr>
<td>Acute pulmonary venous hypertension (step 1)</td>
<td>16.9** ± 1.0</td>
<td>910* ± 94</td>
<td>210 ± 36</td>
<td>354 ± 61</td>
<td>4.406 ± 0.131</td>
</tr>
<tr>
<td>Acute pulmonary venous hypertension (step 2)</td>
<td>28.6** ± 1.4</td>
<td>1376** ± 154</td>
<td>227 ± 39</td>
<td>383 ± 56</td>
<td>5.158 ± 0.172</td>
</tr>
<tr>
<td>Chronic pulmonary venous hypertension</td>
<td>11.3* ± 0.4</td>
<td>1211** ± 259</td>
<td>361** ± 11</td>
<td>609** ± 19</td>
<td>12.998** ± 0.013</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM. \( P_a \) = left atrial pressure; \( Z_m \) = impedance to mean flow \(|P|/|Q|\); \( Z_o \) = characteristic impedance, 7-11 Hz; \( C_o \) = pulse wave velocity derived from Womersley’s equation; \( E \) = Young’s elastic modulus from \( C_o \) and the Moens-Korteweg relationship.

* \( P < 0.05 \) different from control, ** \( P < 0.001 \).

Tachycardia, modest increase in cardiac output, and a slight fall in mean aortic pressure. These changes reflect an enlarged systemic intravascular space. The pulmonary vascular resistance increased approximately 70% because the fall in left atrial pressure was not accompanied by an equivalent fall in pulmonary artery pressures. Returning the left atrial pressures to the pre-\( \alpha \)-block value in these animals by infusion of dextran resulted in increased pulmonary artery pressures, increases in cardiac output, and a return to normal pulmonary vascular resistances.

The maxima and minima of the impedance moduli spectra were altered markedly when the animals were under \( \alpha \)-blockade with the concomitant fall in left atrial pressure (Fig. 5). The first minimum moved to lower frequencies indicating an increased predominance of distal reflecting sites, presumably the precapillary region since the PVR increased. The phase spectra were altered modestly with an absence of return to negative phase angles in the higher frequencies. However, when the left atrial pressures were returned to pre-\( \alpha \)-blockade values, the impedance moduli shifted to slightly higher amplitudes in the lower frequencies (Fig. 5) while the maxima and minima returned to pre-block frequencies. The pulmonary vascular resistance returned to normal. The phase angles did not change. Thus, the first minimum of the impedance modulus seems to be primarily pressure dependent and independent of \( \alpha \)-adrenergic tone.

Despite alterations in maxima and minima, there were no changes in the characteristic impedances \((Z_o)\) of these animals either with \( \alpha \)-blockade or with relatively rapid changes in left atrial pressures.

Discussion

The basic similarity of the impedance spectra in acute venous hypertension as compared to controls shows that the effect of acutely increasing pulmonary venous pressures to 28.6 mm Hg is purely in terms of vascular recruitment as evidenced by the falling mean pressure gradient and resistance. It appears that the viscoelastic properties of the pulmonary vessels were not altered (Table 2). In contrast, the pulmonary arteries of dogs with chronic pulmonary venous hypertension were approximately four times stiffer than the controls. The
TABLE 3  Animals with Shunts Investigated with α-Blockade

<table>
<thead>
<tr>
<th></th>
<th>Prior to α-blockade</th>
<th>α-blockade</th>
<th>α-blockade and intravascular volume repletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pp_L (mm Hg)†</td>
<td>±0.3</td>
<td>±0.3</td>
<td>±0.2</td>
</tr>
<tr>
<td>Pp_s (mm Hg)†</td>
<td>±0.1</td>
<td>±0.5</td>
<td>±0.4</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>±2</td>
<td>±5</td>
<td>±7</td>
</tr>
<tr>
<td>Pp_d (mm Hg)†</td>
<td>±4.1</td>
<td>±2.0</td>
<td>±2.4</td>
</tr>
<tr>
<td>Pp_d (l/min)</td>
<td>±1.34</td>
<td>±1.86</td>
<td>±2.3</td>
</tr>
<tr>
<td>PVR (dynes sec)cm⁻³</td>
<td>367</td>
<td>628*</td>
<td>269</td>
</tr>
<tr>
<td>Zₒ (dynes sec)</td>
<td>327</td>
<td>357</td>
<td>360</td>
</tr>
<tr>
<td>Z_m (dynes sec)cm⁻³</td>
<td>1392</td>
<td>845*</td>
<td>683</td>
</tr>
</tbody>
</table>

Results are expressed as means ± SEM. Pp_L = mean left atrial pressure; Pp_s = systolic pulmonary artery pressure; Pp_d = pulmonary artery diastolic pressure; HR = heart rate; Pp_d = mean aortic pressure; Qp_d = pulmonary blood flow; PVR = pulmonary vascular resistance; Zₒ = characteristic impedance averaged 7-11 Hz; Z_m = impedance to mean flow (zero harmonic).

* Different from animals without α-blockade, \( P < 0.05 \).
† Transmural pressure.

Elevated characteristic impedance was not reversed by either α-blockade or the accompanying reduction of left atrial pressure. This may indicate a chronically increased proximal stiffness, perhaps representing a slower alteration in the passive viscoelastic properties of the vessels.

Acute and chronic pulmonary venous hypertension in this study were characterized by markedly different impedance spectra which may represent alterations in vascular physical properties by several mechanisms. Previously, Oakley et al. (1962) obtained simultaneous pulmonary artery pressure and blood volume measurements in unanesthetized men and showed that these vessels could be affected by both active and passive mechanisms and that measured alterations in PVR were not necessarily equivalent to changes in pulmonary vascular caliber. Thus, the terms vasoconstriction and vasodilation are problematical when applied to the pulmonary vascular bed. Vasoconstriction can occur as a caliber change of the large pulmonary vessels or as a decrease in the cross-sectional perfusing area at the precapillary level. This latter mechanism tends to be more effective in raising resistance, while the former elevates characteristic impedance. The two "vasoconstriction sites" can act together or in opposite directions. Similar considerations apply to vasodilation: which can mean capillary recruitment or actively increased vascular compliance (increased diameters at same or lower pressures). Passive vasodilation can occur with increased stiffness as a consequence of increased transmural pressures. In the present study, acute pulmonary venous hypertension provoked capillary recruitment (decreased resistance) without alterations in vessel compliance (unaltered characteristic impedance) while chronic pulmonary venous hypertension induced increased vascular stiffness.

In a classic impedance study of chronic pulmonary hypertension in humans, Milnor and others measured pulse wave velocity and pulsatile pressure and flow in seven patients with pulmonary hyperventilation. Figure 5 shows the impedance spectra for five dogs with chronic pulmonary venous hypertension (filled triangles), after α-blockade with low left atrial pressure (filled boxes), after α-blockade and volume expansion with return of left atrial pressures to ±15 mm Hg (stars). Despite marked changes in reflections and therefore altered lower frequency moduli, the high frequency data oscillate about similar values of Zₒ.

**Figure 5** Impedance spectra for five dogs with chronic pulmonary venous hypertension (filled triangles), after α-blockade with low left atrial pressure (filled boxes), after α-blockade and volume expansion with return of left atrial pressures to ±15 mm Hg (stars). Despite marked changes in reflections and therefore altered lower frequency moduli, the high frequency data oscillate about similar values of Zₒ.
tension as a consequence of mitral stenosis and found elevations of both \( C_0 \) and \( Z_0 \) (Milnor et al., 1969). The average increase in \( Z_0 \) was similar in magnitude to the increase in our dogs with chronic venous hypertension.

Although virtually the entire pulmonary vascular space is involved in pulsatile flow and pressure, it is theoretically the more proximal vessels that make the major contribution to determining the characteristic input impedance (Attinger, 1963). Thus, the alterations as assessed by \( Z_0 \) should be primarily in the larger arteries. Could the increased impedance of chronic venous hypertension by a consequence simply of proximal geometric changes without alterations in the elastic modulus? The pulmonary blood flows of the shunted animals averaged 67% of the controls which, in a static tube model \((\pi R^2 L)\), would effect a passive 18% decrease in radius neglecting alterations in length, known nonlinearities, and changes in distribution of intravascular blood volumes. Using the Womersley-Moens-Korteweg relationship, approximately a 30% reduction in radius would be required to account completely for the elevated \( Z_0 \) without an elastance change (again neglecting alterations in wall thickness and other variables). Additionally, our own static measurements of the main pulmonary artery circumference revealed no change after shunting. Thus, although dynamic dimensions were not measured simultaneously with the impedance measurements, it is quite unlikely that the \( Z_0 \) elevations were primarily on the basis of decreased effective proximal pulmonary arterial radius receiving the right ventricular systolic volume.

It has been assumed previously that \( \alpha \)-adrenergic mechanisms were important in the control of proximal pulmonary vascular compliance (Pace, 1971; Porcelli and Bergofsky, 1973). This has been demonstrated during electrical sympathetic nerve stimulation (Ingram et al., 1970). While this may be a real mechanism for acute adjustments of proximal myogenic tone, the present study shows that \( \alpha \)-adrenergic mechanisms do not have a major role in the increased impedance associated with chronic pulmonary venous hypertension. This suggests that these changes are slowly induced, not necessarily reversible, and therefore may represent a stiffer "resetting" of the viscoelastic state of the larger vessels or smooth muscle changes not under adrenergic control. This is perhaps analogous to the pulmonary hypertension associated with mitral stenosis which has been shown to be slowly but not necessarily completely reversible after valve replacement (Braunwald, et al., 1965).

This study demonstrates that chronic pulmonary venous hypertension is an extremely potent stimulus for increasing pulmonary arterial impedance. This may explain the clinical significance of associated venous hypertension in determining the rate and degree of progression of pulmonary vascular obstructive disease. It is important to conceptualize the injurious stimulus leading to pulmonary hypertension as the energy dissipation across a portion of the pulmonary vascular bed. The target vessels for pulmonary vascular obstructive disease are the small arteries and precapillary arterioles (Wagenvoort et al., 1961). This is also the region of the greatest pressure drop and hence dissipation of energy (Bergofsky, 1974). Just as the damage to tissue by a bullet is proportional to the dissipated energy, so pulmonary vessel wall changes may be proportional to chronically elevated rates of energy dissipation. The energy dissipated in the pulmonary vascular bed = (input potential energy + input kinetic energy) – (output potential energy + output kinetic energy). These can be separated into both pulsatile and mean components by measuring impedance as demonstrated by Milnor et al. (1966). For example, the component of mean potential power dissipation = (mean pulmonary artery flow \( \times \) mean pulmonary artery pressure) – (mean pulmonary venous flow \( \times \) mean pulmonary venous pressure). The energy distribution in the pulmonary circulation has been explained more fully in two classic papers by Skalak et al. (1966a, 1966b) which led them to describe the "effective pulmonary resistance" on the basis of energy dissipation rather than the pressure drop alone. With this conceptual framework, the relative flow tolerance and pressure intolerance of the pulmonary vascular bed can be understood. First, parallel vascular recruitment reduces the pressure increases associated with increased flows. Second, decreased pulmonary vascular impedance associated with chronically elevated pulmonary blood flow results in greater attenuation of the pulsatile pressure and flow waves proximal to the precapillary vessels (Hopkins et al., 1979). And third, since outflow equals inflow, and the pressure consequences of increased flow are minimized by the first two mechanisms, the amount of energy dissipated across the vascular bed is kept small despite increased flows. Thus, elevated flows (as in atrial septal defects) are well tolerated, whereas elevated arterial pressures (as in ventricular septal defects) are not. Given the importance of the pressure drop in increasing total energy dissipation across the vascular bed in the development of vessel wall changes, then the role of pulmonary venous hypertension in accelerating pulmonary vascular disease may at first seem paradoxical since the transpulmonary pressure gradient can even be decreased. However, if the energy dissipations across the target vessels is the critical factor, then the explanation resides in the impedance changes as documented in this study. Not only is the total amount of energy dissipated important, but also of importance is where in the vascular bed this dissipation occurs. When impedance is increased primarily by increased vascular stiffness, such as seen in this study by chronically elevated pulmonary
venous pressures, then less attenuation of the pressure waves would occur proximally and more energy would be dissipated across the target "resistance" vessels (distal arterioles) despite reduced flows. Thus, one of the major deleterious effects of chronically elevated outflow pressures is probably by its effect of increasing pulmonary vascular impedance and proximal vascular stiffness and the subsequent enhancement of energy transmission to the smaller vessels and not just by a direct increase in pulmonary artery pressure. Measurements of resistance instead of impedance would entirely ignore these mechanisms and would not demonstrate changes until pulmonary hypertensive disease had become manifest.

In summary, these data show that the effects of acute and chronic pulmonary venous hypertension in the awake canine model are quite different as assessed by hydraulic input impedance. Vessel viscoelasticity and proximal geometry as assessed by measurements of characteristic impedance are not altered significantly by acute pulmonary venous hypertension, but resistance is decreased, indicating capillary-arteriolar recruitment. In contrast, chronic pulmonary venous hypertension induces a markedly elevated pulmonary arterial impedance.

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