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Distensibility of Small Pulmonary Blood Vessels[1]

Although vasomotor activity in small pulmonary vessels has been studied extensively in the past, using the concept of resistance to flow, information on the distensibility of these vessels is very sparse. In an attempt to reduce this deficit, we adapted a theoretical method developed for small systemic vessels, to estimate distensibility of pulmonary resistance vessels in experimental animals and man. Pressure-flow data from 11 dogs and 10 human subjects (5 control subjects and 5 patients with long-standing left heart failure) were used to calculate distensibility of small pulmonary vessels. The conductance, G, was calculated from these data as the ratio of blood flow to driving pressure. The slope of the relationship between the logarithm of $G^{1/4}$ and the average distending pressure (ADP) provides a graphic picture of circumferential extensibility, E, defined as percent change in radius for an infinitesimal change in ADP. Results indicate that: (1) the value of E in dogs was 1.85 ± .40 $mmHg^{-1}$ for the control state, which decreased to 1.45 ± .43 $mmHg^{-1}$ during norepinephrine administration; however, the decrease in the value was not statistically significant ($p = 0.53$); (2) the value of E in control human subjects was 3.38 ± .47 $mmHg^{-1}$ and the value of E in patients with left heart failure was −0.64 ± 0.39 $mmHg^{-1}$; the difference was significant ($P = .0001$). Moreover, at a given ADP in the range of overlapping pressures, the "average" radius of small pulmonary vessels in patients with left heart failure was smaller than that in the control subjects; and (3) small pulmonary vessels were more distensible than both the small systemic vessels and the large pulmonary arteries.

Introduction

The concept of resistance to flow has been extensively used in the past to study vasomotion in the pulmonary vascular bed of man and animals. These previous studies have provided useful information on the responses of the small pulmonary vessels (i.e., pulmonary "resistance" vessels) in various disease states and/or during administration of various drugs [1, 2, 3]. Although all such studies provide information about the "average" radius of the resistance vessels in the pulmonary vascular bed, none of these studies provide information concerning the distensibility of the resistance vessels in vivo. In fact, most information on distensibility of small pulmonary vessels has come from in vitro studies [4, 5, 6] rather than from the intact animal or man. The availability of such in vivo information could prove very useful to the basic scientist as well as the clinician. Accordingly, the purpose of this report is to adapt a theoretical method previously described for estimation of distensibility of small systemic vessels [7], to similar pulmonary vessels in experimental animals and man. Pressure-flow data from the pulmonary vascular bed of 11 dogs and 10 human subjects (5 control and 5 with long-standing left heart failure) were used to calculate distensibility to illustrate the method. The results appear to be plausible, promising, and internally consistent.

Methods

Experimental: The theoretical method to estimate vascular distensibility [7] requires the calculation of the conductance, G, which is the ratio of blood flow to the driving pressure, at various levels of distending pressures; the fourth root of G vs the average distending pressure (ADP) is then plotted on semilogarithmic paper. The slope of this curve is proportional to the distensibility of the resistance vessels.

Previously obtained pressure-flow data from the pulmonary vascular beds of 11 dogs [2] was used to calculate the small vessel distensibility presented in this report. We also incorporated human data obtained from 5 control subjects and 5 subjects with advanced left heart failure of various etiologies. The control subjects were patients who had cardiac catheterization for evaluation of chest pain and were found to have a normal coronary arteriogram and essentially normal values of pulmonary vascular resistance (80 to 160 dynes-s-cm^{-5}).

The eleven dogs were studied under intravenous pentobarbital anesthesia (26 mg/kg). With the dog lying on its back, the chest was opened by a mid-sternal incision to expose the heart and pulmonary vessels. The dogs were ventilated with a positive pressure respirator that was momentarily interrupted at a pressure of 3 mmHg during periods of data collection.

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Pressures in the main pulmonary artery and left atrium were measured simultaneously using Statham pressure transducers. Flow in the main pulmonary artery was monitored continuously by an electromagnetic flowmeter. The pulmonary vascular pressure was varied either by dextran infusion or by bleeding so that pressure-flow data could be obtained at various levels of distending pressures in any given experiment. This procedure permitted a much more accurate determination of small vessel distensibility. After collecting control data, norepinephrine was administered by an intravenous drip (0.6 to 4.3 μg/kg/min of Levophed base) to study its effect on the pulmonary vascular bed.

In the 5 control subjects (ages 33 to 63 yrs; 4F, 1M) and in 5 patients with advanced left heart failure (ages 59 to 82 yrs; 3F, 2M), right heart catheterization was performed in the supine position, and pressures were measured in the pulmonary artery and pulmonary capillary wedge position, using a triple lumen balloon tipped catheter. The cardiac output was determined using the thermal dilution technique. In the control subjects the pulmonary vascular pressures were varied by raising both legs, by applying tourniquets to the legs, or by rapid infusion of normal saline; thus, each subject provided data over 4 to 5 levels of pressure. In patients with left heart failure repeated pressure-flow measurements were made over a period of 3 to 7 days. The pulmonary vascular pressures were varied by the therapeutic administration of Dobutamine and small doses of Dopamine.

Theory and Data Analysis. From pressure-flow data, we calculated G for the pulmonary vascular bed as:

$$G = \frac{F}{\Delta P} \tag{1}$$

where F is blood flow in ml/min which was normalized for body surface area in man to obtain the cardiac index, and ΔP is the driving pressure in mmHg calculated as the difference between the mean pulmonary artery pressure and left atrial pressure (pulmonary capillary wedge pressure in man). The mean values for these pressures were obtained electronically. As with electrical circuitry, conductance is the reciprocal of resistance. In this case, conductance is the reciprocal of pulmonary vascular resistance (PVR), a parameter that is very familiar to the basic scientist as well as the clinician; thus $G = 1/\text{PVR}$.

The ADP of the pulmonary vascular bed was calculated as:

$$\text{ADP} = \frac{\text{mean pulmonary artery pressure} + \text{left atrial (or pulmonary capillary wedge) pressure}}{2} \tag{2}$$

We used ADP rather than the transmural pressure (i.e., the pressure on the outer wall of a blood vessel minus the lumen pressure) which actually determines the size of a vessel, because: 1) in dogs the respirator was momentarily interrupted at 3 mmHg during data collection and therefore the pressure on the outer wall of the small vessels was a constant 3 mmHg. Since the transmural pressure in this case is ADP-3 mmHg, it would differ from ADP only by a constant; and 2) in man the pressure on the outer wall of the small vessels, in the supine position would be somewhere between the average alveolar pressure and the intrathoracic pressure, neither of which was available. However, we assumed that the net effect of these pressures would be small and relatively constant during quiet breathing. If a constant pressure on the outer wall were used to determine the transmural pressure, the plot of $G^{1/4}$ versus transmural pressure would be shifted to the left without altering the slope of the curve.

Assuming that Poiseuille's law applies to this situation, as is done in the case of resistance to flow (8), then G can be represented by the following relationship:

$$G = \frac{\pi}{8}\frac{R^4}{\eta L} \tag{3}$$

where R is the "average" radius of the "resistance" vessels, L is the length of the vascular bed, and η is the blood viscosity. Hence,

$$G^{1/4} = KR \tag{4}$$

if η and L are assumed to be constant in a given experiment. Thus, $G^{1/4}$ is proportional to R of the "resistance" vessels of the pulmonary vascular bed. Moreover, a plot of $G^{1/4}$ versus ADP is comparable to a pressure-radius curve for these vessels. However, it has been shown (7) that when $G^{1/4}$ versus ADP are plotted on semi-logarithmic paper, the slope of the curve is proportional to the circumferential extensibility, E, expressed as:

$$E = \frac{dR/R \times 100}{d(\text{ADP})} = \frac{2.3d(\log_{10}G^{1/4}) \times 100}{d(\text{ADP})} \tag{5}$$

where $d(\log_{10}G^{1/4})/d(\text{ADP})$ is the slope of the curve $G^{1/4}$ versus ADP plotted on semilogarithmic paper and dR is the change in R for a given change in ADP. Thus, using Eq. (5) one can calculate the value of E from the slope of the semilogarithmic plot of $G^{1/4}$ versus ADP. Although we used a linear measurement (E) in this study to demonstrate the elastic behavior of the blood vessel, it is in fact, directly related to the distensibility D, which is defined as:

$$D = \frac{\Delta V/V \times 100}{\Delta(\text{ADP})} \tag{6}$$

where V is the initial volume and ΔV is the change in volume for a given change in ADP. If the vessel length remains constant under inflation, and if the change in R is small, then $E = 1/2D$. In addition, the semilogarithmic plot of $G^{1/4}$ versus ADP will also provide some information about the radius of the pulmonary "resistance" vessels since the numbers on the ordinate will represent the actual values of $G^{1/4} = KR$ at various levels of ADP.

To calculate E from Eq. (5) using the data log ($G^{1/4}$) versus ADP, as shown in Figs. 1 and 2, a regression analysis was carried out using a SAS software package, to obtain a value for the slope of the regression line and the standard error of estimate around the slope. The results were shown as the mean value of $E \pm$ standard error of the mean. Any comparison for equality of the two slopes was done using the student t-test. A p value $< .05$ was considered significant.

It is important to point out that the value of E or D obtained here is that of a "model" small blood vessel, which is equal to the average extensibility or distensibility of all resistance vessels in the pulmonary vascular bed. In this connection all small pulmonary vessels e.g., small arteries, arterioles, capillaries, and venules offer resistance to flow and thus, in theory, may contribute to the distensibility. However, it is fair to say that essentially it is the small pulmonary artery and the arteriole that make the dominant contribution to the distensibility as measured in these experiments. It is also important to point out that since Eqs. (5) and (6) follow from Poiseulle's law (Eq. (3)), all assumptions used in its derivation will also apply to these equations.

Finally, we note that, in spite of its limitations, the use of the concept of resistance to flow which is a global concept has served us well for a long time. Similarly, we hope this global estimate of distensibility of resistance vessels may also prove useful, as a first step. It may also lead to mathematical mo-

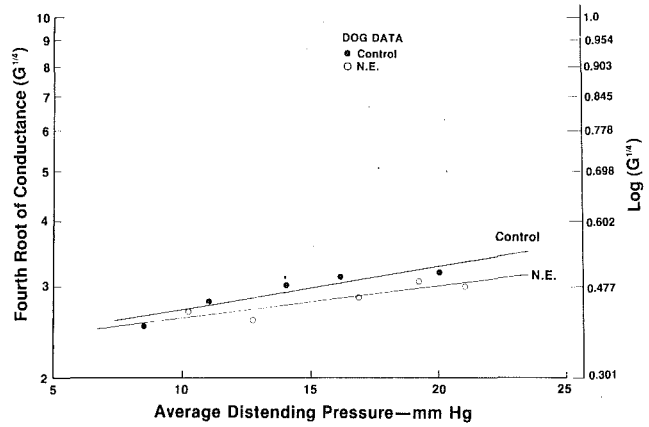

Fig. 1 Semilogarithmic plot of the fourth root of conductance ($G^{1/4}$) versus average distending pressure from dogs in the control state and during norepinephrine (NE) administration. A linear least-squares fit to each set of data is also shown in the figure. The slopes of the regression lines are proportional to the circumferential extensibility, *E*. Note that a logarithmic scale for the data is shown on the right-hand side which will permit a more direct determination of *E*, as $E = 2.3 \times \text{slope} \times 100$ mmHg^{-1}.

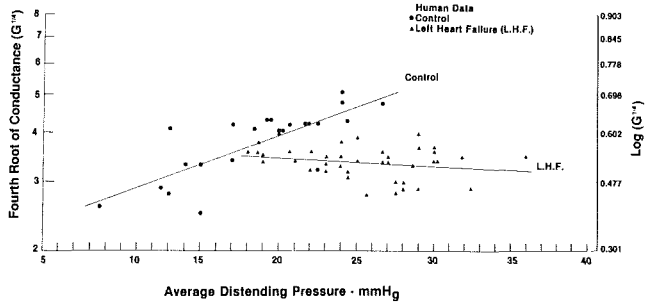

Fig. 2 Semilogarithmic plot of the fourth root of conductance ($G^{1/4}$) versus average distending pressure from human subjects in the control state and patients with left heart failure. A linear least-squares fit to each set of data is also shown in the figure. The slopes of the regression lines are proportional to the circumferential extensibility, *E*. Note that a logarithmic scale for the data is shown on the right-hand side which will permit a more direct determination of *E*, as $E = 2.3 \times \text{slope} \times 100$ mmHg^{-1}.

delling to predict distensibility of various subgroups of resistance vessels as shown by Zhuang et al. [9].

Results

Figure 1 is a semilogarithmic plot of $G^{1/4}$ versus ADP from 11 dogs during the control state and during norepinephrine administration. The data points (38 control and 21 norepinephrine) were averaged for each increment of 3 mmHg ADP. This resulted in 5 "average" points for the control state and 5 for norepinephrine administration as shown in the figure. The correlation coefficients for these data were $r = 0.93$ ($p = .02$) for the control state and $r = .88$ ($p = .05$) during norepinephrine administration. The linear least-squares regression lines for these data are also shown in the figure.

It can be seen in Fig. 1 that the average radius of the small pulmonary vessels appears to decrease, as reflected by the values of $G^{1/4} = KR$, which suggests that PVR may have increased during norepinephrine administration. This was indeed the case ($p < 0.01$) in the original data [2] when the control and norepinephrine values of PVR were compared at the same distending pressure. The values of E for the small pulmonary vessels of dogs were also calculated, using Eq. (5), from the slopes of the regression lines shown in the figure. The average value of E for the control state was 1.85 ± 0.40 mmHg^{-1} which decreased during norepinephrine administration to 1.45 ± 0.43 mmHg^{-1}. However the difference in E between the two states, at comparable values of ADP, did not achieve statistical significance ($p = .53$).

Figure 2 is a semilogarithmic plot of $G^{1/4}$ versus ADP for the human data. The 5 control subjects provided 23 data points and the 5 heart failure patients provided 40 data points. The correlation coefficients for these data were $r = 0.79$ ($p = .0001$) for the control subjects and $r = -0.22$ ($p = .17$) for the heart failure patients. The linear least-squares regression lines for the data are also shown in the figure.

Figure 2 shows that the average radius of the small pulmonary vessels is significantly larger ($p < .01$) in control subjects than in the heart failure patients in the overlapping region of ADP. This also implies that PVR in the heart failure patients is increased at comparable values of ADP. The values of the circumferential extensibility, E, for the small pulmonary vessels as calculated, using Eq. (5), from the slopes of these regression lines were 3.38 ± 0.47 mmHg^{-1} for the control subjects and -0.46 ± 0.39 mmHg^{-1} for the heart failure patients, and the difference between the two slopes was significant ($p = .0001$).

Discussion

General Remarks: When considering the factors that may influence the elastic behavior of blood vessels, as represented by such properties as compliance, distensibility and stress-strain relationships, it is important to recognize that geometric factors (including size and shape) as well as vasomotor tone will also influence the results as shown in Table 1. It is also important to realize that the vessel wall is a composite structure made up of smooth muscle, elastin and collagen fibers. The smooth muscle component may be placed in a relaxed state experimentally [10, 11] in order to measure the passive elastic properties of the wall. Conversely, the smooth muscle may undergo contraction with varying degrees of vasomotor tone when the active elastic properties are measured. The correct interpretation of data on the elastic properties of blood vessels should account for the contributions of all of the above factors.

In the present study, the circumferential extensibility, E, was computed for the pulmonary "resistance" vessels with resting vasomotor tone. Assuming that the shape of these vessels remained constant, this distensibility parameter E, which corrects for size (Eqs. (5) and (6)) was used as an *index* of true material properties of the vessel wall at resting levels of vasomotor tone. This parameter would provide a useful clinical tool to evaluate blood vessel properties since a stress-strain relationship is difficult to obtain from living subjects. This index (distensibility parameter) unlike compliance (Table 1), would not be influenced by recruitment of vessels that occurs in the pulmonary vascular bed with an increase in the distending pressure, since it will correct for the volume changes at each instant and thus normalize the data.

We found that the pulmonary resistance vessels in the heart failure patients are narrower and much stiffer (essentially rigid) than those in the control subjects. This is not surprising when one considers the long standing congestion in the pulmonary vascular bed of these patients which could lead to interstitial edema as well as structural changes in the small pulmonary arteries and arterioles with fibrosis and narrowing of the lumen. In addition, the sympathetic nervous contribution to vascular tone in these patients may also be elevated. The slightly negative slope of the regression line seen in these patients may indicate a myogenic response of the small pulmonary arteries to an elevated intravascular pressure.

Comparison With Other Studies: Most of the information in the literature on the distensibility of small pulmonary vessels has come from postmortem studies in humans [4] and in vitro

Table 1 Elastic Parameters

Parameter*	Influencing factors	Ease of measurement in a clinical setting
Compliance $C = \frac{\Delta V \times 100}{\Delta(\text{ADP})}$	Shape, size, and wall properties	Very easy for large vessels [8, 13]
Distensibility $D = \frac{\Delta V/V \times 100}{\Delta(\text{ADP})}$	Shape and wall properties (corrects for size)	A little more difficult to measure total volume; V; but possible to compute D indirectly in both large and small vessels [7, 14]
Stress-strain relations	Wall properties (corrects for shape and size; with realistic assumptions, the elastic constants computed from such data could provide true material properties)	Very difficult but may become possible in large vessels with recent ultrasonic and other techniques.

*All these parameters may be studied in the active or passive state.
ΔV = change in volume, V; Δ(ADP) = change in average distending pressure.

studies in animals [5, 6]. In the human lungs, Yen and Sobin [4] used casts of small pulmonary vessels made at varying pressures, due to the effect of gravity, from apex to base. The average value of E calculated from their postmortem data for the arterioles and venules was 0.80 $mmHg^{-1}$. In the present study, we obtained a value for E of 3.38 $mmHg^{-1}$ for small pulmonary vessels in control subjects. Similarly, the value of E calculated for arterioles and venules from in vitro studies in lungs from cats [5] was 1.77 $mmHg^{-1}$. We obtained a value for E of 1.85 $mmHg^{-1}$ for vessels of comparable sizes in open-chested living dogs (Fig. 1). The differences noted above between the in vivo and in vitro studies could best be explained by assuming that the in vitro vessels are stiffer than the in vivo vessels studied in intact man. Moreover, the difference tends to diminish when the in vivo vessels are exposed and studied in an open-chested animal preparation, as this study demonstrated.

It is well known that the pulmonary vascular bed is very distensible and can accommodate a large cardiac output at relatively low pressures. This property of the pulmonary circulatory system is evident when E for pulmonary resistance vessels from the present study is compared with that for the systemic resistance vessels from a previous study [7]. The results show that in man, the distensibility of the pulmonary resistance vessels (E = 3.38 $mmHg^{-1}$) is significantly greater ($p < .02$) than that of the forearm resistance vessels (E = 1.00 $mmHg^{-1}$) with resting vasomotor tone. On the other hand, when the value of E for the pulmonary resistance vessels in man (E = 3.38 $mmHg^{-1}$) or dogs (E = 1.85 $mmHg^{-1}$) was compared with a similar value computed for the main pulmonary artery (E = 1.30 $mmHg^{-1}$) from a previous study [12], the resistance vessels were much more distensible. Similar results have been reported by Maloney et al. [6]. This latter finding, could prove very important in modelling the pulmonary vascular bed.

Finally, a note of caution is necessary when describing the elastic behavior of the pulmonary vascular bed that can become fully distended and essentially rigid at relatively low pressures. For example, in order to accurately determine E for these vessels, it is important to obtain accurate pressure-flow measurements; it is also equally important to vary ADP in a given experiment. It should be possible to vary ADP passively in a given subject by raising or lowering the legs, rapid volume infusion, or other maneuvers during cardiac catheterization to obtain 4 or 5 data points, as was done in this study.

In conclusion, we have adapted a theoretical method previously described for systemic "resistance" vessels to compute distensibility of pulmonary "resistance" vessels in vivo. The method is illustrated by using data from dogs and from man with and without left heart failure. The results indicate that at a given ADP, the values of the average radius and distensibility (as indicated by E) for the pulmonary "resistance" vessels in control subjects were higher than similar values obtained from patients with chronic left heart failure. In dogs both of these parameters were slightly lower during norepinephrine administration than in the control state. The method provides an important new tool to evaluate the distensibility of pulmonary "resistance" vessels under various experimental and/or diseased states in animal or man. The method can also be used to study the effect of various drugs on these vessels.

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