Importance of Transmural Pressure and Lung Volume in Evaluating Drug Effect on Pulmonary Vascular Tone

By Dali J. Patel, M.D., Ph.D., Alexander J. Mallos, B.S., and Flavio M. de Freitas, M.D.

Measurement of pulmonary vascular resistance has frequently been used in the study of vasoactive drugs to indicate changes in pulmonary vascular tone. However, as pointed out by Borst et al. and Fowler, it is not possible in many of these studies to separate vasoactive drug effects from purely mechanical effects resulting from changes in transmural pressure and lung volume. It is the purpose of this study to separate these two effects by using a method applicable to intact animals and man.

Pulmonary vascular resistance (PVR) is defined as the ratio of the mean pressure drop across the pulmonary vascular bed to the mean blood flow through the bed. PVR depends on the geometry of the vascular bed and the physical properties of the blood. The geometry of the vascular bed is related to the volume of the lung as well as to the distribution of transmural pressure along the vessels, the number of parallel vessels that are open, and the physical properties of the vessel walls. Most vasoactive drugs will affect the intravascular pressure, the blood flow, and the properties of the vessel walls. Assuming the physical properties of the blood to remain constant, it should be possible to infer the vasoactive effect of a drug on the pulmonary vasculature from measurement of PVR, provided the lung volume and transmural pressures are held constant.

Methods

Eleven dogs were studied under intravenous pentobarbital anesthesia (approximately 26 mg./Kg.). A sternal-splitting thoracotomy was performed and the chest wall retracted so that the lungs were free to expand. The surface of the lung was kept moist by spraying it with normal saline. The dog was ventilated with a constant-stroke-volume, positive-pressure respiratory pump (approximately +3 to +12 mm. Hg) that was momentarily interrupted at a pressure of 3 mm. Hg during periods of data collection. Thus, there was essentially no air flow in lungs during periods of data collection. In such a static system, the intratracheal pressure would deflect the intraluminal pressure as long as the channels connecting the two were patent. Pressures in the main pulmonary artery (PA), left atrium (LA), and trachea were measured simultaneously using Statham strain gauges (P23D) connected to a Sanborn direct-writing recorder. Flow in the main PA was monitored continuously by a Kolin electromagnetic flowmeter. Since both LA and PA pressures influence PVR, the average intravascular pressure (AIP) was estimated as:

\[ \text{AIP} = \frac{\text{mean PA pressure} + \text{mean LA pressure}}{2} \]

It can be readily seen that the passive effect of any change in pulmonary blood flow, pulmonary
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Figure 1

(Top)—Pulmonary vascular resistance (PVR) at various average intravascular pressures (AIP) during the control state and during norepinephrine (Nor-Epi) administration. Airway pressure was held constant at 3 mm. Hg. The time sequence of control and test values of PVR is shown by the solid-line arrows. The points on the norepinephrine curve are numbered in order of increasing dosage. The broken-line arrow indicates the value of PVR obtained soon after the drug was discontinued. (Bottom)—The experiment shown in the top figure was repeated in the same dog after hexamethonium was administered.

Just prior to thoracotomy, the dog was infused with approximately 500 cc. of dextran and then bled of the same volume of blood. This blood was later reinfused to establish the control AIP-vs.-PVR curve. For test studies, l-norepinephrine bitartrate* was administered at a constant rate, by intravenous drip. Dosage varying from 0.6 to 4.3 µg./Kg./min. of Levophed base were employed. In order to make random the effects of spontaneous changes in PVR that may occur following thoracotomy, the order of test and control procedures was varied in different dogs.

Even though the same airway pressure was maintained during each period of data collection, the lung volume could have varied between the control and the test states due to a change in pulmonary compliance. However, any change in PVR due to such a change in lung volume would have been small in these experiments. It has been shown5-8 that an increase in PVR secondary to a change in lung volume per se occurs at extremes of lung inflation, i.e., at collapse and when the lungs are markedly inflated. The control and test data for calculation of PVR in this study were collected at a moderate degree of lung inflation and, therefore, would be relatively insensitive to small changes in lung volume.

Results and Discussion

Figure 1 (top) illustrates one dog experiment in which values of PVR at various AIP's during the control state and during norepinephrine (NE) administration are shown in their proper time sequence as indicated by arrows. The airway pressure was held constant at 3 mm. Hg. A complete course of the drug effect is thus traced out as the NE dosage is increased from 1.1 µg./Kg./min. to 3.2 µg./Kg./min.; the points on the NE curve are numbered in the order of increasing dosage. Note that the absolute value of PVR decreases with an increasing dose of NE, since the increase in AIP has produced vascular distention. In spite of this decrease of PVR, the increase in vascular wall tone caused by the drug is evident from comparison of the two curves. The vasomotor effect of the drug can be obtained by subtracting the control values of PVR from test values at corresponding AIP.

Figure 1 (bottom) shows the experiment repeated in the same dog after the initial tone in the pulmonary blood vessels was abolished by means of hexamethonium* (4 mg./Kg.). It can be seen that the control curve is now relatively flat, indicating that the vascular bed is apparently distended to some rigid limit (which may include newly opened parallel

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*Levophed.

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vascular channels) and does not dilate with further increase in AIP. The dose of NE was increased from 0.65 µg./Kg./min. to 3.1 µg./Kg./min. in this experiment; the points on the NE curve are numbered in the order of increasing dosage.

The results from 11 dogs are shown in table 1. Only the control and test values obtained at the same AIP (within 1 mm. Hg) are included in the table. There was a significant overall increase of 27 per cent in PVR during NE administration as compared with the control value ($P < 0.01$ by statistics of paired data), which indicates active vasoconstriction in the pulmonary vascular bed. Since each value of PVR during NE administration was compared with its corresponding control value at the same AIP and the same airway pressure, the mechanical effects would be excluded. The vasoconstriction appears to be due to a local effect of NE on the pulmonary vascular bed. Since NE produced systemic hypertension in our experiments, this would tend to produce a primary reflex dilation of the pulmonary vascular bed.11

In figure 2, all the data from 11 dogs are shown. A composite control curve was constructed by averaging 38 control values of PVR which fell within increments of 3 mm. Hg in AIP. As noted previously,3 the slope of this control curve is steep initially and then levels off, indicating a distended rigid state of vessels as AIP increases. All values of PVR (from 11 dogs) following NE administration were then compared with this composite control curve by means of the following equation:

\[
\text{normalized PVR}_T = \frac{\text{PVR}_T \times \text{PVR}_{OC}}{\text{PVR}_{OC}},
\]

where \(\text{PVR}_T\) = test value of PVR obtained during NE administration, \(\text{PVR}_{OC}\) = original control value of PVR, and \(\text{PVR}_{OC}\) = control value of PVR obtained from the composite control curve at a corresponding AIP. In this way, all data can be compared with one control curve. The test values lying above the composite control curve would indicate active vasoconstriction; those lying on the curve would indicate no effect; and those below the control curve would indicate active vasodilation. Since most of the points lie above the composite control curve, the overall effect during NE administration is active vasoconstriction in the pulmonary vascular bed. For purposes of this discussion, it would be interesting to consider a test value of PVR lying above the composite control curve but below the broken line which indicates the initial control value* of PVR. Now, if this test value is compared with the initial control value of

*The initial control value of PVR was chosen between 8 and 9 mm. Hg AIP, since this would be the approximate value of AIP in a control dog prior to any infusion. It is important to note that such a control value would tend to fall on the steep part of the PVR-vs.-AIP control curve.
Table 1

Results from Eleven Dogs

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<th>Dog no.</th>
<th>State</th>
<th>AIP mm. Hg</th>
<th>ΔP mm. Hg</th>
<th>Flow L./min.</th>
<th>PVR mm. Hg/L./min.</th>
<th>Difference in PVR NE-C</th>
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*Only control and test values obtained at the same average intravascular pressure (within 1 mm. Hg) are included in the table.*

AIP = average intravascular pressure; ΔP = pulmonary artery pressure—left-atrial pressure; PVR = pulmonary vascular resistance; C = control; NE = norepinephrine.

PVR, as indicated by the broken line, a decrease in PVR will be noted. This could be erroneously considered as indicative of active vasodilatation. However, if the corresponding control value of PVR obtained at the same AIP is chosen for comparison, the passive effect is excluded and the PVR is shown to increase, indicating active vasoconstriction. Therefore, it follows that even a qualitative statement regarding the vasoactive drug effect cannot be made in studies in which, during administration of a drug, PVR decreases in the presence of a rise in transmural pressure, or vice versa, as compared with the control value. With the help of figure 2, one could partly explain the existing discrepancy in the literature regarding the effect of NE on PVR. Patel et al. showed an increase in PVR during NE administration in man. Fowler et al. reported that NE produced a variable effect on PVR in man, i.e., NE increased, decreased, or did not change PVR. Since both mean PA and LA pressures increased during NE administration in Fowler's study, it is conceivable that an increase in PVR during NE administration might have been obtained.
in all their subjects had comparisons been made with control values obtained at the same transmural pressure.

Pulmonary vasomotor changes following drug administration have also been more directly demonstrated by several workers. Patel and Burton\(^ {17} \) demonstrated vasoconstriction in small pulmonary arteries of the rabbit by means of arterial plastic casts made following administration of large doses of NE. Borst et al.\(^ {4} \) tested the effect of a drug in one lung of a dog while the other lung served as control. Vasomotor activity was inferred from redistribution of blood flow to the two lungs rather than from changes in PVR. The transmural pressure was allowed to vary in this study. Neither of these methods,\(^ {4,17} \) although indicative of vasomotor changes in their respective preparations, is suitable for application to the intact animal or man. However, the present technique can easily be modified for human application, since the LA pressure can now be conveniently monitored by the transseptal left-heart catheterization,\(^ {18} \) the PA pressure by right-heart catheterization, and the pulmonary blood flow may be obtained by the indicator-dilution method. The intrapleural pressure may be monitored, and the patient may hold his breath, at a fixed point in the respiratory cycle (e.g., at quiet end-expiration). The pulmonary vascular pressures may be raised by infusion of dextran of blood to establish the control curve for AIP vs. PVR. It is realized that to raise these pressures significantly, one may require a large amount of infusion. However, Werko\(^ {10} \) has been able to raise the mean PA pressure up to 15 mm Hg in normal human subjects by means of dextran infusion. Thus, it appears feasible to obtain complete control and test curves of AIP vs. PVR in man, holding the intrapleural pressure, intra-alveolar pressure, and the lung volume constant. This could provide a clearer picture of the vasoactive and mechanical drug effects.

Summary

The effect of norepinephrine (NE) on pulmonary vascular resistance (PVR) was studied in 11 thoracotomized dogs. Comparisons between the test and control states were made at corresponding average intravascular pressures in the pulmonary vascular bed and at the same airway pressure. A significant increase in PVR (\( P < 0.01 \)) suggesting active vasoconstriction was found during NE administration.

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References


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