Some Regulatory Mechanisms of the Human 
Pulmonary Vascular Bed

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THERE IS still a question regarding the presence of active mechanisms of control for the pulmonary vessels in man. The controversy continues, since evidence for active vasomotion has usually been indirect. Because, in the past, it has been assumed that changes in pulmonary vascular resistance necessarily reflect changes in pulmonary vascular caliper, workers have drawn conflicting conclusions from similar experimental results. Recent excellent reviews summarize the present concepts.1-5

The caliber and, therefore, the volume of a vessel depend on (a) the transmural pressure and on (b) the distensibility of its wall. As defined by Burton,6 transmural pressure is the difference between the distending pressure inside and the tissue pressure outside the vessel. Vascular distensibility depends on mural elasticity as well as on active tension or muscular tone.

Theoretically, passive changes in vascular caliper would be associated with concordant changes in pulmonary blood volume and transmural distending pressure, i.e., they would rise together or fall together. Thus, passive narrowing would be associated with a fall both in distending pressure and pulmonary blood volume, whereas passive dilation would be associated with a rise in both these parameters. These changes could occur without concomitant changes in muscular tone.

In contrast, active vasomotion would be marked by discordant changes in pulmonary blood volume and transmural pressure, i.e., they would vary in opposite directions. Thus, active vasoconstriction could be inferred from a decrease in pulmonary blood volume and an increase in distending pressure, whereas active vasodilation would be evidenced by an increase in pulmonary blood volume in the face of a decreased distending pressure.

In this study, changes induced in pulmonary blood volume were correlated with simultaneous changes in pulmonary distending pressure to deduce active or passive mechanisms in the pulmonary circuit.

Clinical Material and Methods

Forty patients with significant mitral valve disease and four patients with mild aortic valve disease were studied by simultaneous right heart and transseptal left atrial catheterization. Four of the 40 patients with mitral valve disease had mild, 15 moderate, and 21 severe disease as determined by clinical and hemodynamic studies, together with the operative findings in some cases. Nine of the severe group had been in cardiac failure, and three still showed evidence of this condition at the time of study. Atrial fibrillation was the established rhythm in 13 patients.

The method for cardiac catheterization, derivation of data therefrom, and the technic and apparatus used for recording indicator-dilution curves in this laboratory have been detailed in previous papers.6-7 Transseptal left atrial catheterization was performed via the right subclavian vein, as described by Ross and associates.8 The zero level for right heart pressure was taken 6.5 cm. below the sternal angle; for left heart pressure, 8.5 cm. below the sternal angle.

Utilizing the method originally described by Milnor and co-workers,9 we recorded dilution curves from the systemic artery after rapidly successive injections of indocyanine green (Cardio-Green) into the pulmonary artery (PA) and into the left atrium (LA). The injections were made within 2 minutes, and the order of injections was
The cardiac output determined in a series of 44 patients by rapidly successive injections of Cardiogreen into the pulmonary (PA) and left atrium (LA). The large circle with a dot in the center indicates identical figures obtained in two determinations. Note that there is a close agreement without systematic error. The mean of the two cardiac output determinations was used for calculation of pulmonary blood volume.

randomized. The average of the two cardiac index measurements obtained from the PA and LA dilution curves was used for all volume calculations. The mean transit time was determined for each curve. The “dead-space” time was subtracted from the calculated mean transit times.

The central blood volume (CBV) is considered to be the volume between the main pulmonary artery and a systemic artery including all the temporarily equidistant branches of the arterial tree. It was calculated by the Stewart-Hamilton method\(^8\) from the mean transit time from the main pulmonary artery to a systemic artery multiplied by the cardiac index:

\[
\text{CBV} = \text{CI} \times T_m (\text{PA} - \text{FA})
\]

Where, CBV = central blood volume (ml./M.\(^2\))
CI = cardiac index (ml./M.\(^2\)/sec.)
\(T_m (\text{PA} - \text{FA})\) = mean transit time from pulmonary artery to systemic artery (sec.)

Pulmonary blood volume (PBV) is composed of the blood in the pulmonary arteries, pulmonary capillaries, and pulmonary veins. It was calculated from the difference between the PA and LA mean transit times multiplied by the cardiac index:

\[
\text{PBV} = \text{CI} \cdot \left[ T_m (\text{PA} - \text{FA}) - T_m (\text{LA} - \text{FA}) \right]
\]

Where, PBV = pulmonary blood volume (ml./M.\(^2\))
\(T_m (\text{LA} - \text{FA})\) = mean transit time from the left atrium to the femoral artery (sec.)

In the present series of patients there was good agreement between 87 cardiac index determinations, and no systematic error was observed (fig. 1). The standard error was 0.318, which means that the difference between the two cardiac indexes will rarely \((p < 0.05)\) exceed 0.90 l./M.\(^2\)/min.

As suggested by Milnor and associates,\(^9\) changes in transmural pressure were inferred from changes in the mean intravascular “distending” pressure \((P_D)\), which is derived by averaging the mean pulmonary arterial and mean left atrial pressures, i.e., \((P_{A_m} + L_{A_m})/2\).

In the present study no information regarding intrathoracic pressure is available. Since we wished to know only the relative changes in transmural pressure, only the “distending” pressure was measured.

**Procedure**

Immediately after control measurements of cardiac output by indicator-dilution curves, pulmonary arterial, systemic arterial, and simultaneous pulmonary wedge and left atrial pressures were recorded. After obtaining the control data, the effects of some physiologic maneuver or pharmacologic agent on PBV and \(P_D\) were again measured.

The studies performed were as follows:

1. **Exercise.** Five patients were exercised using the left foot to pedal a bicycle ergometer; the studies were done between the fifth and ninth minutes of exercise.

2. **Rapid Intravenous Infusion.** Dextran (three patients) or isotonic saline (one patient) was rapidly infused through the intracardiac catheter in amounts of 600 to 1,300 ml.

3. **Hexamethonium.** Hexamethonium, 1 mg./min., was given through the intracardiac catheter to two patients until a definite drop in the systemic and pulmonary pressures had been achieved. The total dose varied between 6 and 20 mg.

4. **Vasovagal Reactions.** Vasovagal reactions were complications of the procedure in two patients. Each of these patients was studied before the reaction was terminated by head-down tilting and administration of atropine, 1 mg., through the intracardiac catheter.

5. **Acute Hypoxia.** Twelve per cent oxygen in nitrogen was administered to five patients through a mouthpiece for a period of 10 to 15 minutes. When the ventilation had become steady, determination of cardiac output by indicator-dilution...
### Table 1

**Effects of Exercise and of Rapid Intravenous Infusion on the Pulmonary Blood Volume**

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BSA = body surface area (M<sup>2</sup>)

MS = mitral stenosis

MI = mitral insufficiency

AS = aortic stenosis

I, II, III, and IV = functional capacity according to the classification adopted by the New York Heart Association

AF = atrial fibrillation

SR = sinus rhythm

A = control period; B = during exercise or rapid intravenous infusion

CI = cardiac index (L/min/M<sup>2</sup>)

SI = stroke index (ml/beat/M<sup>2</sup>)

PA<sub>m</sub> = pulmonary arterial mean pressure (mm. Hg)

LA<sub>m</sub> = left atrial mean pressure (mm. Hg)

P<sub>D</sub> = distending pressure, or (PA<sub>m</sub> + LA<sub>m</sub>) (mm. Hg)

BA<sub>m</sub> = systemic arterial mean pressure (mm. Hg)

PVR = pulmonary vascular resistance (dynes-sec./cm<sup>5</sup>)

MTT<sub>Pa,LA</sub> = mean transit time from the pulmonary artery to the left atrium (sec.)

PBV = pulmonary blood volume (ml./M<sup>2</sup>)

CBV = "central" blood volume (ml./M<sup>2</sup>)

*Infusion of Dextran.

*Infusion of Isotonic saline.
curves and recording of pressures were repeated.

6. *Angiotensin.* A continuous infusion of this agent was given to 10 patients in the amount of 0.03 to 0.06 μg./Kg./min. through a catheter inserted into the saphenous vein alongside the transseptal catheter. Sufficient drug was given to achieve and maintain an increase of 30 to 60 mm. Hg in systemic systolic pressure.

7. *Methoxamine (Vasoxyl).* Methoxamine in the amount of 0.1 to 0.4 mg./Kg. was given to three patients. As the effect of this agent lasts longer than that of angiotensin, it was given through the intraaortic catheter over a period of about 10 to 20 minutes until it brought about a hypertensive response similar to that obtained from angiotensin infusion.

8. *Acetylcholine.* This agent was administered by constant infusion in the amount of 0.03 to 0.08 mg./Kg./min. into the pulmonary artery of five patients. The amount given was sufficient to lower the pulmonary arterial mean pressure without causing wheezing, coughing, or a significant drop in systemic pressure.

**Results**

The changes of the PBV and other parameters during the control and study periods are summarized in tables 1 to 5. In the 44 patients, PBV at rest ranged from 122 to 455 ml./M.² with a mean of 283 ml./M.² (table 6). The standard deviation on duplicate determinations of PBV in 12 patients was 14.7
Regulation of Pulmonary Vascular Bed

The average PBV grouped according to valve lesion (cross-hatched), severity of disease (white columns), and left atrial size (horizontal lines). No significant difference in PBV is seen among the various groups. MS, mitral stenosis; MI, mitral insufficiency; AS, aortic stenosis; AI, aortic insufficiency; TS, tricuspid stenosis; TI, tricuspid insufficiency. LA enlargement is graded on a scale of 1+ to 3+.

Figure 2. This indicates that the values obtained on two successive determinations of PBV in a given subject will rarely (p < 0.05) differ by more than 45 ml./M.². We therefore consider that any deviation of PBV beyond this figure is a significant change.

Figure 3 shows the average PBV of 40 patients with mitral valve disease, grouped according to the lesions, severity, and left atrial size. No significant difference in PBV is seen among the various groups.

Exercise brought about a parallel increase in both PBV and P₉. The increase in PBV exceeded 80 ml./M.² in every subject (fig. 4). All these patients were able to double their oxygen consumption and to raise their cardiac outputs with an increase ranging from 0.7 to 1.8 L./M.²/min. Pulmonary vascular resistance changed little, the maximum being a rise of 116 dynes-sec./cm.⁵ in one patient.

Rapid infusion of Dextran or isotonic saline resulted in a concordant increase in both PBV and P₉ (fig. 4). The cardiac index rose slightly in all these patients. Pulmonary vas-
Table 4

Effects of Angiotensin and of Methoxamine on the Pulmonary Blood Volume

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<th>Rhythm</th>
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A = control period; B = during angiotensin or methoxamine infusion.
Otherwise the abbreviations and units are identical to those used in tables 1 and 2.
The effect of exercise and of rapid intravenous infusion of either Dextran or isotonic saline on PBV and $P_D$. The concordant increase in both PBV and $P_D$ suggests passive distention of the pulmonary vascular bed in each case.

Pulmonary vascular resistance showed no change in three patients but rose significantly in one patient. The effects of systemic vasodilation following hexamethionium administration or during vasovagal reactions in four patients were manifested by a uniform fall in systemic pressure, $LAm$, $PAm$, PBV and CI. As shown in figure 5, there was a concordant fall in both $P_D$ and PBV. Pulmonary vascular resistance changed variably, rising in two and falling slightly in the other two.

During the period of acute hypoxia there was a uniform increase in both $PAm$ and $P_D$ associated with little or no change in $LAm$. The PBV either decreased or remained unchanged (fig. 6). The pulmonary vascular resistance, however, increased significantly in three of five patients.

Angiotensin caused a significant fall in PBV in six patients but no significant change in the remaining four. There was a uniform increase in $P_D$ in all patients, although the magnitude of the rise was rather small in two (fig. 7). Pulmonary vascular resistance, however, did not alter appreciably in four patients, rose in five, and fell in one.
In contrast to angiotensin, methoxamine caused an increase in PBV associated with an increase in PA$_m$ and PD. Pulmonary vascular resistance increased in one of three patients.

In each patient there was an increase in PBV associated with a decrease in PD during acetylcholine infusion (fig. 8). Pulmonary vascular resistance fell appreciably in only two of the five subjects.

Discussion
Measurement of PBV and Possible Sources of Error
As shown in table 6, our figures for PBV are in accord with those reported by Milnor and Dock and their respective co-workers. The PBV in normal subjects probably lies at the lower end of the range of values for patients with mitral valve disease.

It is well to point out here that many disagreements among earlier results, particularly the effects of various agents on CBV are probably explicable by the inherent error of the method, which has been estimated to be at about 200 ml.12-14 Refinements in technique previously mentioned have considerably reduced this error. The sources of error have been discussed by Dock and co-workers,11 and Glick and associates from this laboratory. Two unavoidable sources of potential error are (a) incomplete mixing in the left atrium and (b) uneven rates of flow through different pulmonary segments.

Because good reproducibility of the indicator-dilution curves was consistently achieved with left atrial injection, we believe that in the present study mixing was adequate for arterial sampling. Moreover, as pointed out by Phinney and associates,16 the presence of mitral insufficiency itself may promote adequate mixing.

*Circulation, Volume XXVI, November 1962*
Figure 7

The effects of angiotensin on PBV and \( P_D \). The decrease in PBV despite an increase in \( P_D \) suggests active pulmonary vasoconstriction.

Uneven blood flow through the lungs may produce changes in both the mean circulation time and the cardiac output as determined by the indicator-dilution technic. Thus, an indicator injected into the pulmonary artery that traverses areas of sluggish flow and arrives late at the sampling site will artifactually prolong the downslope and will thereby produce an erroneously large \( T_m \) and CBV, assuming cardiac output remains constant. If an indicator travels through even more sluggish areas of flow, it may not arrive at the sampling site until recirculation has begun. Since such an indicator is lost from the primary circulation, the area of the curve will be erroneously small, which will produce too high an estimated cardiac output and CBV.

Figure 8

The effects of acetylcholine on PBV and \( P_D \). Active pulmonary vasodilation is reflected by an increase in PBV despite a fall in \( P_D \).

In both instances, the calculated PBV will be falsely high, inasmuch as the blood volume between the left atrium and systemic artery would not be affected.

On the other hand, PBV may be underestimated. Blood from nearly stagnant areas of the pulmonary circulation may never receive a share of the injected indicator and would, therefore, not be measured in the calculated CBV, thereby producing a falsely low PBV.

Rationale for Using \( P_D \)

As is well known, the transmural pressure tending to distend the pulmonary blood vessels is the difference between the intravascular and intrathoracic pressures. During inspiration, intrathoracic pressure becomes more negative, and the transmural pressure increases with respect to atmosphere, even though some fall in intravascular pressure may take place. During expiration, the op-
Table 6

Pulmonary Blood Volume in Man

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients Diagnosis</th>
<th>Patients Number</th>
<th>Pulmonary blood volume (ml./M²)</th>
<th>Route to left atrium</th>
<th>Technic used</th>
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<td>126-598</td>
<td>365</td>
<td>Transbronchial or paravertebral</td>
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<td>122-455</td>
<td>283</td>
<td>Transseptal</td>
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</table>

invasive studies, when the lungs were inflated, indicated that the pressure differences observed reflect changes in transmural pressure. This premise is supported by the studies of Feeley et al., who have shown in animals that administration of drugs does not affect mean intrapleural pressure.18

However, if as a result of an experimental intervention either (a) the level of mean intrathoracic pressure changes or (b) the change in transmural pressure occurs mainly as a result of a change in intrathoracic rather than intravascular pressure, then the use of P₀ would not be completely valid.

Evidence for Active and Passive Vasomotion in the Pulmonary Vascular Bed

Passive expansion of the pulmonary vascular bed, as evidenced by a rise in both PBV and P₀, was noted under three circumstances. First was rapid intravenous infusion. In the four subjects studied, the pulmonary vessels were found to accommodate part of the increased circulating blood volume. Werkö and co-workers19 observed in a series of cardiac patients a similar rise in the pulmonary arterial and pulmonary wedge pressure during intravenous infusion of Dextran solution. Although they did not measure pulmonary blood volume, they postulated that the pressure rise might be due to an increase in pulmonary blood volume as a result of an increase in total blood volume.

Second was methoxamine infusion. The mechanism of producing passive expansion of the pulmonary vascular bed with this agent will be discussed in a subsequent section.

Third was exercise. Our data, which clearly demonstrate a rise in CBV together with an increase in PBV during exercise, strongly suggest that the increase in CBV noted by Braunwald and Kelly20 is due to a redistribution of blood into the pulmonary vascular bed.

It should be pointed out that during exercise the change in the intrathoracic pressure may influence the transmural pressure, hence distending pressure, to a certain extent. It has been demonstrated that with exercise the mean intrathoracic pressure in man becomes more negative.21,22 Such a change would increase transmural pressure, thereby increasing pulmonary vascular caliber, and may account, in part, for the passive increase in
REGULATION OF PULMONARY VASCULAR BED

the pulmonary blood volume noted. However, in the patients of the present series, the rise in LA\textsubscript{m} and PA\textsubscript{m} pressures during exercise is mainly due to the presence of an obstructive lesion of the mitral valve, since an equivalent amount of exercise in normal subjects does not cause appreciable elevation of pressure in the pulmonary circuit. Thus, the rise in intravascular distending pressure observed in these patients, irrespective of the change in intrapleural pressure, was undoubtedly another important factor in increasing the pulmonary blood volume.

Passive narrowing, manifested by a concordant fall in both PBV and P\textsubscript{d}, was observed after administration of hexamethonium and during vasovagal reactions and is attributable to pooling of blood in the periphery with diminished venous return. Other workers have shown previously in animals that systemic vasodilation leads to a decrease in PBV.\textsuperscript{23} These results explain the beneficial effect of ganglionic blockade in pulmonary edema.\textsuperscript{24-26}

The presence of active pulmonary vasoconstriction is evidenced by our results with acute hypoxia. There was a rise in PA\textsubscript{m} and P\textsubscript{d}, associated with a decrease in PBV. The LA\textsubscript{m} was not affected by the intervention; therefore, its back pressure effects on the pulmonary circulation need not be considered. The increase in the pulmonary blood flow was relatively small and could not entirely account for the rise in pulmonary arterial pressure. Furthermore, it has been shown by other workers that during acute hypoxia the change in the intrathoracic pressure is minimal.\textsuperscript{4} The most pertinent change was a decrease of pulmonary blood volume in all five cases. This finding in the face of an increasing distending pressure is highly suggestive, if not indicative, of an active increase in the muscular tone of the pulmonary vessels.

Using the technic of indicator-dilution curves or teeter-board,\textsuperscript{14, 27, 28} other workers failed to detect any appreciable change in intrathoracic or “central” blood volume in man during acute hypoxia. Since these measurements included blood in the heart chambers as well as in the aorta and its proximal branches, it would be very difficult to define the changes in true pulmonary blood volume. Our data are at variance with those observed in animal studies, which showed an increase in pulmonary blood volume during acute hypoxia.\textsuperscript{29, 30}

A comparison of the effects of methoxamine and angiotensin gives further insight into the possible mechanism of pulmonary vascular control. Both methoxamine and angiotensin in the doses given produced almost equivalent hypertensive responses, and their effects on cardiac output were similar. In addition, both caused increases in LA\textsubscript{m}, PA\textsubscript{m} and, thereby, in pulmonary distending pressure (P\textsubscript{d}). It is likely that the rise in LA\textsubscript{m} is secondary to a rise in left ventricular end-diastolic pressure, which results from the induced systemic hypertension. It could then be argued that all the changes produced in the pulmonary vascular bed are secondary events resultant upon the rise in LA\textsubscript{m} pressure. The disparate changes noted in pulmonary blood volume, however, suggest that these agents probably act differently on the pulmonary vascular bed.

The concomitant increase in both PBV and P\textsubscript{d} seen during methoxamine infusion supports a purely passive secondary mechanism, probably due to redistribution of blood from the periphery to the pulmonary circuit as a result of systemic vasoconstriction.\textsuperscript{23} This postulation is in accord with the statement of Aviado and Schmidt\textsuperscript{31} that methoxamine has a local constrictive action on almost all systemic vascular beds, but practically no effect on the pulmonary vessels.

In contrast, during angiotensin infusion, PBV decreased or remained unchanged. Such an effect in the presence of a rise in PA\textsubscript{m}, LA\textsubscript{m}, and P\textsubscript{d} pressures strongly suggests active vasoconstriction of the pulmonary vascular bed. This interpretation is further strengthened when it is realized that this lowered or unchanged PBV occurred despite passive distending forces produced by the rise in left atrial pressure. However, we cannot rule out the possibility of differential constrictive effects of angiotensin and meth-
oxamine on the systemic veins. Thus, angiotensin may exert less venous constriction than methoxamine, resulting in a decreased venous return to the right heart and, therefore, to the pulmonary circuit.

Active vasodilation as indicated by an increase in PBV along with a decrease in PD was seen after administration of acetylcholine. These findings are in accord with the previous reports by various workers. A recent report from this laboratory demonstrated a significant increase in CBV and a significant decrease in PA during acetylcholine infusion in a group of 18 patients with mitral stenosis. It is likely that the increase in CBV was largely due to an augmented PBV. The expansion of the pulmonary vascular bed was probably due to a decrease in muscular tone, which resulted in a reduction in distending pressure.

From the data presented in this report, we feel that the presence of active vasomotion in the pulmonary vessels of the intact, unanesthetized human has been clearly demonstrated. Figure 9 is a composite schematic diagram of our results.

This study has not elucidated where these changes in tone occur. It seems reasonable to presume, however, that the changes in pulmonary arterial pressure are principally a result of alterations in arteriolar tone. The neurogenic control is probably not an important factor, since in an unanesthetized man active vasoconstriction and vasodilation may persist even after sympathectic denervation. It should be emphasized that the calculated changes in pulmonary vascular resistance bear no consistent relationship to the actual changes in the caliber or tone of the pulmonary vessels. Changes in resistance can result simply from passive distention or recoil associated with proportional increase or decrease in both transmural pressure and volume.

Since the pulmonary veins contain about 53 per cent of the total pulmonary blood volume, one could speculate that this is the principal site of blood volume change. The fact that the pulmonary wedge and mean left atrial pressures varied together at all times indicates that, under the experimental conditions studied, no sphincter-like mechanism came into play between the pulmonary veins and left atrium. It is quite possible, nevertheless, that widespread changes in venous tone and caliber could occur and, in the absence of a sphincter mechanism, the pulmonary wedge and left atrial pressures would be expected to change to a similar extent.

The capillaries, also, may alter their total volume as is indicated by the increased diffusing capacity and pulmonary capillary blood volume that have been observed during exercise.

It is possible that a given experimental intervention may have different effects on different segments of the pulmonary bed. Thus, one part may dilate as another narrows. The technic used in this study cannot define such changes. It does afford a means of estimating, however, the net effect of an experimental study on the total pulmonary vascular bed.

Conclusions

Pulmonary blood volume was estimated by means of rapidly successive injections of an
indicator into the pulmonary artery and left atrium with sampling of blood from a systemic artery. In 40 patients with mitral valve disease and in four patients with mild aortic valve disease, this volume was found to range from 122 to 455 ml./M.², with a mean of 283 ml./M.².

Changes induced in pulmonary blood volume by physiologic maneuvers and pharmacologic agents were correlated with changes in intravascular distending pressure to deduce active or passive vasomotion in the pulmonary circuit.

Exercise, rapid intravenous infusion or methoxamine were found to cause passive pulmonary vasodilation manifested by a concordant rise in both pulmonary blood volume and intravascular distending pressure. Hexamethonium or vasovagal reactions induced passive narrowing, reflected by simultaneous reduction in both pulmonary blood volume and distending pressure. During acute hypoxia or angiotensin infusion, active constriction of the pulmonary vascular bed was evidenced by an increase in distending pressure but a decrease or no change in the pulmonary blood volume. During acetylcholine infusion, active dilation of the pulmonary vascular bed was reflected by a decrease in distending pressure but an increase in the pulmonary blood volume. However, with a given intervention, the change in the calculated pulmonary vascular resistance was variable.

This study has demonstrated that the pulmonary blood vessels in unanesthetized man can be affected by both active and passive mechanisms and that changes in pulmonary vascular resistance cannot necessarily be equated with change in pulmonary vascular caliber.

Acknowledgment

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References


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