Determination of Pulmonary Blood Volume by Single Intravenous Injection of One Indicator in Patients with Normal and High Pulmonary Vascular Pressures

By Flavio M. de Freitas, M.D., Eduardo Z. Faraco, M.D., Normelio Nedel, M.D., Decio F. de Azevedo, M.D., and Jaime Zaduchliver, M.D.

Most of the methods for estimation of blood volume in the pulmonary circuit are based on the Stewart-Hamilton principle. Different types of indicators (dyes and radioisotopes) are used, and their varying concentrations are determined either from arterial sampled blood or by precordial scanning. Combined right and left heart catheterization provides a more direct measurement of pulmonary blood volume in man, by the indicator-dilution technic. In methods already described, the pulmonary artery and the left atrium are used as sites of injection of the indicators, sampling being made in a peripheral artery. Milnor, Jose, and McGaff use one indicator, which is injected successively in the pulmonary artery and left atrium, or vice versa, whereas the technic of Dock et al. requires the simultaneous delivery into the circulation of two indicators, one for each injection site.

The purpose of this paper is to report and discuss the results obtained with a technic that does not require two indicators or two successive injections of the same indicator, but substitutes peripheral arterial sampling for central sampling (pulmonary artery and left atrium), dye being injected near the right atrium.

Material and Method

Determinations of the pulmonary blood volume were carried out in 12 patients with pulmonary hypertension undergoing cardiac catheterization for diagnostic or follow-up purposes, and in 12 patients with normal pressures in the pulmonary circulation. In all but one case of the first group, the pulmonary hypertension was secondary to mitral stenosis. The exception was a patient who had been submitted to an operation, 6 months before, for the closure of a patent ductus. Cardiac failure or disturbances of the heart rhythm were not present in any of the patients studied. Diagnoses were all confirmed surgically, and cases with mitral regurgitation of any degree were excluded from this study. Cases in the second group had no signs of cardiovascular disease or diffuse pulmonary disease, with the exception of two patients who were considered to have essential arterial hypertension. All patients received a thorough explanation about the nature of the procedure, and their express consent was required for execution of the study.

At the time of the study, the patients were in the fasting state, in recumbent position, on a fluoroscopic table, and had received 100 mg. of phenobarbital orally and 100 mg. of meperidine intramuscularly 1 hour before. Right heart catheterization was performed via the left antecubital vein. The tip of a 7F 125-cm. Teflon catheter (USCI T-52) was placed in the pulmonary artery, just distal to the pulmonary valve. The modification of the Ross transseptal technic proposed by Brockenbrough and Braunwald was used for left heart catheterization. For this procedure, a 70-cm. Teflon catheter (USCI BR-70) was employed and advanced through the atrial septum into the left ventricle and then pulled back so that its tip was just proximal to the mitral valve. An Odman Ledin 40-cm. polyethylene radiopaque catheter (Kifa, yellow) was also introduced percutaneously through the left femoral vein, by the Seldinger technic, and positioned in the inferior vena cava near the right atrium. This catheter was used exclusively for the injection of dye for dilution curves. The femoral artery was cannulated with a Cournand needle.

Intravascular and intracardiac pressures were measured by means of Statham P23Db transducers connected to a cathode-ray photographic...
PULMONARY BLOOD VOLUME

The zero level for the recorded pressures was referred to an imaginary horizontal plane passing through the midaxillary line of the patient lying in supine position. Mean pressures were obtained by electronic integration and were measured during at least three respiratory cycles.

The cardiac output and the pulmonary blood volume were determined from dilution curves recorded simultaneously from the pulmonary artery and the left atrium, following the rapid injection of 1.0 to 1.5 ml. of indocyanine (Cardiogreen) via the catheter placed in the inferior vena cava. The syringe for dye injection was manually operated, and the use of a short, large bore catheter made possible a time of injection not exceeding 0.5 second. The catheter was not flushed with saline immediately after the dye injection, since the catheter was kept filled with the indicator and the injections were made by displacement. In vitro experiments have shown that very small quantities of the indicator in the distal end of the catheter may diffuse slowly into the blood stream between injections. This source of error in the amount of dye delivered was reduced to a minimum by partial refilling (0.2 ml.) of the catheter, 30 seconds before each new injection. Blood was sampled through the catheters placed in the pulmonary artery and left atrium by the use of a modified infusion-withdrawal pump,† which permits two syringes to be driven by the same motor and, consequently, at the same speed. The sampling rate was 0.6 ml. per second. Curves were recorded in the cathode-ray photographic system with the use of two cuvette densitometers ‡ of identical characteristics. The output of both densitometers was found to be linear in the range of dye concentrations used. The response speed to a sudden change in optical density was about 70 per cent of the full-scale deflection in 0.05 second. To avoid a possible systematic error due to small differences between densitometers, the cuvettes were interchanged, after each pulmonary blood volume determination, by inversion of their connections with the catheters. Sterilization of the cuvettes, sampling syringes, and tube connections allowed all the blood withdrawn for dye-dilution curves to be returned to the patient. In all curves obtained, maximal concentration and recirculation peaks were clearly delineated. The average ratio of the least concentration to the peak concentration deflection was 0.03 and 0.11, for pulmonary artery and left atrium curves, respectively. Curves were re-plotted on semilogarithmic paper and recirculation was excluded by extrapolation of the disappearance slope. Cardiac output and mean transit time were calculated as described by Hamilton, Moore, Hinsman, and Spurling,12 with the use of the volumetric technic of Lenkei, Fox, and Lynn13 for calibration. During the calibration process the two densitometers were connected in tandem, and the same blank and standard dilution samples were passed through both cuvettes. The volume, in milliliters, from the tip of each catheter to the middle of each cuvette was accurately measured and divided by the rate of sampling flow, in milliliters per second, for the calculation of the delay in the collecting system. The internal volumes of the right and left heart catheters used in this study were not equal and varied from 1.5 to 1.6 ml. Calculated delays were subtracted from the respective mean transit time measurements. Dilution volume, or the volume of blood between the site of injection and the site of sampling, was obtained by multiplying cardiac output, in milliliters per second, by the appropriate mean transit time, in seconds. The average of the two cardiac output measurements obtained from the pulmonary artery (PA) curve and from the left atrium (LA) curve was used for the calculation of the dilution volumes. Since dye was injected into the inferior vena cava (IVC), the pulmonary blood volume was calculated by subtracting the IVC-PA mean transit time from the IVC-LA mean transit time, and multiplying the result by the cardiac output. Two or three pairs of dye curves for the evaluation of cardiac output and pulmonary blood volume were recorded from each patient, at intervals of several minutes.

The Fick principle for the determination of flow was utilized as a comparative reference for the cardiac output values obtained from dilution curves. For this purpose, simultaneous samples of blood were taken from the femoral and pulmonary arteries, during the collection of expired air in a neoprene bag. The oxygen contents of blood samples were determined by the method of Van Slyke and Neill,14 and expired air was analyzed by the Scholander technic.15

The pulmonary vascular resistance (PVR) and the average intravascular pressure (AIP) in the pulmonary circulation were calculated as follows:

\[
PVR = \frac{PA - LA}{CO} \times 80
\]

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

In the above formulae, \(PA\) and \(LA\) are the mean

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† No. 600-950, Harvard-Apparatus Company, Inc., Dover, Massachusetts.
‡ X-250, Waters Corporation, Rochester, Minnesota.

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### Table 1

**Summary of Data**

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<th>CO (Fick) L/min</th>
<th>CO₉ₐ L/min</th>
<th>CO₉ₐ Dye L/min</th>
<th>CI L/min/M²</th>
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Group II. Patients with normal pressure in the pulmonary circulation

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<th>CO (Fick) L/min</th>
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Abbreviations: BSA, body surface area; HR, heart rate; CO, cardiac output; CO₉ₐ, cardiac output calculated from the pulmonary artery dye-curve; CO₉ₐ, cardiac output calculated from the left atrium dye-curve; CI, average cardiac index (dye); SI, stroke index; MTT, mean transit time; IVC, inferior vena cava; PA, pulmonary artery; LA, left at-
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rium; BV, blood volume; PBV, pulmonary blood volume; PA, mean pulmonary arterial pressure; LA, mean left atrial pressure; AIP, average intravascular pressure in the pulmonary circuit; PVR, pulmonary vascular resistance.
pulmonary arterial and left atrial pressures, in mm. Hg, respectively. CO is the average cardiac output, in liters per minute, calculated from the dye curves. Results for resistance were expressed in dynes sec. cm.⁻⁵

The average intravascular pressure was used for a rough estimation of the transmural pressure in the pulmonary circulation¹.¹⁶ and to calculate the relative compliance of the pulmonary vascular bed, as proposed by Milnor, Jose, and McGaff.¹

**Results**

The results obtained in the two groups studied are summarized in table 1. Figures for flows, circulation times, volumes, and pressures represent the average of two or three determinations in each patient.

**Cardiac Output**

As can be seen from figure 1, which includes the 58 determinations of the cardiac output performed in the 24 patients, with use of the indicator-dilution technic, there was a close agreement (correlation coefficient \( r = +0.928 \)) and no systematic differences between the flows calculated from the curves recorded by the simultaneous sampling of the pulmonary arterial and left atrial blood. Mean figures, for all patients, were 4.78 ± 1.00 L./min., for PA curves, and 4.86 ± 1.05 L./min., for LA curves, with an average ratio COPA/COLA equal to 0.98.

When the average cardiac output of each patient, as calculated from the dye curves, was compared with the flow estimated by the Fick principle, again, a good correlation (\( r = +0.982 \)), with no systematic error, was found (fig. 2). Mean values obtained were 4.91 ± 1.15 L./min., by the Fick principle, and 4.82 ± 1.02 L./min., by the dye method. Mean cardiac index was 2.76 ± 0.82 L./min./M.², for patients of group I, and 3.33 ± 0.50 L./min./M.², for patients of group II. This difference was of no statistical significance.

**Pulmonary Mean Transit Time**

Though an overlap of results has been

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*All figures are the mean ± standard deviation.*

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observed among the two groups studied, there was a tendency for the pulmonary mean transit time to be longer in patients with pulmonary hypertension than in patients with normal pulmonary intravascular pressures. Mean results for both groups were 8.8 ± 3.4 and 5.6 ± 1.0 seconds, respectively. This difference was statistically significant \((p < 0.02)\).

A highly significant \((p < 0.01)\) negative correlation \((r = -0.716)\) was demonstrated between pulmonary mean transit time and cardiac index in group I. Such an inverse relationship was not present in group II.

**Pulmonary Blood Volume**

The mean pulmonary blood volume was 375 ± 97 ml./M.², for group I, and 310 ± 21 ml./M.², for group II. This difference was considered to be significant \((p < 0.05)\). Analysis of the values obtained from the two or three determinations performed in each patient has shown very good reproducibility of the results, expressed by an average percentile variation around the mean values equal to 3.2 ± 2.7. This signifies that two determinations of the pulmonary blood volume carried out in one patient, under the same conditions, would rarely differ more than 12 per cent.

No correlation was evident in group I or II, between pulmonary blood volume and cardiac index. As could be expected, however, pulmonary blood volume and pulmonary mean transit time correlated well in both groups, coefficients being \(r = +0.743\) for patients with pulmonary hypertension, and \(r = +0.778\) for patients with normal pressures in the lesser circuit. These correlations were found to be of high statistical significance \((p < 0.01)\).

In patients of group I, a significant inverse relationship between pulmonary blood volume and stroke index \((r = -0.579, p < 0.05)\) has been shown to occur. However, no correlation of these variables could be demonstrated in group II.

The pulmonary blood volume did not correlate, either in group I or II, with the pulmonary vascular pressures or resistance.

The relative pulmonary vascular compliance, which is simply the ratio of pulmonary blood volume to the average intravascular pressure, was \(13 \pm 9 \text{ ml./mm.Hg}\) for patients with pulmonary hypertension, and \(34 \pm 16 \text{ ml./mm.Hg}\) for patients with normal pressures in the pulmonary circuit. This difference was found to be statistically significant \((p < 0.01)\).

**Discussion**

**Advantages and Limitations of the Method**

Discussion about the theoretical basis and accuracy of the indicator-dilution method for measuring flow and volume, in the living circulation, is beyond the scope of this report. Many excellent publications dealing with these aspects can be found in the medical literature.\(^{17-22}\) Some pertinent problems directly related to the technic here proposed deserve more extensive comments.

**Sampling through Catheters**

The use of catheters for sampling introduces a distortion which influences differently the two curves recorded, since the catheters differ in length and caliber. It has been pointed out, however, that modifications in shape do not affect the calculation of flow, since the area under the curve does not change.\(^{26}\) Similarly, for volume computation, appropriate corrections of mean transit time can be achieved by subtraction of the mean time spent by the indicator particles in traveling from the tip of each catheter to the middle of each cuvette.\(^{20}\) This estimation can be easily accomplished by an in vitro method.

**Time of Injection**

For mean transit time calculations to be correct, either an instantaneous injection of the indicator or the subtraction of the mean time of the injection process from the over-all mean transit time is necessary.\(^{20}\) Since a true instantaneous injection is not feasible, this source of error has been minimized by making the injection as rapid as possible and by taking the midpoint of the injection time as

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the starting point of measurements. In the method here proposed, the use of a single injection of one indicator affects equally the curves recorded from pulmonary artery and left atrium. Consequently, any error due to improper timing of the delivery of the dye would influence both curves and be canceled out in the determination of mean transit time in the pulmonary circulation. The same may not be true when the indicators are either successively or simultaneously injected in pulmonary artery and left atrium.\textsuperscript{1, 2}

Use of Two Densitometers

Though the densitometers used in this investigation had similar characteristics, the possibility must be admitted that they can introduce different errors in the curves recorded. As one-color instruments, they have no compensation for some nonspecific changes in the optical density of blood.\textsuperscript{23} Nevertheless, it is thought that the effect of the eventual differences can be disregarded if more than one determination is made with alternate connections of the cuvettes to the catheters, as was done in this study.

Distribution of Indicator to Both Lungs

Since an equal velocity of blood flow through both lungs has not been proved to occur, either in health or disease, it is important to obtain an equal distribution of the indicator to the two lungs, so that the determination of the pulmonary blood volume may be accepted as valid. As pointed out by Dock et al.,\textsuperscript{2} it is improbable that such an equal distribution could be achieved when the indicator is injected in the pulmonary artery. In the method here proposed, however, the dye traverses a mixing chamber (the right ventricle) before going into the pulmonary vasculature. Therefore, it is reasonable to assume that even distribution of the indicator to the two main branches of the pulmonary artery is, by far, more likely to occur than when injection is made in the pulmonary trunk.

Bronchial Circulation

By this method, the amount of flow entering the pulmonary circulation through bronchial anastomoses would influence only the indicator curve recorded from the left atrium. This constitutes an unavoidable cause of error which can be lessened by using, for the calculation of the pulmonary blood volume, the average of the two outputs measured from the curves. It is thought, however, that in most cases studied* the flow passing through the anastomoses with the bronchial circulation represents only a very small part of the total pulmonary blood flow.\textsuperscript{2, 24} Further support for this point of view can be found in the lack of systematic difference between the results obtained from the left atrium and pulmonary artery (table 1, fig. 1) and in the agreement of the average dye cardiac output with the flow estimated by the Fick principle (table 1, fig. 2).

Left Atrial Volume

In the methods of Milnor, Jose, and McGaff\textsuperscript{1} and of Dock et al.,\textsuperscript{2} the assumption is made that the left atrial volume is excluded from the pulmonary blood volume. As these authors recognize, however, this would be true only if a complete mixing of the indicator injected in the left atrium could be assured. Since there are many reasons to believe that this constitutes the exception rather than the rule, a variable portion of the left atrial volume may be included in the pulmonary blood volume determined by the above-mentioned methods. The magnitude of this variable portion would depend on many factors, such as the size of the left atrium, the position of the catheter used for injection, the competence or incompetence of the mitral valve, the time of injection in relation to

* Possible exceptions would be cases 16 and 24 (table 1), both having bronchiectasis, which is known to be commonly accompanied by an increase of the anastomoses between the bronchial and pulmonary vessels.\textsuperscript{24} Nevertheless, they were included in this study because bronchiectases, in both, were limited to small portions of the lung and in view of the fact that the flow determined by the Fick principle was closer to the output calculated from the LA curve than to that from the PA curve. The inverse would be expected if the difference were due to bronchial flow.\textsuperscript{24}
the cardiac cycle, etc. Therefore, the error introduced cannot be estimated and may be different from patient to patient, and, in the same patient, from moment to moment. The technic here proposed almost certainly includes the entire left atrial volume in the calculated pulmonary blood volume. This may eliminate, at least, some moment-to-moment differences which could be important in studies designed to demonstrate eventual alterations of the pulmonary blood volume induced by drugs or other agents.

**Effect of Valvular Regurgitation**

When the indicator is injected into the inferior vena cava, the presence of tricuspid or pulmonary valvular regurgitation affects almost equally the curves recorded from the pulmonary artery and left atrium. The valvular incompetence being severe, it may be difficult to segregate the exponential decay portion of the curve from the recirculation. This may lead to a considerable error in the flow and volume calculations. In the event of mitral insufficiency, however, only the left atrial curve would be influenced, and the errors introduced could be even greater. Furthermore, in case of mitral regurgitation, the possibility exists of the left ventricle volume being partially or completely included in the computed pulmonary blood volume.

**Comments on the Results**

**Values for Pulmonary Blood Volume**

The results for pulmonary blood volume obtained in this study are similar to others already published in the literature.\(^1\), \(^2\), \(^9\), \(^25\)–\(^27\). The significant difference between patients with hypertension and with normal pressures in the pulmonary circulation could, at least in part, be explained by a difference in the mean size of the left atrium, the whole volume of which is probably included in the pulmonary blood volume calculated by this technic. Arvidsson\(^28\) carried out angiocardiographic determinations of the volume of the left atrium in a group of patients with pure mitral stenosis and normal sinus rhythm, which from the pulmonary venous pressure standpoint could be compared with group I of this report. Indeed, the average mean pulmonary wedge pressure in Arvidsson's patients was 23 mm.Hg, as compared to 21 mm.Hg for the mean left atrial pressure in this series. In the above-mentioned group of cases, Arvidsson has found a mean left atrial volume of about 85 ml. per M.\(^2\) of body surface area. Though no equivalent data are available for the average normal left atrial volume, it is reasonable that figures for it would be much lower. Therefore, it may be assumed that if the appropriate deductions were made from the results here reported, the mean values for the "true" pulmonary vascular volume would not be significantly different in the two groups studied.

**Relationships between Pulmonary Blood Volume and Other Variables**

The pressure-volume relationship in a distensible compartment depends largely on the physical properties of its walls. In the living circulation, the physical properties of a vascular bed may change not only in accordance with alterations in the structure of the vessel walls\(^29\) but also under the influence of different physiologic states or under the action of a variety of vasoactive agents.\(^25\), \(^30\) Therefore, it is perfectly understandable that the pressure-volume characteristics of the pulmonary vascular bed may vary in normal individuals and, even more, in patients with pulmonary hypertension, in which different degrees of structural changes can be demonstrated in the small and large pulmonary vessels. Similar patient-to-patient differences of the pressure-volume relationship may be expected to occur in the left atrium.\(^28\), \(^31\), \(^32\) These considerations are well illustrated by the lack of correlation between arterial or venous pressure and volume in the pulmonary circuit, with ample variations, both in and between the two groups studied, in the ratio of pulmonary blood volume to the average intravascular pressure.

The poor correlation encountered in this study between the pulmonary blood volume and the cardiac output, in both groups, and the stroke index, in group II, as well as the negative correlation between pulmonary
blood volume and stroke index, in group I, is also worthy of comment. These findings are in partial agreement with those reported by Dock and co-workers but are in opposition to the observations of Milnor, Jose, and McGaff, which were confirmed in a more recent paper. Varmauskas et al. reported a direct correlation between the amount of blood in the lungs and the stroke volume, but no correlation between pulmonary blood volume and cardiac output. The factors governing the heart rate, the stroke volume, and, consequently, the cardiac output being so many, these discrepancies are not surprising. More than the blood volume itself, is the relationship between the volume and the distensibility of the venous part of the systemic and pulmonary circuits (right and left atria included) which may determine the filling pressure of the ventricles and their stroke volume and work. Moreover, changes in ventricular contractility may change stroke volume and work independently of alterations in filling pressure. This explains why modifications of the stroke volume or cardiac output do not always run in parallel with changes in pulmonary blood volume, as has been observed in many physiologic and pathologic states or during the action of vasoactive agents. As a matter of fact, present knowledge indicates that the mechanisms of circulatory adjustment designed to meet the ever-changing organic demands throughout life can vary regional or total blood flow in a wide range, while pulmonary blood volume is maintained within narrow limits.

Summary

Determinations of the pulmonary blood volume were carried out in 12 patients with pulmonary hypertension and in 12 patients with normal pressures in the pulmonary circulation, by the use of a single intravenous injection of one indicator, blood sampling being made through catheters in the pulmonary artery and left atrium and connected with two densitometers of similar characteristics. Pulmonary blood volume measured by this technic includes the major portion of, or the entire left atrial volume. Values obtained from duplicate or triplicate determinations performed in each patient have shown that this technic provides very good reproducibility of the results expressed by an average percentile variation around the mean equal to 3.2 ± 2.7. The mean pulmonary blood volume as referred to body surface area was 375 ± 97 ml./M² for patients with pulmonary hypertension, and 310 ± 21 ml./M² for patients with normal pulmonary intravascular pressures. This difference was found to be significant (p < 0.05) but was attributed, at least in part, to a difference in the mean left atrial volume between the two groups studied.

Some possible advantages and limitations of the method, as well as the poor correlation between pulmonary blood volume and other variables, like pulmonary intravascular pressures, stroke volume, and cardiac output, were discussed.

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References


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PULMONARY BLOOD VOLUME


34. RUSHMER, R. F.: Effects of nerve stimulation and hormones on the heart; the role of the heart in general circulatory regulation. In Handbook of Physiology, edited by W. H.
The history of this disease, and its symptoms, is nearly as follows:—

A child, or an adult, is affected with scarlatina, or some other acute disease; or has indulged in the intemperate use of ardent spirits for a series of months or years: he is exposed to some casual cause or habitual source of suppressed perspiration: he finds the secretion of his urine greatly increased, or he discovers that it is tinged with blood; or, without having made any such observation, he awakes in the morning with his face swollen, or his ankles puffy, or his hands oedematous. If he happen, in this condition, to fall under the care of a practitioner who suspects the nature of his disease, it is found, that already his urine contains a notable quantity of albumen: his pulse is full and hard, his skin dry, he has often headache, and sometimes a sense of weight or pain across the loins. Under treatment more or less active, or sometimes without any treatment, the more obvious and distressing of these symptoms disappear; the swelling, whether casual or constant, is no longer observed; the urine ceases to evince any admixture of red particles; and, according to the degree of importance which has been attached to these symptoms, they are gradually lost sight of, or are absolutely forgotten. Nevertheless, from time to time the countenance becomes bloated; the skin is dry; headaches occur with unusual frequency; or the calls to micturition disturb the night's repose. After a time, the healthy colour of the countenance fades; a sense of weakness or pain in the loins increases; headaches, often accompanied by vomiting, add greatly to the general want of comfort; and a sense of lassitude, of weariness, and of depression, gradually steal over the bodily and mental frame. Again the assistance of medicine is sought. If the nature of the disease is suspected, the urine is carefully tested; and found, in almost every trial, to contain albumen, while the quantity of urea is gradually diminishing.—Original Papers of Richard Bright on Renal Disease. Edited by A. Arnold Osman. London, Oxford University Press, 1937, pp. 94-95.
Determination of Pulmonary Blood Volume by Single Intravenous Injection of One Indicator in Patients with Normal and High Pulmonary Vascular Pressures

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