Determination of Pulmonary Blood Volume by Injection into Pulmonary Artery and Sampling in Left Atrium*

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Dye dilution technique for measuring pulmonary blood volume is usually done by successive injections of the indicator into the pulmonary artery and the left atrium and sampling in the brachial artery. Pulmonary blood volume is measured as the product of the pulmonary mean transit time and cardiac output. Whether an indicator, which is injected into the pulmonary artery, can be sampled from the left atrium without any preferential sampling from one of the pulmonary veins is not certain. There is also doubt as to whether an indicator would be thoroughly mixed without passing through a cardiac chamber (Dock *et al.*, 1961). Levinson, Frank, and Hellems (1964) have reported the measurement of pulmonary blood volume by injection of indocyanine green dye into the pulmonary artery and sampling in the left atrium. Samet *et al.* (1966) have examined the accuracy of pulmonary artery injection-left atrial sampling curves, and have concluded that this technique grossly overestimates the pulmonary blood volume. Milnor and Jose (1960) have indicated that dye dilution curves, when recorded by sampling through cardiac catheters, are distorted due to the large volume of the sampling system. The present investigation was conducted to assess the accuracy of measuring the pulmonary blood volume by injection into the pulmonary artery and sampling in left atrium after correction of the indicator dilution curve for volume: flow ratio of the sampling system, according to Milnor's formula.

SUBJECTS AND METHOD

A total of 12 patients was examined. Haemodynamic studies were performed in the post-absorptive state after premedication with pentobarbitone sodium, 100 mg., and diphenhydramine hydrochloride, 50 mg. A No. 7, 100 cm. long, Rodriguez-Alvarez catheter was introduced into a branch of the right antecubital vein, and advanced into the pulmonary artery and positioned immediately above the pulmonary valve. A No. 18T Courmand needle was inserted into the right or left brachial artery. Employing the Seldinger percutaneous and Brockenbrough transseptal technique (Brockenbrough, Braunwald, and Ross, 1962), a No. 8-1/2 Brockenbrough transseptal catheter was positioned in the left atrium. Cardiac output was obtained by the direct Fick principle. Injection of 1 ml. of 5 mg./ml. Cardiogreen* was made into the pulmonary artery and left atrium successively and sampled in the brachial artery (pulmonary artery-brachial artery and left atrium-brachial artery curves). Injection was also made into the pulmonary artery and sampled in the left atrium (pulmonary artery-left atrial curves). The order of injection was randomized. The interval between each injection was 3 minutes. Cardiogreen was withdrawn into a calibrated tube and rapidly flushed with 10 ml. normal saline solution. The time of injection was marked when the dye was cleared from the tube and was completed in less than a second. In some cases the beginning and the end of injection were marked by an electrical signal attached to the syringe. The output of the densitometer was amplified and recorded on the Electronics for Medicine Photographic Recorder, Model DR 8. Blood was withdrawn at a constant rate of 0.9 ml./sec. through a Gilford cuvette densitometer and constant withdrawal system. The volume of the left atrial sampling system was 2.24 ml. (Brockenbrough catheter and teflon connecting tube) with a volume:

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* Manufactured by Hynson, Westcott and Dunning, Inc., Baltimore, Maryland.

FIG. 1.—Case 9. Dye dilution curves: *left*—injection is made into the pulmonary artery (PA) and sampled in the brachial artery (BA); *middle*—injection into the left atrium (LA) and sampling in the brachial artery; *right*—injection into the pulmonary artery and sampling in the left atrium. Time lines are at one-second intervals.

flow ratio of 2.48. Three-point calibration of densitometer (2 mg., 4mg., and 8mg. per litre) was made immediately after the completion of the studies with the patient's arterial blood which was drawn before the dilution studies and with the same dye used in the patient. Calculation of cardiac output and mean transit time were obtained by the method of Hamilton *et al.* (1932) or Lilienfield and Kovach (1956). Pulmonary mean transit time was measured by the difference between pulmonary artery-brachial artery and left atrium-brachial artery mean transit times, and also by measuring directly from the curve of the pulmonary artery-left atrium. Mean transit time obtained by pulmonary artery-left atrial curve was corrected for volume:flow ratio by Milnor and Jose's formula (1960): Δ mean transit time = $0.140 + 0.901 (V/F) - 0.00933 (V/F)^2$. This was equal to 2.31 seconds. Correction was not applied for the double injection, double sampling technique, since the sampling system was identical in both. The data were subjected to statistical analysis for small samples. The significance of the difference between the results was determined by paired analysis using Student's *t* test (Snedecor, 1956). The degree of correlation was measured by the product moment correlation coefficient.

RESULTS

Figure 1 shows a typical dye dilution study, and the Table shows the individual values of each determination.

Comparison of Cardiac Output Values by Fick Principle and Indicator Dilution Technique. Figure 2 shows the relation between dye dilution values compared with Fick. The solid line is the line of ideal regression and the broken lines are 15 per cent deviations from this line. Although one Fick output was used for three dye dilution outputs and the time lag between Fick output and different dilution

outputs was not the same, most of the values were within the 15 per cent limit. This is within the range of errors of the technique.

Comparison of Pulmonary Mean Transit Time by Two Methods. Figure 3 shows the graph of pulmonary mean transit time by the 2-injection, 2-sampling technique, as compared to the single-injection and sampling technique. The light solid

FIG. 2.—Comparison of dye dilution cardiac output (ordinate) with Fick cardiac output (abscissa). Each cardiac output by the Fick method is compared with 3 dye dilution outputs. The solid line is the ideal regression line and the broken lines are 15 per cent deviations from this line. Cases 10 and 12 are not included.

TABLE

COMPARISON BETWEEN VALUES OF CARDIAC OUTPUT BY FICK PRINCIPLE AND DYE DILUTION TECHNIQUE; PULMONARY MEAN TRANSIT TIME BY TWO METHODS AND PULMONARY BLOOD VOLUME

Case No.	Age (yr.), sex	Diagnosis	Cardiac output (l./min.)				Mean transit time (sec.)				Pulmonary blood volume (ml.)			
			Fick	Dilution technique			PA-BA LA-BA		Pulmonary MTT		CO used for calculation			
				PA-BA	LA-BA	PA-LA			PA-BA minus LA-BA	PA-LA	PA-BA	LA-BA	PA-BA and LA-BA	PA-LA
1	43 F	Mitral stenosis	4.13	3.92	3.89	3.82	12.22	6.50	5.72	5.73	373	370	371	364
2	43 M	Aortic stenosis (Starr-Edwards valve)	5.6	6.4	6.55	6.3	10.2	5.5	4.70	5.56	501	513	507	583
3	19 F	Right coronary artery, right ventricle communication	3.4	3.83	3.75	3.37	8.5	4.46	4.04	4.65	257	252	255	261
4	52 M	Hypertrophic subaortic stenosis	5.3	6.35	5.17	6.05	9.08	4.60	4.48	5.14	457	386	430	518
5	33 M	Mitral stenosis	3.82	3.38	4.16	3.94	25.6	12.1	13.5	13.20	760	935	848	866
6*	48 M	Aortic stenosis and regurgitation	5.75	5.13	5.4	5.6	17.10	8.70	8.4	7.50	718	756	737	699
7	18 F	Mitral stenosis	5.5	5.84	5.65	5.79	13.73	6.04	7.69	7.94	748	724	736	766
8	61 M	Aortic stenosis	4.5	4.55	4.54	5.16	20.76	12.76	8.0	8.52	606	605	606	733
9	43 F	Mitral stenosis	2.8	1.89	2.08	2.12	16.87	8.73	8.14	8.48	256	282	269	299
10*	47 F	Mitral regurgitation	3.6	5.27	6.20	5.47	15.26	7.24	8.02	9.04	704	828	766	824
11	35 F	Mitral stenosis	3.9	4.45	4.52	4.23	14.18	5.83	8.35	8.43	619	629	624	594
12	22 M	Hypertrophic subaortic stenosis	6.0	8.59	8.11	8.36	10.43	5.56	4.87	5.20	698	659	678	725
		Mean	4.47	4.57	4.57	4.63			7.15	7.44	558	578	568	602
		SD ±	0.97	1.35	1.17	1.31			2.52	2.33	178	210	191	195
		SEM ±	0.30	0.42	0.37	0.41			0.72	0.67	51	60.6	55.2	59

* PA-BA and LA-BA indicate dye dilution curves with injection into pulmonary artery and left atrium, respectively, and sampling in brachial artery. PA-LA indicates injection into pulmonary artery and sampling in left atrium. Except for Case 6, with insignificant aortic regurgitation, and Case 10, with moderate degree of mitral regurgitation, the remainder of the patients did not have regurgitant lesions. In Case 12, with hypertrophic subaortic stenosis, dye dilution cardiac outputs were obtained during isoprenaline infusion. These last two cases are not included in mean values of cardiac output determinations.

MTT = mean transit time.

line is the line of identity and the broken lines are 15 per cent deviations from this line. The heavy solid line is the best fit line. There is a high degree of correlation ($r=0.95$) with no statistically significant

difference between the two methods ($p>0.05$). The mean difference between the two was 0.32 sec., with a standard deviation of 0.55 sec. (or 7.5% of average pulmonary mean transit time).

FIG. 3.—Comparison of pulmonary mean transit time by the two methods. The light solid line is the ideal regression line. The heavy solid line is the best fit line. The broken lines are 15 per cent deviations from the identity line.

Comparison Between Values of Pulmonary Blood Volume. The relation between the values of pulmonary blood volume as measured by different dye dilution cardiac outputs is shown in Fig. 4. The solid line is the line of identity and the broken lines are 15 per cent deviations from this line. Most of the values are within this limit.

DISCUSSION

The major hindrance in measuring pulmonary mean transit time by injection into the pulmonary artery and sampling from the left atrium is the possibility of incomplete mixing and/or preferential sampling from the pulmonary veins corresponding to the areas with different rates of transit time. Moreover, a distorted curve would cause an error in mean transit time, which is relatively greater than the error in calculation of cardiac output. It has been speculated that if dye is not traversing a cardiac chamber, uniform mixing may not occur. In the calculation of pulmonary mean transit time and pulmonary blood volume, it is assumed that the dye is distributed to both lungs equally. This assumption

FIG. 4.—Comparison between the values of pulmonary blood volume using cardiac output obtained by pulmonary artery-left atrial curve (ordinate) with pulmonary blood volume obtained using cardiac output values of pulmonary artery-brachial artery; left atrium-brachial artery and average of the two (abscissa). The solid line is the ideal regression line and the broken lines are 15 per cent deviations from this line.

pertains to both techniques regardless of its certainty. In pulmonary artery injection-left atrial sampling technique, at least part of the bronchial circulation is included in the measurement of pulmonary blood volume. It is possible that bronchial circulation does affect pulmonary artery-left atrial curves; however, this most likely produces an insignificant distortion of the dilution curve. In this study patients with significant mitral regurgitation were excluded, since this lesion will affect the pulmonary artery-left atrial curve significantly. Only one patient with a mild degree of regurgitation was included. If injection of dye is made through an end-hole catheter, it is possible that the dye may stream into one pulmonary artery or a branch of the pulmonary artery. Figure 5 shows a dye dilution recording in which the dye was injected through an end-hole catheter. The downslope of the curve is distorted. This was not encountered in any patient in whom the dye was injected through a catheter with side-holes and no end-hole. We attribute this distortion of the curve to streaming of dye in pulmonary circuit. It is also important to consider whether or not Cardiogreen dye injected into the pulmonary artery and sampled a short time later in the left atrium is photometrically stabilized. Studies by Bassingthwaite, Edwards, and Wood (1962) have shown that light

FIG. 5.—Distorted dye dilution curve: injection was made into the pulmonary artery through an end-hole catheter and sampled in the left atrium. The downslope is very slurred. Time lines are at one-second intervals.

absorption of Cardiogreen becomes stabilized within one or two seconds after injection *in vivo*. Since the initial photometric measurement in left atrial sampling exceeds this period of time, no error will be produced by sampling at this site.

The volume of sampling system is of extreme importance in such a study. Milnor and Jose (1960) have studied in detail the volume:flow relationship of the sampling system. To maintain a satisfactory volume:flow ratio of 0.5, if volume of the sampling system is increased, the flow should increase to maintain this ratio. However, to maintain this ratio while withdrawing blood through a cardiac catheter requires extremely large flow rates. Hence, though the flow rate was increased to 0.9 ml./sec., the pulmonary mean transit time by pulmonary artery-left atrial curve had to be corrected by the use of Milnor's formula. The results indicate that such correction is necessary to obtain an accurate measurement of the pulmonary mean transit time by single injection and sampling technique. The values of cardiac output by dye dilution techniques are compared with values by the Fick method. In such studies a single determination of Fick was made against three determinations by the dye dilution technique. Most of the subjects fall within the 15 per cent limit of the identity line. The results are

similar to the published reports where dye dilution and Fick cardiac outputs are compared (Hamilton *et al.*, 1948; Werkö *et al.*, 1949; Taylor and Shillingford, 1959; Kopelman and Lee, 1951; Sekelj *et al.*, 1958; Eliasch, 1952). Although the pulmonary mean transit time and pulmonary blood volume by single injection and sampling are slightly higher than the conventional technique, this has not produced a significant error and the results are well within the accepted values for dye dilution measurement of these parameters. In the report by Dock *et al.* (1961) an over-all error of 20–30 per cent in calculation of the pulmonary blood volume was estimated. In none of the individual determinations by the two methods did this difference occur. Opdyke and Sniffen (1959) have pointed out that up to 30 per cent variation in cardiac output can occur during the respiratory cycle. Since dye dilution curves are usually completed in 10–12 seconds, as compared to the Fick method, which is usually accomplished in 3 minutes, the respiratory effects on dye dilution method are much more marked. Since the injection of dye was made at random relative to the respiratory cycle, a difference in the pulmonary blood volume may be expected.

The results of the present investigation are at variance with those of Samet *et al.* (1966). We believe that the reason for the overestimation of the pulmonary blood volume in Samet's study lies in their method. Although they corrected the delay in the sampling, there was no correction for the distortion of the dilution curve due to the large volume of the sampling system in the left atrial sampling. Using Samet's figures of 1.5 ml. and 3 ml. for volume of the sampling system and 25 to 30 ml./min. for withdrawal rate, the change in mean transit time as calculated by Milnor's formula varies from 2.76 sec. to 6.15 sec. In addition, these authors have mainly studied patients with rheumatic heart disease. As mentioned earlier, a significant degree of mitral regurgitation will distort the pulmonary artery-left atrial curve considerably. Unfortunately in Samet's report, the number of patients with mitral regurgitation is not indicated. Our results are more in agreement with Levinson's report. The methods in Levinson's study were similar to ours. The flow rate of sampling was 0.7 ml./sec., as compared to 0.9 ml./sec. in our study. Indeed, the faster flow rate decreases the magnitude of distortion of the dilution curves. In 10 cases studied by Levinson and colleagues, there was only one case with mitral regurgitation; thus the incidence of distorted curves due to mitral regurgitation was not frequent.

An advantage of this method over the 2-injection, 2-sampling method is the determination of the

pulmonary mean transit time and pulmonary blood volume during acute experiments. By this method the effect of therapy on pulmonary blood volume can be measured during the desired "instant", in contrast to the 2-injection, 2-sampling technique, in which a time lag between the 2 injections must be allowed for elimination of dye. If the 2 injections are made in rapid succession, the second injection may be affected by the background dye.

In conclusion, this study indicates that by injection of indicator into the pulmonary artery and sampling in the left atrium, an accurate measurement of cardiac output and pulmonary mean transit time, and hence, pulmonary blood volume, can be obtained. The slight differences in pulmonary mean transit time and pulmonary blood volume are within the range of errors of the dye dilution technique.

SUMMARY

Pulmonary blood volume by injection of indocyanine green dye into the pulmonary artery and sampling in the left atrium was determined in 12 patients. Since the large volume of the sampling system causes distortion of the indicator dilution curves, pulmonary mean transit time was corrected by the use of Milnor's formula. To diminish the volume:flow ratio of the sampling system, the flow rate of sampling was increased to 0.9 ml./sec. The results correlate quite well with those of the double injection and sampling technique. The method is reliable when the volume:flow ratio of the sampling system is taken into consideration and mean transit time is corrected for this ratio.

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