THE PULMONARY BLOOD VOLUME IN MITRAL STENOSIS¹

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The Stewart-Hamilton indicator dilution method for the measurement of intrathoracic blood volume has provided the basis for an extensive study of the "pulmonary" blood volume in patients with mitral stenosis (1-7). There appears to be a lack of uniformity in the results of various studies reported in the literature, however, despite the use of the same indicator, Evans Blue dye and similar methodology. In these various studies, the only significant technical differences lay in the site of indicator injection—the most common sites being either a peripheral vein or the pulmonary artery.

Borden, Ebert, Wilson, and Wells (1), using pulmonary artery injections, found no essential difference in central blood volumes between 10 patients with mitral stenosis and 12 normal subjects. Kopelman and Lee (2) found slight, probably insignificant, increases in intrathoracic blood volume in patients with mitral stenosis as compared to normals. Most of these were studied with peripheral vein dye injections, although a small number in whom injection was made into the pulmonary artery also failed to show a significant increase. Ball, Kopelman, and Witham (3) utilized antecubital vein injections and failed to find intrathoracic blood volume greater than in normals. They reasoned that cardiomegaly in the patients with mitral stenosis results in a greater intracardiac blood volume than in the normal group and, therefore, that there must actually be a decrease of blood volume in the lung vessels. Tompkins, Burchell, and Wood (4), using peripheral injections, studied 25 patients with severe

mitral disease, and 16 normals. There was a tendency for the pulmonary blood volume to be higher in the normals, although the difference was not statistically significant. Wade, Werkö, Eliasch, Gidlund, and Lagerlöf (5), using peripheral artery injections, found no difference in average volumes in 34 cases covering all the various functional subgroups of mitral stenosis. The cardio-pulmonary blood volume was seen to remain approximately a constant fraction of total blood volume. Their results confirmed previous studies from this group (6) that there is no significant change in the pulmonary blood volume in mitral stenosis, although a good correlation was shown between the cardio-pulmonary volume and the "pulmonary capillary" pressure. Finally, Doyle, Wilson, Lépine, and Warren (7) demonstrated an increased pulmonary blood volume in six patients with mitral stenosis utilizing Evans Blue dye injected through a pulmonary artery catheter.

The findings in the majority of these studies of a cardio-pulmonary blood volume not significantly different from the normal are somewhat surprising in view of the multitude of clinical, hemodynamic and pathological evidences that would tend to suggest that this volume might be increased. The present study was undertaken in an attempt to re-evaluate this problem by correlating the "pulmonary" blood volume with other variables measured by right heart catheterization; pulmonary blood volume was determined by the Bradley arteriovenous equilibration method (8, 9) as well as by the traditional Stewart-Hamilton method (10, 11, 12) and the simultaneous use of both a plasma tag, Evans Blue dye and chromium⁵¹ tagged red cells.

METHODS

Nineteen right heart catheterizations and pulmonary blood volume determinations were performed in 16 patients with mitral stenosis; 3 patients were studied be-

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fore and after mitral valve surgery. Six cc. of homologous packed red cells were re-suspended in 10 cc. saline and incubated with approximately 125 microcuries of sodium chromate⁵¹ at 37° for one hour. After centrifugation, the packed cells were washed twice with normal saline. Four cc. of the radioactive packed red cells were then pipetted into a glass beaker. An equal amount of .5 per cent Evans Blue dye solution which previously had been diluted with 1 to 2 cc. of hypertonic saline for isotonicity was added to make an 8-cc. mixture of cells and Evans Blue dye. From this mixture, 6 cc. were placed in a Gibson syringe which was calibrated by weight to deliver a known volume through the catheter. Cardiac catheterization was performed in the usual manner with a special double lumen catheter with the openings separated by 25 centimeters. After obtaining the "pulmonary capillary" pressure, the catheter was withdrawn under fluoroscopic control until the distal tip rested in the main pulmonary artery, and the proximal end opened into variable sites in the right atrium depending on the size of the heart. An 18-gauge Cournand needle was placed in each brachial artery. One minute following collection of arterial and mixed venous blood and a 3-minute sample of expired air for direct Fick cardiac output determination, the 6-cc. mixture of Evans Blue dye and chromium⁵¹ tagged red cells was injected through the proximal lumen of the double lumen catheter into the right atrium. Injections took on the average 2 seconds. In all cases, the time of injection was plotted as the mid point of the injection interval (13). Coincident with injection, sampling was begun simultaneously from the pulmonary artery and one brachial artery by means of a constant suction pump in a manner previously described (9). Multiple samples were collected continuously at 30 to 40-second intervals for 5 or 6 periods. All samples were taken in calibrated tubes containing approximately 0.1 cc. purified dried heparin. Simultaneously, samples were collected at 2-second intervals from the Cournand needle in the opposite brachial artery in a multiple fraction collector for construction of arterial dye and red cell indicator dilution curves. Flows approximating 1.0 cc. per second were obtained through a polyethylene segment 1.0 cc. in volume. Blood samples for total plasma and red cell volume determination were collected at 10 and 20 minutes; the plasma dye concentration was extrapolated to zero time. Hematocrits were spun with a centrifuge radius arm of 19 cm. for 30 minutes at 3,000 rpm in Wintrobe tubes and corrected for trapped plasma as advocated by Gregersen (14).

One-cc. aliquots of whole blood were pipetted into culture tubes and the radioactivity determined in a well-type scintillation counter for sufficient time to insure less than a one per cent standard error. A one-cc. aliquot of the mixed red cell Evans Blue dye injectate was diluted 1 to 200 as a standard, and counted in a similar manner. The whole blood samples were then centrifuged and the removed undiluted plasma read against control plasma in a Beckman DU Spectrophotometer at 620 mμ. Microcuvettes were used for determining dye concentration in the samples from which the indicator dilution curve was

constructed; however, the volume of the samples obtained from the constant suction pump were sufficient to permit use of standard macrocuvettes. A dye standard was made from each patient's plasma using the hypertonic saline diluted dye injectate. The activity of the remaining packed red cells in random samples was redetermined after removal of plasma to insure that no appreciable counts had been present in the plasma.

Blood oxygen analyses were performed by the method of Van Slyke and Neill (15). Pressures were measured with Sanborn electromanometers or Statham P-23D pressure transducers and recorded on a Sanborn Poly-Viso recording oscillograph. Mitral valve area and pulmonary vascular resistance were calculated in the routine manner (16). Cardiac output was determined by both the direct Fick and by the indicator dilution method of Stewart as modified by Hamilton (10, 12). "Pulmonary" blood volume was determined as the sum of pulmonary plasma and red cell volumes by the Stewart-Hamilton method, as follows:

"Pulmonary" plasma volume

$$= C.O.^{EBD} \times \frac{MTT^{EBD}}{60} \times (1 - Hct)$$

and

"Pulmonary" red cell volume

$$= C.O.^{Cr^{51}} \times \frac{MTT^{Cr^{51}}}{60} \times Hct$$

where

C.O.^{EBD} and C.O.^{Cr⁵¹} = Cardiac output in cc. per minute determined with Evans Blue dye and Cr⁵¹ tagged red cells, respectively.

MTT^{EBD} and MTT^{Cr⁵¹} = Mean transit time of dye or labelled red cells in seconds.

Hct = Hematocrit corrected for trapped plasma and expressed as a decimal.

Similarly, "pulmonary" blood volumes were calculated by the equilibration method of Bradley and his associates (8, 9) according to the formula:

"Pulmonary" plasma volume

$$= \frac{C.O. \times T \times (PAmd - BAmc) \times (1 - Hct)}{Ceq}$$

"Pulmonary" red cell volume

$$= \frac{C.O. \times T \times (PAmc - BAmc) \times Hct}{Ceq}$$

where

C.O. = cardiac output as the average of flows determined by dye and tagged cells in cc. per second.

T = time in seconds from injection until equilibration of indicator concentration, either red cell or plasma, in the pulmonary and brachial arteries.

PAmd and PAmc = mean pulmonary arterial indicator concentration during time T in mgm. per cc. (dye) or counts per minute per cc. (cells), respectively.

BAmc and BAmc = mean brachial arterial indicator concentration during time T in mgm. per cc. (dye) or counts per minute per cc. (cells), respectively.

Ceq = indicator concentration at equilibration in mgm. per cc. (dye) or counts per minute per cc. (cells), respectively.

RESULTS

Cardiac output determined with either Cr^{51} tagged red cells or Evans Blue dye agreed well with those determined by the direct Fick method (Figure 1). The average of the ratios of cardiac outputs obtained in individual patients by the Evans Blue dye dilution method to the Fick method was .96 (s.d. = .14). The ratios of cardiac outputs obtained by the chromium⁵¹ tagged red cell dilution method to the outputs obtained with the direct Fick method had a mean of .96 (s.d. = .13). The average of the ratios of cardiac outputs in individual patients using Evans Blue dye to those determined with chromium⁵¹ red cells was 1.00 (s.d. = .05). No evidence of a systematic error could be discerned either between the indicator dilution method and the Fick method or between the two indicator dilution techniques themselves.

The mean transit time of plasma indicator was always longer than that of tagged red cells. Dye to cell mean transit time ratios obtained in individual patients averaged 1.05 (s.d. = .03).

The pulmonary hematocrit is the ratio of the pulmonary red cell volume measured by Cr^{51} to

FIG. 1. THE CARDIAC OUTPUT IN MITRAL STENOSIS

Simultaneous cardiac outputs obtained by the use of chromium⁵¹ tagged red cells, Evans Blue dye and the direct Fick methods.

the sum of the red cell pulmonary and the Evans Blue dye plasma pulmonary volumes. When calculated by the Stewart-Hamilton method, the pulmonary hematocrit averaged 97 per cent of large vessel hematocrits (s.d. = 2 per cent) and 91 per cent (s.d. = 7 per cent) when calculated by the Bradley method. Total body hematocrit, the ratio of total red cell volume to total red cell and plasma

TABLE I

Pt.	Pulmonary red cell volume cc./M. ²		Pulmonary plasma volume cc./M. ²		Pulmonary blood volume cc./M. ²		Pulmonary hct. %		Large vessel hct. %	Body hct. %	Total red cell volume cc./M. ²	Total plasma volume cc./M. ²	Total blood volume cc./M. ²
	Indicator dilution	Equilibration	Indicator dilution	Equilibration	Indicator dilution	Equilibration	Indicator dilution	Equilibration					
K. K.	522	202	889	487	1,411	689	37.0	29.3	38.6	34.1	1,371	2,645	4,016
B. P.	341	243	323	351	664	594	51.4	40.9	52.4	50.7	1,047	1,018	2,065
F. D.	307	338	353	389	660	727	46.5	46.5	49.9	48.2	822	882	1,704
L. T.	661	566	657	640	1,318	1,206	50.1	46.9	49.7	45.7	1,496	1,792	3,288
M. deJ.	244	219	355	305	599	524	40.7	41.7	42.7		1,003		3,640*
A. W.	221	146	374	277	595	423	37.1	34.5	39.6	36.9	716	1,225	1,941
L. D.	248	230	368	369	616	599	40.2	38.4	41.3	41.4	855	1,207	2,062
B. G.	338	321	420	399	758	720	44.6	44.6	45.1	43.3	1,027	1,345	2,372
J. D.	342	288	445	518	787	806	43.5	35.8	44.4	42.3	1,108	1,508	2,616
K. U.	316	323	497	521	813	844	38.8	38.3	41.9	38.8	915	1,443	2,358
R. B.	414	345	572	551	986	896	42.0	38.5	43.2	41.9	1,225	1,702	2,927
Post-op	241	270	462	460	703	730	34.3	27.2	33.3	31.3	948	2,084	3,032
J. F.	275	190	424	312	699	502	38.4	37.9	40.2	37.6	738	1,225	1,963
M. C.	295		397		692		42.7		43.4			2,462	3,902*
Post-op	248		393		641		38.7		40.3	33.7	807	1,592	2,399
L. P.	322	256	354	279	676	535	47.6	47.8	48.5	43.0	982	1,302	2,284
Post-op	228	158	397	299	625	457	36.4	34.5	37.0	33.5	745	1,477	2,222
L. B.	463	266	572	339	1,035	607	44.7	44.0	46.1	41.1	1,153	1,653	2,806
A. N.	462	274	551	317	1,013	591	45.6	46.4	45.6	40.8	1,132	1,642	2,774

* Based on large vessel hematocrit.

TABLE II

Pt.	B.S.A. M. ²	Cardiac output L./min.			Mean transit time seconds		Pressures mm. Hg				Pulmonary vascular resistance dynes sec. cm. ⁻⁵	Mitral valve area cm. ²	
		Fick	Dye	Cr ⁵¹	Dye	Cells	BA	"PC"	PA	RA		Gorlin formula	Surgeon's estimate
K. K.	1.59	3.35	3.33	3.16	41.5	40.8	124/74(91)	32	83/38(52)	17	470	0.6	
B. P.	1.98	4.08	4.43	4.59	18.2	16.9	137/77(95)	18	35/19(25)	9	98		
F. D.	1.88	4.14	5.32	4.93	14.9	14.1	128/92(104)	22	37/22(26)	6	77	1.1	1.2
L. T.*	1.79	3.44	2.69	3.04	52.1	47.0	117/79(94)	24	57/38(46)	10	512	0.6	2.3
M. deJ.	1.55	5.14	3.81	3.81	15.2	13.9	98/58(74)	19	31/15(23)	0	150	1.2	0.7
A. W.	1.38	2.08	2.45	2.27	20.9	20.3	100/75(84)	23	73/41(53)	5	800	0.6	0.9
L. D.	1.45	4.19	4.44	4.51	12.3	11.6	97/53(76)	15	28/13(19)	0	138	1.1	1.0
B. G.	1.77	4.47	4.85	4.98	16.8	16.0	116/75(95)	13	29/13(19)	2	142	1.1	1.0
J. D.	1.97	3.23	3.23	3.23	29.3	28.2	112/72(85)	30	68/41(53)	7	575	0.6	0.8
K. U.	1.41		3.63	3.41	20.0	18.7	98/61(80)	11	26/9(16)	-1	90	0.9	0.9
R. B.	1.87	6.38	5.67	5.75	19.9	18.7	94/60(79)	17	42/21(29)	4	118	1.0	1.0
Post-op	1.84		5.61	6.07	13.6	13.2	108/65(78)	12	23/12(17)	8	85	1.6	
J. F.	1.52	3.83	3.20	3.22	20.2	19.4	120/67(83)	29	72/32(43)	4	292	0.8	0.4
M. C.	1.50	2.84	2.82	2.88	22.4	21.3	113/69(83)	27	104/41(65)	9	914	0.6	0.8
Post-op	1.49	3.90	2.87	2.74	20.5	20.1	116/68(87)	21	100/40(63)	11	841	0.9	
L. P.	1.63	2.83	2.59	2.67	26.0	24.3	98/73(87)	22	42/23(30)	6	312	0.5	
Post-op	1.63	3.59	3.09	3.14	19.9	19.1	103/69(81)	13	40/12(21)	8	214	1.4	
L. B.	1.58	2.98	3.01	2.99	33.4	31.8	147/76(105)	20	50/19(28)	12	242	0.5	
A. N.	1.33	2.51	2.19	2.15	37.6	36.9	162/84(116)	22	40/23(30)	15	207	0.6	

* Predominant mitral insufficiency at operation.

volume, averaged 92 per cent (s.d. = 4 per cent) of large vessel hematocrits.

Table I lists the values calculated for the pulmonary blood volume by the two methods. The circulating pulmonary blood volume determined by the Stewart-Hamilton method averaged 805 cc. per M.² (range of 595 to 1,411) representing the sum of mean pulmonary plasma and red cell volumes of 463 cc. per M.² and 341 cc. per M.², respectively. The pulmonary blood volume averaged 31.9 per cent of total blood volume (range 23.2 to 40.1 per cent).

The circulating pulmonary blood volume determined as the sum of the plasma and red cell volumes by the arteriovenous equilibration method averaged 674 cc. per M.² (range of 423 to 1,206) representing the sum of an average pulmonary plasma volume of 401 cc. per M.² and red cell volume of 273 cc. per M.². The pulmonary blood volume by this method averaged 27.2 per cent of total blood volume (range 17.1 per cent to 42.7 per cent).

Table II lists the pertinent hemodynamic data obtained at catheterization in these patients.

DISCUSSION

Cardiac output

Cardiac output can be accurately calculated by the indicator dilution technique with use of only

a single indicator, either red cell or plasma, since the presence of a significantly lower pulmonary hematocrit compared to large vessel hematocrit is of no consequence in the determination of cardiac output by these methods (13). Figure 1 illustrates the correlation between cardiac outputs obtained by the chromium⁵¹, dye and Fick methods. These results lend further confirmation to the generally accepted view that arterial indicator dilution curve values of cardiac output are closely comparable to those obtained by the direct Fick method. The observations of Eliasch (17) that grades III and IV patients with mitral stenosis had average dye outputs significantly higher than Fick outputs were not confirmed in this study.

The mean of the ratios of individual Evans Blue dye to chromium⁵¹ red cell outputs was 1.00 with only a 5 per cent standard deviation. This indicates that dye in significant amounts does not leak out of the pulmonary circulation during its initial circulation despite the high pulmonary capillary pressures bordering on pulmonary edema levels in many of these cases. If dye had left the circulation, outputs calculated by the dye method would have been erroneously higher than those calculated with tagged red cells, which presumably do remain within the vessels.

Dow (18) quotes Ring to the effect that dye outputs exceed tagged cell outputs when the two

indicators are simultaneously injected initially, and that this discrepancy disappears on the subsequent injections in the same dog. The implication that Evans Blue dye is taken out of the pulmonary circulation unless the system is primed or saturated by previous injections was not born out by the results in the present study.

Pulmonary blood volume

It has been proposed by Braunwald, Cournand, and Fishman (19), on the basis of model experiments, that the high flow to volume ratio of the pulmonary bed precludes measurement of the pulmonary blood volume by the Bradley technique. The Bradley formulation is an arithmetic relationship from which, assigning the approximate flow to volume ratio which exists in the pulmonary bed in man, one can readily predict that the mean arteriovenous difference of indicator concentration will be close to 15 per cent of the final equilibration concentration. This implies that an analytical error of one per cent may result in as much as a 6 to 7 per cent error in the final volume. In their model experiments, Braunwald, Cournand, and Fishman (19) used a direct writing densitometer for recording dye concentration. It would seem logical to ascribe an analytical error with this methodology of roughly 5 per cent. This in turn could result in considerably more error in the final pulmonary volume determined by the Bradley formula. The method might well prove valueless under this experimental situation. However, it is to be emphasized that in the experiments reported in this communication, dye analyses for the Bradley volumes were carried out in macrocuvettes on a Beckman DU Spectrophotometer using undiluted plasma and with duplicate checks to well within one per cent. At the same time, the red cell radioactivity was measured sufficiently long to insure less than a one per cent standard error. Under these analytical conditions, it was our feeling that one might well be able to measure the pulmonary blood volume in man with reasonable accuracy despite the relatively high flow to volume ratio.

This hope appears to have been justified by the results shown in Figure 2, which illustrates the relationship between pulmonary blood volumes obtained by the traditional Stewart-Hamilton

FIG. 2. THE PULMONARY BLOOD VOLUME IN MITRAL STENOSIS

"Pulmonary" blood volumes determined by the Stewart-Hamilton indicator dilution method are compared to volumes simultaneously obtained by the Bradley arteriovenous equilibration method.

technique and volumes obtained simultaneously by the Bradley method. A significant correlation between these volumes, $R = +.82$ ($p < .01$), was obtained. The indicator dilution values were generally higher, but this was expected since they included the additional volume of the right ventricle and a portion, if not all, of the right atrium. The overall agreement is satisfactory and would seem to substantiate the fact that the arteriovenous equilibration method is a suitable one for the measurement of the pulmonary blood volume in man. In those situations where cardiac output is markedly depressed, valvular insufficiency is present, or pulmonary blood volume markedly increased, the exponential downstroke of the indicator dilution curve may be difficult to separate from the effects of indicator recirculation. Under these circumstances, extrapolation of the curve may produce considerable error in the determination of pulmonary volume by the indicator dilution method. The Bradley method is at its height of accuracy under these same conditions of low flow or increased volume. Therefore, in these circumstances the Bradley method may actually become the preferable one. It might be noted that the validity of the indicator dilution curve for determination of volume can be established by comparing cardiac output calculated from the same curve:

with the direct Fick method. However, it should also be noted that the reliability of volume is worse than the reliability of flow resulting from errors in downstroke extrapolation, particularly if recirculation is early. A 10 per cent flow error may lead to as much as a 30 per cent error in volume determination.

Factors influencing the pulmonary blood volume

The arteriovenous equilibration method measures the vascular compartment from the pulmonary artery sampling site to that in the brachial artery, and includes the volume in other arteries temporally equidistant from the base of the aorta to the brachial artery needle. The volume yielded as the product of the mean transit time and cardiac output in these experiments represents the volume of a portion of the right atrium, where injection was made, and the right ventricle, as well as the rest of the volume measured by the arteriovenous equilibration method. Therefore, the difference in mean values obtained by the two methods may in part be explained. Right atrial injection was made necessary by the requirement that blood sampled from the pulmonary artery for the Bradley method be thoroughly mixed with indicator, and thus truly representative of the indicator concentration entering the pulmonary bed. The actual volumes obtained by both the Bradley and the Stewart-Hamilton methods in these patients with

FIG. 3. THE EFFECT OF "PC" PRESSURE ON PULMONARY BLOOD VOLUME

No correlation is seen between "pulmonary capillary" pressure and the "pulmonary" blood volume.

FIG. 4. THE EFFECT OF CARDIOMEGALY ON PULMONARY BLOOD VOLUME IN MITRAL STENOSIS

The absence of correlation between pulmonary blood volume and heart size judged roentgenologically is demonstrated.

mitral stenosis varied over a wide range of values (Table I) with a mean still within the upper range generally seen in normals (6). Since the wide range of values incorporated one or two which were low, many normals, and several which were increased, the hemodynamic data were analyzed to see what factors, in addition to mitral stenosis, might contribute to the volumes in any individual case. Specifically, an attempt was made to correlate the volumes obtained by the two methods with other variables measured by cardiac catheterization.

Figure 3 demonstrates the poor relationship between "pulmonary capillary" pressure and pulmonary blood volume. This confirms the findings of Doyle, Wilson, Lépine, and Warren (7) and of Johnson (20), but is in contrast to the findings of Wade, Werkö, Eliasch, Gidlund, and Lagerlöf (5) who were able to demonstrate such a relationship. On the surface, it would appear difficult to explain the absence of correlation between these two variables, since presumably the increased "pulmonary capillary" pressure in mitral stenosis must be dependent upon either an increase in volume of blood in this bed or an increase in pulmonary venous and left atrial tone. However, when one takes into consideration that the methodology permits detection of volume changes only if greater than 100 cc. or so (7), it becomes apparent that significant changes in volume which could cause increases in pressure might remain undetected.

There was perhaps some tendency for patients with the smallest valve areas calculated by the Gorlin formula (21) to have the larger volumes, but there was no significant correlation, as examination of Tables I and II reveals.

The Stewart-Hamilton method as performed in these experiments included the volume of all the heart chambers, and the Bradley method included the volume of the left heart. It was therefore considered that cardiomegaly in certain individual cases might be predominantly responsible for the volumes which were obtained. Figure 4, however, demonstrates that there was no correlation whatsoever between heart size as judged roentgenologically and the pulmonary blood volumes calculated by the Bradley method. A similar absence of correlation was seen with the Stewart-Hamilton volumes.

Figure 5 illustrates the relationship between the pulmonary blood volume and pulmonary vascular resistance. Despite the three values in the range between 450 and 600 dscm⁻⁵, which obviously grossly deviate, the data were found to fit quite well an exponential curve of the general form $\log y = -.3 \log x + 3.75$, where y = pulmonary blood volume and x = pulmonary vascular resistance. The correlation coefficient, derived by the computation of least squares, between

FIG. 5. THE EFFECT OF PULMONARY VASCULAR RESISTANCE ON PULMONARY BLOOD VOLUME

The relationship between pulmonary resistance and "pulmonary" blood volume fits quite well an exponential curve when plotted logarithmically.

FIG. 6. THE EFFECT OF CARDIAC OUTPUT ON PULMONARY BLOOD VOLUME

A significant correlation is seen between the level of cardiac output expressed as the average of the Evans Blue dye and chromium⁵¹ values and the "pulmonary" blood volume.

the theoretical variables and the actual measured values was 0.9982. This relationship is quite similar to that noted previously between cardiac output and pulmonary resistance in patients with mitral stenosis (22), as well as in other situations where pulmonary resistance is raised (23, 24). Consequently, it immediately suggested to us that the pulmonary blood volume would be correlated with the level of cardiac output in these patients.

Indeed, a correlation was demonstrated in this study between cardiac output and pulmonary blood volume (Figure 6). The probability of the correlation coefficient of $+ .75$ occurring by chance is less than one in a thousand. A similar correlation was seen between stroke output and pulmonary blood volume. Thus, when cardiac output tended to be maintained at normal levels despite the mitral lesion, pulmonary blood volumes in these cases were in the higher range of normal or increased, whereas in those cases where cardiac output was reduced the pulmonary blood volume tended to be low normal or occasionally reduced. This correlation is in contrast to the findings of Ball, Kopelman and Witham (3) but is in close agreement with similar observations made in a large number of normal subjects by Johnson (20), and also in the group studied by Doyle, Wilson, Lépine, and Warren (7).

Doyle and his associates concluded that such a

correlation is inherent in the calculation of pulmonary blood volume since cardiac output appears in the formula. However, this conclusion does not appear to be justified. As long as the expressions involved in the calculation of pulmonary blood volume are completely independent variables, this correlation is not merely a mathematical certainty but is of biological significance. Mean transit time is an independently measured function which may increase, decrease, or remain unchanged as cardiac output varies. For example, an increase in cardiac output may be matched by a corresponding decrease in mean transit time with the result that pulmonary blood volume would be unchanged. In other words, the calculated volume bears no obligate relationship to any variable used in its determination either with the Stewart-Hamilton or the Bradley formula, and the demonstration of a correlation between pulmonary blood volume and cardiac output would, therefore, appear to have a fundamental significance. Johnson (20) interprets these findings in his normals to indicate that pulmonary blood volume tends to act as a reservoir or blood depot supplying the left ventricle with an increased volume when the needs of the periphery require an increase in cardiac output. We cannot be sure that such a teleological explanation can be accepted, although it is plausible that the pressure volume curve of the capillary-venous bed of the lungs and left heart is such as to require considerable increase in volume in order to cause the small rise in filling pressure of the left ventricle which presumably occurs when the stroke volume of the heart increases. In any case, it would appear clear that the important variable, on which pulmonary blood volume depends, is the cardiac output. Whether pulmonary blood volume will be increased or not in a given patient with mitral stenosis appears predominantly dependent on whether cardiac output is maintained or whether it has been reduced by the processes of mitral valve obstruction and increased pulmonary vascular resistance.

The implication of this relationship between pulmonary blood flow and volume is that the volumes in mitral stenosis, though generally within the normal range, are elevated in respect to the low outputs. To better validate this premise, it would be necessary to know:

1) The pulmonary blood volume in "normals" through the entire range of cardiac outputs, particularly low outputs.

2) How this volume varies with changes in output.

3) What would be the volumes in patients with mitral stenosis if their outputs were higher (normal range).

We have not made a systematic study of this problem as yet, but three separate studies that have been carried out provide some evidence suggesting that the pulmonary blood volume in mitral stenosis is indeed elevated when considered in relation to the cardiac output. This evidence is as follows:

1) Rest and exercise studies of the cardiac output and pulmonary blood volume were determined by the Stewart-Hamilton method and a plasma indicator injected into the pulmonary artery in 7 additional cases of mitral stenosis. The results (Table III) indicate that the volume increased only in those cases (4 patients) in which there was a significant increase in cardiac output. In the 3 patients in whom the output failed to increase appreciably, the volume remained unchanged. The "pulmonary capillary" pressure rose significantly during exercise in all patients regardless of whether or not there was a volume change.

2) The production of acute experimental pulmonary edema in 7 dogs by infusion of a systemic vasoconstrictor substance (methoxamine) was attended uniformly by left atrial and pulmonary

TABLE III
*Effect of exercise on "pulmonary" blood volume in mitral stenosis**

Pt.	Rest		Exercise	
	Cardiac output L./min.	"Pulmonary" blood volume cc.	Cardiac output L./min.	"Pulmonary" blood volume cc.
Alt.	5.9	1,222	7.0	1,632
Kea.	5.1	733	6.0	1,012
St. P.	4.3	884	8.1	1,064
Bar.	5.7	998	7.4	1,319
O'Co.	5.3	912	5.8	845
Les.	4.2	561	3.8	602
Koz.	3.7	1,387	4.1	1,451

* Cardiac output and "pulmonary" blood volume were studied in seven additional patients with mitral stenosis before and during exercise using Evans Blue dye injected into the pulmonary artery.

venous and capillary hypertension and a markedly reduced cardiac output (25). The alteration of pulmonary blood volume, however, was not uniform, showing no change from control levels in 3, a fall in 2, and an increase in 2. Thus, pulmonary vascular hypertension was not accompanied by a predictable change in volume, a finding qualitatively similar to that of the present study. Similarly, the volumes appeared out of proportion to the very low level of cardiac outputs which averaged but 28 per cent of initial control values.

3) Acute occlusion of one main branch of the pulmonary artery in dogs (26) has no significant effect on the cardiac output, and causes, at most, only slight increases in pulmonary artery pressures; thus the flow through the unoccluded lung essentially doubles. Since the calculated pulmonary blood volume remains constant, it is evident that the vascular volume of the unoccluded lung nearly doubles; therefore, the flow to volume ratio in that lung remains constant. These observations provide evidence for the existence of a relationship between flow and volume. Additional studies of this relationship in animals and humans are clearly indicated and are being considered.

Pulmonary hematocrit

It was observed in all patients that the mean transit time of red cells through the lung is faster than that of plasma. Since the total quantity per unit time of red cells and plasma going into the lung in the steady state is essentially the same as that leaving the lung, it follows that overall pulmonary hematocrit must be lower than that of blood circulating in the large vessels. Therefore, one may say unequivocally that pulmonary hematocrits by the Stewart-Hamilton method were distinctly lower than large vessel hematocrits in these patients. However, when the calculated hematocrits are subjected to statistical analysis, the mean ratio of pulmonary to large vessel hematocrit is .97 (s.d. = .02), which indicates a probability of between 5 and 10 per cent of occurrence by chance. However, calculation of pulmonary to large vessel hematocrit ratio in this manner incorporates any errors in measuring cardiac output and also reflects any errors present in reading the hematocrit of large vessel blood or in correcting it for trapped plasma. These errors are not introduced in the calculation of mean transit times, which become a

more accurate reflection of the existing pulmonary hematocrit.

The pulmonary to large vessel hematocrit ratio as computed by the Bradley method had a mean of .91 which was statistically significant ($p < .01$). It is somewhat difficult to explain the significantly lower pulmonary hematocrit by the Bradley method as compared to the Stewart-Hamilton method. It is true that an additional volume of large vessel blood contained in the right ventricle and right auricle which seems to be included in the volume yielded by the indicator dilution method, does not appear in the determination of the pulmonary hematocrit by the arteriovenous equilibration method. However, this in itself seems incapable of altering the mean to this extent, and other limitations and assumptions in both methods, which have been detailed elsewhere (8, 9, 13), may also play a role. In any case, the ability to demonstrate by both these methods that pulmonary hematocrit was less than large vessel hematocrit is of considerable significance, for both methods measure a huge amount of large vessel blood as contrasted to the actual amount of blood in small vessels. Estimates of pulmonary capillary volume (27) indicate that the pulmonary capillary bed probably makes up less than 10 per cent of the total volume measured by these techniques. Therefore, a demonstration of lowered overall hematocrit implies that the hematocrit of the pulmonary capillary bed itself must be very low, undoubtedly something less than 75 per cent of large vessel blood.

These findings contrast with those reported by Lilienfield and his colleagues (28) for normal man, where a significant lowering of pulmonary hematocrit by the Stewart-Hamilton method could not be demonstrated. Our observations are in accord, however, with our findings in normal dogs (29), as well as those of Dow, Hahn, and Hamilton (30) and those of Lawson, Cantrell, Shaw, Blackburn, and Adams (31). It would appear from these results that the pulmonary capillary bed does contribute to the overall lowering of total body hematocrit in comparison to large vessel hematocrit in patients with mitral stenosis. In this series, the ratio of total body to large vessel hematocrit had a mean of .92 with a standard deviation of .04, which is in good agreement with the ratio found by others (32) in man over a wide range of large vessel hematocrits.

SUMMARY

1. The Stewart-Hamilton and Bradley methods for "pulmonary" blood volume determination were simultaneously studied 19 times during right heart catheterization in 16 patients with mitral stenosis utilizing chromium⁵¹ tagged red cells and Evans Blue dye.

2. No correlation was demonstrated between "pulmonary" blood volume and mitral valve area, heart size, or "pulmonary capillary" pressure. A straight-line relationship when plotted logarithmically between "pulmonary" blood volume and pulmonary vascular resistance was demonstrated, which suggested that another variable related to resistance affected the level of pulmonary blood volume. When the relationship between cardiac output and "pulmonary" blood volume was examined a significant linear correlation was found, suggesting that pulmonary blood flow would appear to be the predominant variable governing "pulmonary" blood volume. Evidence is presented to suggest that "pulmonary" blood volume is elevated out of proportion to the existing blood flow in mitral stenosis, and that it is the presence of a reduced cardiac output in many patients with mitral stenosis which results in a mean "pulmonary" blood volume within the normal range.

3. No evidence of a systematic error in cardiac output was discerned between the two indicator dilution methods themselves or with the direct Fick method. This suggests that Evans Blue dye in significant amounts does not leak out of the pulmonary bed during its initial circulation despite high "pulmonary capillary" pressures.

4. A good correlation was seen between individual volumes calculated by the Bradley arteriovenous equilibration method and those calculated by the traditional Stewart-Hamilton method. Results indicate that with careful analytic technique the Bradley method can be satisfactorily applied to measurement of "pulmonary" blood volume.

5. Average mean transit time was shorter for tagged cells than for dye in all patients. As a result "pulmonary" hematocrit was lower than large vessel hematocrit. Since the methods used measure blood volumes predominantly situated in large vessels rather than in capillaries, the demonstration of a lower "pulmonary" hematocrit indicates

that the hematocrit of the pulmonary capillary bed itself must be considerably less.

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