Determinants of Pulmonary Blood Volume

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ABSTRACT Pulmonary blood volume was determined by the radiocardiographic technique in 49 patients coming to cardiac catheterization. Since this method has not been directly compared with the more commonly used double injection of dye, 25 comparisons were carried out in 13 patients of the series. Agreement was good over a range of 4.5–21.1 heart cycles since there was no statistically significant difference between transit time values measured by the two methods.

The relation of pulmonary blood volume to other hemodynamic factors in these 49 patients, with and without cardiac or pulmonary disease, was evaluated by means of multiple regression analysis. The analysis carried out for mean transit time indicates that this parameter varies predominately with flow. Pulmonary blood volume, in this series of resting recumbent individuals, varies to a significant degree only with total blood volume and with pulmonary venous pressure. No parameters of vascular distensibility, such as pulmonary vascular resistance, were found to affect the volume of blood in the lungs.

The fact that variations in pulmonary blood volume among the subjects could be described by a multiple regression equation linear with respect to total blood volume and pulmonary venous pressure indicates that these variations are the result of passive distention of components of the vascular bed.

INTRODUCTION

Measurement of pulmonary blood volume has contributed to understanding of pulmonary hemodynamics. Numerous reports of data obtained by the injection of indicator into the pulmonary artery and left atrium are available in both patients with heart disease (1–10) and in normal subjects (3, 5, 11, 12). Nevertheless, there is conflicting data on the relationship of lung blood volume to other hemodynamic factors, and hence the control of the size of this compartment is not clear, even in the resting state.

An alternative method of measuring pulmonary blood volume from precordial radioactive isotope dilution curves (radiocardiograms) (13) has been reported by Giuntini, Lewis, Sales Luis, and Harvey (14). The method is in use in this laboratory; and since only right heart catheterization is required, pulmonary blood volume measurements have been made in a wider variety of clinical states than usually described. The present report presents an analysis of this data which indicates that variations in pulmonary blood volume in all subjects studied, regardless of pathology, can be related to variations in only two factors, total blood volume and pulmonary venous pressure.

The radiocardiographic measurement of pulmonary blood volume is considered to have ill-defined anatomic limits by some authors (15) because the method is based on certain assumptions regarding the central circulation which cannot be evaluated in each subject. For this reason a comparison of the radiocardiographic and dye dilution methods in the same subjects is also included in this report to validate the statistical analysis of the data.

METHODS

Data from 57 consecutive cardiac catheterizations form the basis of the present report. Studies were not completed in eight patients; pertinent clinical data and diagnoses in the remaining 49 patients appear in Table I. This group of 49 patients will be referred to as Group A. Data from a subsequent series of 21 patients, entitled Group B, are also included in this report for the purpose of assessing the accuracy of estimating equations for pulmonary blood volume derived from studies in Group A patients.

All patients were studied after an overnight fast. The volunteers, patients with cirrhosis, and patients with pulmonary disease were not sedated before the procedure. Other patients received 100 mg of secobarbital 30 min before the procedure; in many cases 50 mg of meperidine was also given intramuscularly.

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TABLE I
Clinical Data

Patient	Age	Clinical diagnosis	Rhythm	Previous CHF	Digitalis (at cath.)
	yr				
Group A					
Normal					
1001*	41	Essential hypertension	NSR	0	0
1265	44	Lung abscess, essential hypertension	NSR	0	0
1279	44	Hemochromatosis	NSR	0	0
1287	44	Pulmonary Tbc, MA, active	NSR	0	0
1288	40	Pulmonary Tbc, min, inactive	NSR	0	0
1295	39	Bronchial asthma	NSR	0	0
1325	38	Tbc pleural effusion, right	NSR	0	0
Laennec's cirrhosis					
854	40		NSR	0	0
1281	49		NSR	0	0
1294	58	Status post porto-caval shunt and colonic exclusion	NSR	0	0
1350	42	Status post porto-caval shunt	NSR	0	0
1363	58	UHD, EH	AF	0	+‡
1373	41		NSR	0	0
1481	31	Status post porto-caval shunt	NSR	0	0
Chronic obstructive pulmonary disease					
500	54	Diabetes mellitus	NSR	0	+‡
783	56	RBBB	Sinus tachycardia	0	0
786(1)	48		NSR	0	0
(2)	49	Cor pulmonale	NSR	+	+
789	63		NSR	0	0
798*	47	Cor pulmonale	NSR	0	0
821	44		NSR	0	0
863*	59		NSR	0	0
897	39	Cor pulmonale	NSR	+	0
1064	42	Bullous emphysema; status post resection of bullae	NSR	0	0
1271	39		NSR	0	0
1310	50	Abnormal A-V conduction	NSR	0	0
Pulmonary hypertension of other etiology					
850	46	Ulcerative colitis; pulmonary emboli; cor pulmonale	NSR	0	0
935	48	Silico-tuberculosis; Tbc pericarditis; cor pulmonale	NSR	+	+
986*	50	Alveolar hypoventilation syndrome, cor pulmonale	Sinus bradycardia	+	0
1038	53	Polymyositis; alveolar hypoventilation syndrome; UHD	NSR	+	+
1376	50	Pulmonary emboli; cor pulmonale, RBBB	NSR	+	+
Valvular heart disease					
229	53	RHD, LVE, AS	NSR	+	+
327*	38	RHD, LAE, RVE, MS, MI; status post mitral commissurotomy	AF	+	+
778	45	UHD, LVE, AS	NSR	0	0
853	39	RHD, EH, MS, MI	AF	+	+
925*	46	RHD, LVE, LAE, MI	NSR	0	0
962*	49	RHD, EH, AS, AI, LBBB	NSR	+	+
963*	47	RHD, MS	NSR	0	0
980	44	RHD, LAE, MS	NSR	+	+
990	39	RHD, LAE, MS	NSR	+	+
1008*	43	RHD, MS	AF	0	+‡
1017*	54	UHD, LVE, AS, AI	NSR	+	0
1019*	42	RHD, EH, MS, MI	NSR	+	+
Other heart disease					
445	47	Constrictive pericarditis; LVE; status post pericardiectomy	AF	0	0
559*	47	UHD, LVE, LAE	AF	+	+
855	38	Alcoholic heart disease, EH	NSR	+	0
864	45	UHD	NSR	+	+
893*	53	ASHD, coronary sclerosis, CS, EH	Sinus tachycardia	+	+
918	38	UHD, EH	NSR	+	+
Group B					
Normal					
1478	30	Peptic ulcer	NSR	0	0
1487	37	Extrapulmonary Tbc	NSR	0	0
1496	54	Tuberculoma	NSR	0	0
1525	55	Bronchogenic carcinoma	NSR	0	0
1550	49	Bronchogenic carcinoma	NSR	0	0
1557	69	Bronchogenic carcinoma	NSR	0	0
Pulmonary disease					
1381	49	COPD, interstitial pulmonary fibrosis	NSR	+	+
1464	40	Scleroderma, pulmonary Tbc, FA, inactive	NSR	0	0
1475	42	COPD	NSR	0	0
Valvular heart disease					
1448	48	RHD, MS	NSR	+	0
1507	41	RHD, EH, MI	NSR	+	+
1598	41	RHD, LAE, MS	NSR	0	0
1620	50	RHD, LAE, MS	NSR	+	+
Other heart disease					
1433	38	Pericarditis	NSR	0	+
1476	60	UHD, COPD	AF	+	+
1511	41	UHD, EH	NSR	+	+
1512	54	UHD, EH, labile hypertension	AF	+	+
1527	42	UHD, EH	AF	0	+‡
1528	62	ASHD, AS	NSR	+	+
1564	58	ASHD, coronary sclerosis, EH, anginal syndrome	NSR	+	+
1585	53	ASHD, EH, intermittent A-V block	AF	+	0

CHF, congestive heart failure; NSR, normal sinus rhythm; AF, atrial fibrillation; UHD, unknown heart disease; EH, enlarged heart; RBBB, right bundle branch block; RHD, rheumatic heart disease; LVE, left ventricular enlargement; LAE, left atrial enlargement; RVE, right ventricular enlargement; MS, mitral stenosis; MI, mitral insufficiency; AS, aortic stenosis; AI, aortic insufficiency; ASHD, arteriosclerotic heart disease; COPD, chronic obstructive pulmonary disease.
* Patients in whom pulmonary mean transit time was measured both by radiocardiography and by double injection of dye.
‡ Digitalis administered for control of cardiac rhythm.

Pulmonary artery catheterization was carried out in the usual manner. In studies where the left atrium was entered, the Ross technique was used (16). The left ventricle was approached in retrograde fashion, via the femoral artery, by the Seldinger technique (17). For the injection of indicator a disposable radio-opaque polyvinyl catheter (0.064 in O.D.) was introduced into the right atrium through an antecubital vein. An indwelling arterial needle was utilized for sampling of blood.

Pressures were recorded by means of Statham P 23 A transducers on a photographic recorder.[1] Zero level for pressure readings was taken at 5 cm below the angle of Louis. A single fluid reservoir was connected to all pressure transducers and all amplifiers were adjusted to equal gain. The transducers were calibrated with a mercury manometer at the end of each catheterization. Systolic and diastolic pressures were read over two respiratory cycles and expressed as an average; mean pressure was obtained by planimetry of an electrically damped tracing during a similar period.

In 22 patients left atrial pressure was measured directly and in 20 others pulmonary "wedge" pressure was measured. In two patients, without mitral stenosis, left ventricular end diastolic pressure was used as a measure of pulmonary "venous" pressure. In the five remaining patients only pulmonary artery pressures were recorded. The diastolic pressures in these five patients ranged from 7 to 10 mm of Hg. Since Kaltman, Herbert, Conroy, and Kossmann have reported that in this range pulmonary artery diastolic pressure varies little from left atrial pressure, these patients were included in the series (18).

The precordial dilution curves were recorded by means of a scintillation counter consisting of a 1.5×1.0 in NaI (Th) crystal and photomultiplier housed in a cylindrical lead collimator.[2] The photomultiplier was connected to a ratemeter from which the output was fed into the photographic recorder. The injectate, radioiodinated human serum albumin (RISA), was diluted to contain 100 μCi of ^{131}I/ml. For each curve approximately 0.5 ml was delivered via the right atrial catheter. Cornwall syringes[3] were utilized for injection of indicator; injectates have shown consistent reproducibility in vivo and in vitro.

Cardiac output was determined from the radiocardiograms by the method of Donato, Rochester, Lewis, Durand, Parker, and Harvey (19). Typically, precordial isotope dilution curves present two activity peaks as tracer passes first through the right heart chambers and then through the left. Valid determinations of cardiac output may be obtained from such double curves if a calibration factor for the composite system of vascular sections is determined as described by Veall, Pearson, Hanley, and Lowe (20) and by Donato, Qiuntini, Lewis, Durand, Rochester, Harvey and Cournand (13).

Pulmonary mean transit time (PMTT) was calculated from the radiocardiograms as the difference between mean transit time of the right heart activity curve and the time of peak activity of the left heart curve. The theoretical background and method of analysis are discussed by Giuntini et al. (14). Pulmonary blood volume (PBV) was obtained as the product of PMTT, measured in terms of heart cycles, and stroke volume (SV).

In 13 patients PMTT as measured from a radiocardiogram was compared with that derived from injection of indocyanine green dye into the pulmonary artery and left atrium. Approximately 2.5 mg of dye was injected manually, first into the pulmonary artery catheter and subsequently through the Ross needle into the left atrium. The curves were recorded and analyzed in the usual manner (21, 22). Blood flow was determined from the pulmonary artery injection curves. Mean transit time through the pulmonary circulation was obtained as follows:

$$PMTT = MTT_{PA-D} - MTT_{LA-D} \quad (1)$$

where MTT_{PA-D} is the mean circulation time from the pulmonary artery to densitometer and MTT_{LA-D} is the mean circulation time from the left atrium to the densitometer.

In all patients total blood volume (TBV) was calculated from the dilution of RISA as determined from blood samples drawn before and after each injection. When several radiocardiograms were recorded, the increases in plasma counting rate after each injection were averaged (ΔCR) and plasma volume was obtained by the following:

$$\text{Plasma volume} = \frac{\text{No. of counts injected}}{\Delta CR} \quad (2)$$

Total blood volume (TBV) was calculated from plasma volume and hematocrit (Hct) by the following:

$$TBV = \frac{\text{Plasma volume}}{1 - Hct} \quad (3)$$

Hematocrits were corrected for trapped plasma according to the graph of Chaplin and Mollison (23). Circulating blood hematocrit was converted to total body hematocrit using a factor of 0.896 (24).

In 29 patients TBV was also determined with T-1824 dye. 2–4 ml of undiluted dye were injected from a Cornwall syringe into the pulmonary artery catheter which was then flushed with 10 ml of saline. Samples of arterial blood obtained at known intervals of time after injection were analyzed for plasma concentration of dye in a Beckman DU spectrophotometer at 630 mμ. These concentrations were plotted against time on semilogarithmic paper and the curve extrapolated to obtain the concentration at zero time, C_0. Plasma volume was calculated as follows:

$$\text{Plasma volume} = \frac{\text{milligrams of dye injected}}{C_0} \quad (4)$$

Total blood volume was derived from plasma volume and hematocrit as indicated above.

The principal texts used as an aid in the subsequent statistical analysis were those of Steel and Torrie (25) and of Ezekiel and Fox (26).

RESULTS

Validation of method. The overall success rate of the radiocardiographic method was 86%. In four patients poor definition of the right and left heart activity curves resulted from severe reduction in blood flow (arteriovenous oxygen difference range 9.0–14.9 volume per cent). In four other patients in whom cardiac output was not severely impaired (arteriovenous oxygen difference range 4.6–7.3 volumes per cent), inadequate radiocardiograms were the result of faulty collimation. These eight studies were excluded from the series. Hemodynamic data from the remaining 49 and from all subjects in Group B appear in Table II.

[1] Electronics for Medicine, Inc., White Plains, N. Y.
[2] Tracerlab, Waltham, Mass.
[3] Becton-Dickinson & Co., Rutherford, N. J.

Comparison of PMTT measured by the double injection of dye and by radiocardiography is presented in Fig. 1. 25 determinations were made in the course of 13 cardiac catheterizations. The patients in whom these comparisons were made are indicated by an asterisk in Table I. The regression equation for PMTT, expressed in heart cycles (HC), is the following:

$$PMTT_{RISA}\ (HC) = -0.1235 + 1.0988\ PMTT_{Dye}\ (HC) \quad (5)$$

The correlation coefficient is 0.942; the standard error of estimate $s_{y \cdot x}$ is 1.86 HC. The regression line and line of identity are not significantly different from each other ($t = 1.208$, df 23, $0.3 > P > 0.2$). A similar analysis of the data, expressed in terms of seconds rather than heart cycles, results in a correlation coefficient of 0.855; $s_{y \cdot x} = 1.57$ sec. Agreement is better when measured in heart cycles since some discrepancies due to variations in heart rate are eliminated.

Reproducibility of the radiocardiographic method was evaluated by subtracting the value of the second PMTT measurement from that of the first. These differences were averaged to obtain the mean value, $\bar{\Delta}$, and the standard deviation of differences about this mean, SD_Δ, was calculated. Duplicate determinations of $PMTT_{RISA}$ were available on 34 patients (Fig. 2). The mean difference for duplicate $PMTT_{RISA}$ determinations was 0.2 ±0.8 HC, not significantly different from zero ($t = 1.631$, $0.2 > P > 0.1$). Expressed as per cent of the mean of duplicate values, SD_Δ was 9% for $PMTT_{RISA}$ and 11% for PBV_{RISA}, indicating that in all probability two determinations which differ by more than 20% represent a true change in the volume of blood in the lungs.

19 comparisons of cardiac output measured by radiocardiography and by dye dilution are presented in Fig. 3. The mean difference between Q_{RISA} and Q_{DYE} was not significantly different from zero ($\bar{\Delta} = 63$ ml ±718 ml; $t = 0.38$, $P > 0.8$). Reproducibility of both methods was also good. The mean difference between duplicate determinations was not significantly different from zero for either method; SD_Δ was 10% of the mean of duplicates for Q_{RISA} and 7% for Q_{Dye}.

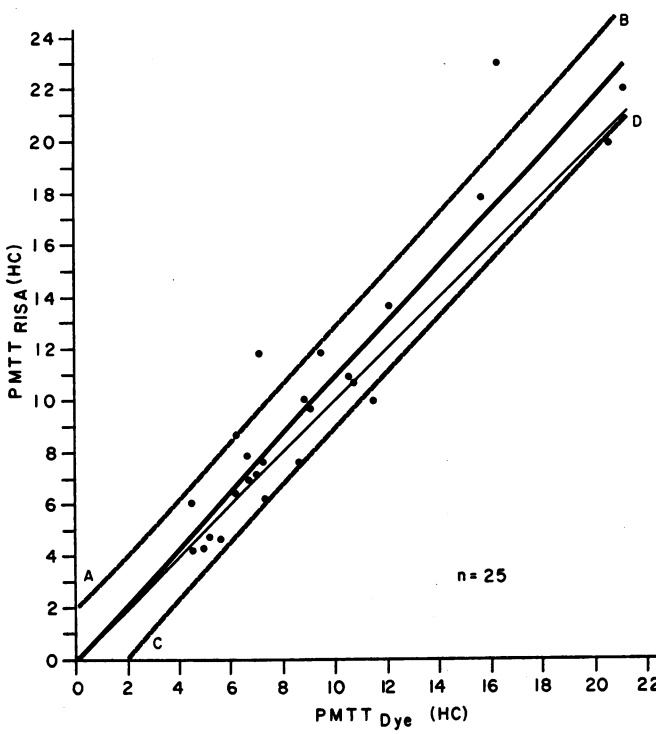

FIGURE 1 Comparison of pulmonary mean transit time (PMTT) values determined by two indicator dilution techniques. $PMTT_{RISA}$ = transit time determined from precordial radiocardiograms. $PMTT_{Dye}$ = transit time determined from the injection of indocyanine green into pulmonary artery and left atrium. HC = heart cycle. 25 determinations in 13 patients are presented. The fine solid line is the line of identity. The heavy solid line is the regression line and the broken lines, AB and CD, represent one standard error of estimate of the regression.

TABLE II

Hemodynamic Data

Patient No.	BSA	C.O.	HR	SV	PMTT		PBV	PBV	P_{PA}	P_L	P_{BA}	PVR	TBV
	m²	*ml/min*		*ml*	*HC*	*sec*	*ml*	*ml/m²*	*mm Hg*	*mm Hg*	*mm Hg*	*RU*	*ml*
Group A													
Normal													
1001	1.88	5935	84	71	6.1	4.4	433	230	20/7(13)	(8)*	160/102(118)	1.6	3948
1265	1.63	5462	78	70	6.5	5.0	455	279	13/7(9)	(6)	159/96(122)	0.9	4709
1279	1.64	5577	79	71	5.6	4.3	398	243	18/9(13)	(5)	132/77(100)	2.4	6073
1287	2.05	5322	70	76	5.5	4.7	418	204	24/14(19)	(4)	122/72(94)	5.8	4479
1288	2.15	8947	75	119	5.6	4.5	666	310	25/13(16)	(8)	122/67(89)	1.9	5891
1295	1.69	5329	71	75	5.2	4.4	390	231	16/7(10)	(6)	123/75(96)	1.3	4243
1325	1.68	7371	83	89	5.4	3.9	481	286	14/7(10)	7‡	116/62(87)	0.7	5374
Laennec's cirrhosis													
854	1.88	11982	100	120	4.1	2.5	492	262	22/10(15)	10‡	116/68(85)	0.8	7451
1281	2.14	7468	69	108	6.0	5.3	648	303	18/7(11)	7‡	114/66(85)	1.2	7034
1294	2.05	7481	72	104	5.3	4.4	551	269	54/22(36)	(15)	187/78(127)	5.8	5037
1350	2.10	9439	92	103	5.7	3.7	587	280	27/7(12)	7‡	—	1.1	5710
1363	1.66	5069	95	53	9.2	5.8	488	294	24/11(17)	(11)	126/66(89)	2.0	4736
1373	1.82	9044	95	95	6.6	4.2	627	345	19/6(11)	(5)	132/68(91)	1.2	5503
1481	2.06	11293	87	130	5.8	4.0	754	366	18/9(12)	(8)	—	0.7	6555
Chronic obstructive pulmonary disease													
500	1.88	4823	72	67	5.5	4.5	369	196	26/11(17)	(8)*	118/58(81)	3.5	4048
783	1.70	4474	112	40	10.0	5.3	400	235	24/9(16)	9‡	—	2.7	4144
786(1)	1.59	5920	96	62	6.6	4.1	409	257	23/11(15)	(8)	116/65(83)	1.9	3960
(2)	1.46	7757	109	71	10.6	6.1	753	516	52/4 RV	1§	161/77(107)	—	3605
789	1.69	7963	81	98	7.4	5.8	725	429	25/10(14)	10‡	132/64(88)	0.9	6254
798	1.50	5972	76	79	7.6	6.0	600	400	23/8(14)	(2)*	112/64(75)	3.0	4732
821	1.86	7113	75	95	6.1	4.9	580	313	23/9(13)	9‡	109/63(83)	1.0	5527
863	1.64	7862	98	80	10.1	6.2	808	493	33/16(20)	(5)*	124/79(96)	3.1	5890
897	2.18	7625	98	78	7.5	4.6	585	268	33/14(23)	(1)*	144/72(94)	6.3	6682
1064	1.86	5820	95	61	6.5	4.1	399	213	27/15(20)	(5)	—	4.8	5477
1271	1.96	5453	81	67	4.9	3.6	328	167	35/16(23)	(12)	138/72(100)	4.0	5128
1310	1.74	4923	64	77	5.7	5.3	439	252	17/6(10)	6‡	158/89(116)	1.4	5151
Pulmonary hypertension of other etiology													
850	1.84	6589	81	81	7.9	5.9	640	348	98/38(57)	(12)	127/71(93)	12.6	5166
935	1.66	5003	91	55	7.1	4.7	391	236	72/19(37)	(3)	131/75(97)	11.3	5818
986	1.98	7078	47	151	4.4	5.5	664	335	57/24(33)	(9)	147/70(98)	6.7	5235
1038	2.20	8247	91	91	6.7	4.4	610	277	34/13(22)	(10)	138/82(91)	3.2	6348
1376	1.79	4650	67	69	9.8	8.9	676	378	85/28(48)	(3)*	—	16.7	5266
Valvular heart disease													
229	1.97	5054	76	66	11.6	9.2	766	389	46/23(31)	(24)*	97/64(77)	2.6	5915
327	1.69	4036	69	59	11.8	10.4	696	412	31/14(24)	(15)*	107/64(74)	3.4	5041
778	1.75	6900	76	91	9.0	7.0	819	468	—	(19)*	89/68(76)	—	6191
853	2.10	5779	75	80	11.7	9.7	936	446	47/25(32)	(22)*	139/71(86)	3.6	6104

C.O., cardiac output; HR, heart rate in beats per minute; SV, stroke volume; PMTT, pulmonary mean transit time; HC, heart cycle; PBV, pulmonary blood volume; P_{PA}, pulmonary artery pressure; P_L, pulmonary venous pressure, measured as pulmonary "wedge" pressure unless otherwise specified; P_{BA}, brachial arterial pressure; PVR, pulmonary vascular resistance; RU, resistance units defined as gradient between pulmonary arterial and left atrial mean pressures (in mm Hg), divided by cardiac output (in liters/min per m² BSA); TBV, total blood volume.

* Left atrial pressure.

‡ Pulmonary arterial diastolic pressure.

§ Left ventricular end diastolic pressure.

TABLE II (*Continued*)

Patient No.	BSA	C.O.	HR	SV	PMTT		PBV	PBV	P_{PA}	P_L	P_{BA}	PVR	TBV
	m^2	*ml/min*		*ml*	*HC*	*sec*	*ml*	*ml/m²*	*mm Hg*	*mm Hg*	*mm Hg*	*RU*	*ml*
Valvular heart disease (*Continued*)													
925	1.66	4291	82	52	10.7	7.9	556	335	50/18(28)	19§	120/66(94)	3.5	4119
962	1.58	3055	83	38	17.9	13.0	680	430	76/32(47)	(29)*	135/51(78)	9.3	4793
963	1.86	4385	63	70	6.9	6.6	483	260	24/10(12)	(8)*	115/64(85)	1.7	3660
980	2.00	5121	60	85	7.2	7.2	612	306	27/11(14)	(11)	115/61(78)	3.5	5475
990	1.56	3226	69	47	9.9	8.5	465	298	—	(28)*	121/75(97)	—	3200
1008	2.04	4717	73	65	11.8	9.7	767	376	32/15(18)	(11)*	104/63(71)	3.0	5461
1017	1.78	4609	58	79	6.0	6.2	474	266	24/10(13)	(10)*	148/73(95)	1.2	4150
1019	2.13	4368	116	38	23.1	12.0	878	412	104/47(61)	(35)*	125/91(102)	12.7	6867
Other heart disease													
445	1.86	4042	77	53	8.2	6.4	435	234	25/9(15)	(9)*	—	2.8	5166
559	1.80	5220	51	102	7.8	9.1	796	442	24/12(17)	(12)*	101/50(65)	1.7	5222
855	1.94	8855	90	98	5.8	3.9	568	293	12/4(7)	(3)*	138/63(87)	0.9	6047
864	1.86	5720	92	62	10.4	6.7	645	347	33/17(22)	(10)*	174/89	3.9	5118
893	1.77	3724	90	41	14.3	9.6	586	331	23/10(14)	(2)*	120/71(83)	5.7	4526
918	1.94	3580	77	47	13.5	10.6	635	327	22/10(14)	(4)*	101/68(79)	5.4	5050
Group B													
Normal													
1478	1.79	5685	55	103	6.2	6.8	639	357	22/10(15)	10‡	124/74(94)	1.6	4847
1487	1.55	6300	91	69	6.0	3.8	414	267	22/14(18)	(10)	128/97(110)	2.0	3892
1496	1.64	8042	79	102	4.9	3.7	500	305	29/10(18)	(9)	137/22(101)	1.8	3969
1525	2.04	7063	89	79	5.2	3.5	411	201	26/12(16)	(6)	151/85(112)	2.9	5960
1550	2.02	9981	72	139	4.9	4.1	681	337	20/6(11)	(2)	154/83(112)	1.8	5266
1557	1.83	6399	78	82	5.7	4.4	467	255	21/8(14)	(6)	161/64(103)	2.3	4862
Pulmonary disease													
1381	1.64	3869	97	40	8.9	5.5	356	217	86/44(59)	(11)	119/66(81)	20.4	5021
1464	1.93	5622	93	60	4.4	2.9	264	137	38/13(22)	(0)	124/71(95)	7.6	5324
1475	2.22	7420	90	82	4.1	2.7	336	151	24/10(16)	(5)	137/81(97)	3.3	5449
Valvular heart disease													
1448	1.72	4814	65	74	8.2	7.6	607	353	25/8(15)	(7)	119/66(88)	2.9	4482
1507	1.64	3772	114	33	18.8	9.9	620	378	74/33(42)	(33)	111/77(86)	3.9	4808
1598	1.66	5117	73	70	7.5	6.1	525	316	36/13(21)	(13)	112/56(73)	2.6	4183
1620	1.67	6767	64	106	6.6	6.2	700	419	59/23(36)	(21)	118/55(75)	3.7	5080
Other heart disease													
1433	1.95	9003	73	123	5.8	4.8	713	366	20/7(11)	(7)	121/72(94)	0.9	4666
1476	1.80	3524	88	40	11.1	7.6	444	247	24/10(15)	(9)	111/63(83)	3.1	4106
1511	2.20	4295	99	43	18.2	11.1	783	356	47/30(37)	(29)	102/65(80)	4.1	6324
1512	1.83	4867	77	63	10.1	7.9	636	348	42/17(26)	(12)	193/116(136)	5.3	5217
1527	1.84	2770	67	41	9.8	8.8	402	218	32/13(19)	(9)	160/93(114)	6.6	4206
1528	1.98	5250	74	71	7.2	5.8	511	258	28/14(17)	(6)	153/77(105)	4.1	5169
1564	2.04	5700	58	98	7.9	8.2	774	379	30/13(18)	(12)	155/67(94)	2.1	5299
1585	1.87	5543	67	83	6.7	6.0	556	297	48/19(30)	(19)	203/79(115)	3.7	5100

Total blood volume measured by dilution of RISA was compared with values obtained by dilution of T-1824 dye in 22 patients. The mean difference between TBV_{Dye} and TBV_{RISA} was 46 ±354 ml/m² BSA which is not significantly different from zero ($t = 0.613$, $P > 0.50$).

Determinants of pulmonary blood volume. A multiple regression analysis was used to identify the determinants

of pulmonary blood volume. Since PBV is not measured directly but is calculated from transit time and flow measurements, analysis was first carried out for PMTT. The independent variables included in the multiple analysis are those showing a significant correlation to PMTT and PBV in simple linear regression equation listed in Table III. The data for cardiac output, PMTT, and TBV are those derived from injection of RISA. Where duplicate radiocardiograms were recorded, only data from the first curve were used in the statistical analysis.

A highly significant estimating equation for pulmonary mean transit time in the resting recumbent individual was calculated from the data as follows:

$$\text{PMTT (HC)} = \frac{6.658\ P_L + 0.097\ \text{TBV}}{\text{SV}} \qquad (6)$$

This equation includes only three independent variables, stroke volume, pulmonary "venous" pressure, and total blood volume, and passes through the origin; regression coefficient (R) = 0.980; the standard error of estimate is 1.82 heart cycles.

Using this estimating equation for PMTT and the hemodynamic data obtained in the 21 patients of Group B, the observed and predicted values of PMTT for this group of patients are compared in Fig. 4. 16 of the 21 comparisons fall within one standard error of estimate

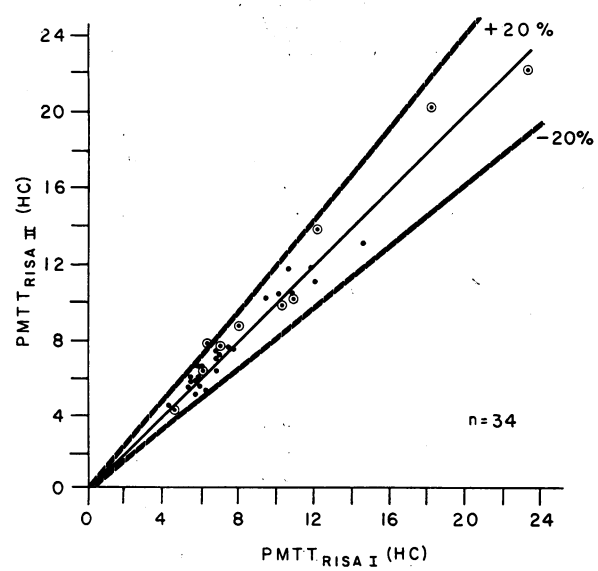

FIGURE 2 Reproducibility of $PMTT_{RISA}$ in 34 patients. The circled points represent data from patients in whom $PMTT_{Dye}$ studies were also made.

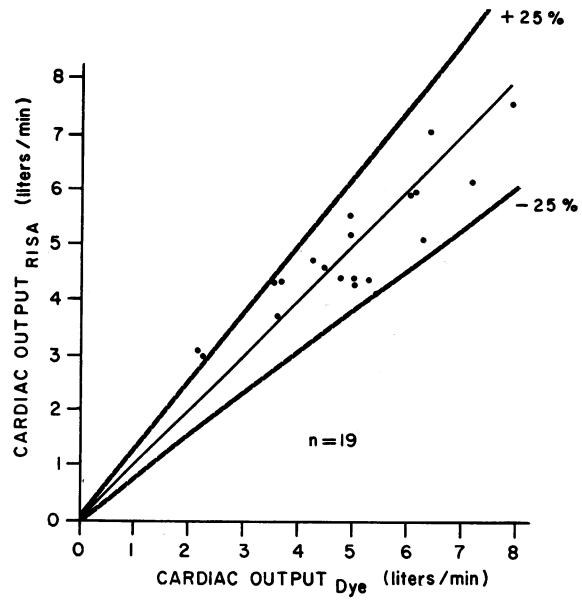

FIGURE 3 Comparison of cardiac output values obtained from radiocardiograms, and from injection of indocyanine green dye into the pulmonary artery. 19 determinations in 13 patients are presented. The solid line is the line of identity.

and all but two points within two standard errors of the line of identity.

The form of equation 6 derives from the observation, illustrated in Fig. 5, that PMTT bears an inverse relationship to stroke volume as follows:

$$\text{PMTT} = \frac{K}{\text{SV}} \qquad (7)$$

This implies that pulmonary blood volume, the product of PMTT and stroke volume, is a constant (K). However, such a conclusion is not substantiated by the data in Group A patients (Table II). Alternatively, the points in Fig. 5 might be fitted by a family of hyperbolic regression lines each with a different value of K or PBV. The individual values of K might be the result of variation in some other hemodynamic factor. To evaluate this possibility multiple regression equations were constructed maintaining the hyperbolic form, and the following was found to explain the largest fraction of the variance of PMTT, i.e., 75%.

$$\text{PMTT} = 0.802 + 7.249\ (P_L/\text{SV}) + 0.087\ (\text{TBV/SV}) \quad R = 0.867 \qquad (8)$$

The significance of both these ratios, P_L/SV and TBV/SV, in the multiple regression equation was established by analysis of variance as seen in the ac-

companying table based on equation 8:

Tabulation (based on Equation 8)

Source	df	Sum of squares	Mean square	F
Total	48	618.56		
Reg on TBV/SV	1	299.48	299.48	
Residual	47	319.08	6.79	44.11
Reg on P_L/SV	1	165.42	165.42	
Residual	46	153.66	3.34	49.53

Other parameters, specifically pulmonary artery systolic pressures (P_{PAs}), mean intravascular pressure (MIP), pulmonary vascular resistance (PVR), and the gradient between pulmonary artery diastolic and left atrial mean pressure (ΔP) do not contribute significantly to an explanation of the variance of PMTT when used in multiple regression equations involving three independent variables.

The simplification of equation 8 to equation 6, which has the form of a rectangular hyperbola, is justified since the Y intercept of equation 8 (0.802) falls within one standard error of estimate of the regression line (1.8 heart cycles). Hence the Y intercept may in fact be zero. Equation 6 was obtained by the method of least squares assuming that the regression line passes through the origin rather than the mean. Analysis of variance indicates that the reduction of unexplained variance of PMTT to be gained by fitting the regression to the mean (equation 8) is not significant ($F = 0.581$).

By a simple mathematical transposition, equation 6 becames an estimating equation for pulmonary blood volume as follows:

$$(\text{PMTT} \times \text{SV}) = 6.658\ P_L + 0.097\ \text{TBV} \quad (9)$$

This equation includes only two independent variables. The regression coefficient (R), obtained by multiplying the sum of square for each independent variable by the partial regression coefficient for that variable, is 0.950 (25). The standard error of estimate is 118 ml.

TABLE III

*Regression Equations Relating Pulmonary Mean Transit Time and Pulmonary Blood Volume to Other Hemodynamic Parameters**

N	Parameter	Regression equation	S_b	r	t_r	P_r
Pulmonary mean transit time						
49	SV	$Y = 15.39 - 0.09\ X$	0.01	0.629	5.566	<0.001
49	1/SV	$Y = 0.13 + 567\ X$	22.62	0.753	7.845	<0.001
49	P_L	$Y = 5.41 + 0.29\ X$	0.06	0.592	5.060	<0.001
49	TBV	$Y = 8.40 - 0.03\ X$	0.55	0.015	0.103	>0.90
49	TBV/SV	$Y = 0.60 + 0.12\ X$	0.01	0.821	9.871	<0.001
46	MIP	$Y = 4.04 + 0.27\ X$	0.05	0.638	5.500	<0.001
46	P_{PAs}	$Y = 5.13 + 0.09\ X$	0.02	0.535	4.213	<0.001
46	$\bar{P}_{PA} - P_L$	$Y = 7.1 + 0.09\ X$	0.05	0.254	1.740	>0.05
46	PVR	$Y = 6.39 + 0.85\ X$	0.25	0.461	3.440	<0.01
38	$P_{PAd} - P_L$	$Y = 5.11 + 0.06\ X$	0.10	0.106	0.639	>0.50
46	$P_{PAs} - P_{PAd}$	$Y = 5.79 + 0.12\ X$	0.04	0.456	3.403	<0.01
Pulmonary blood volume						
49	SV	$Y = 478.3 + 1.36\ X$	0.87	0.223	1.570	>0.10
49	P_L	$Y = 507.0 + 7.56\ X$	2.76	0.373	2.763	<0.01
49	TBV	$Y = 239.4 + 0.067\ X$	0.02	0.337	2.450	<0.02
46	MIP	$Y = 472.4 + 7.09\ X$	2.35	0.425	3.125	<0.01
46	P_{PAs}	$Y = 493.5 + 2.48\ X$	0.96	0.369	2.636	<0.02
46	$\bar{P}_{PA} - P_L$	$Y = 554.0 + 2.35\ X$	1.97	0.161	1.081	>0.20
46	PVR	$Y = 556.2 + 11.73\ X$	11.14	0.160	1.074	>0.20
38	$P_{PAd} - P_L$	$Y = 567.9 + 2.66\ X$	3.77	0.114	0.687	>0.40
46	$P_{PAs} - P_{PAd}$	$Y = 520.2 + 3.11\ X$	1.56	0.294	2.042	>0.05

N, number of observations; S_b, standard error of correlation coefficient; t_r, "Student's t" calculated for correlation coefficient; $t = r/(1 - r^2/N - 2)$; SV, stroke volume; P_L, pulmonary venous pressure; TBV, total blood volume; MIP, mean intravascular pressure; P_{PAs}, pulmonary artery systolic pressure; $\bar{P}_{PA}$, mean pulmonary artery pressure; P_{PAd}, pulmonary artery diastolic pressure; PVR, pulmonary vascular resistance.

* Simple linear regression equations were calculated by the method of least squares. The dependent variable, Y, is either PMTT or PBV, as indicated. The independent variable, X, is listed in column labeled "parameter."

DISCUSSION

Validation of the method. Of the two methods under discussion, the radiocardiographic method of measuring pulmonary blood volume has the distinct advantage of not requiring left atrial injection or sampling. Hence it can be applied in studies of the pulmonary circulation of patients who would not ordinarily come to left heart catheterization. Nevertheless, this method has not found wide application presumably because the mathematical basis has not been validated by a direct comparison in the same individuals with the double-injection dye technique.

The present report indicates that agreement between the two methods is good over a wide range of transit times. The apparent tendency of $PMTT_{RISA}$ to exceed $PMTT_{Dye}$ is not statistically significant. Although individual discrepancies of greater than 25% were observed in four of the 25 comparisons, this proportion is not greater than that reported by Samet, Bernstein, Lopez, and Levine who compared two dye injection methods of measuring PMTT (27).

The method of analysis of radiocardiograms proposed by Giuntini et al. (14) is based on assumptions regarding size of ventricular chambers and distribution of pulmonary transit times in addition to the usual assumptions underlying the use of indicators to measure the volume of vascular sections. These assumptions may not be valid for every patient, thus giving rise to indeterminate errors in measurement of PBV. In their original publication, from analysis of curves generated by a digital computer incorporating different chamber sizes and transit time distributions, these authors concluded that the magnitude of error between true, i.e. imposed, mean transit time and calculated PMTT would rarely exceed three heart cycles. In fact, in the present comparisons only two of 25 $PMTT_{RISA}$ values were more than three heart cycles different from $PMTT_{Dye}$. Assuming $PMTT_{Dye}$ values to represent true mean transit times, the range of errors of $PMTT_{RISA}$ closely approximates the prediction and justifies the simplifying assumptions.

Reproducibility of PBV_{RISA} determinations in this laboratory is not substantially different from the experience of several groups measuring pulmonary blood volume. Giuntini, Maseri, and Bianchi (28) report an

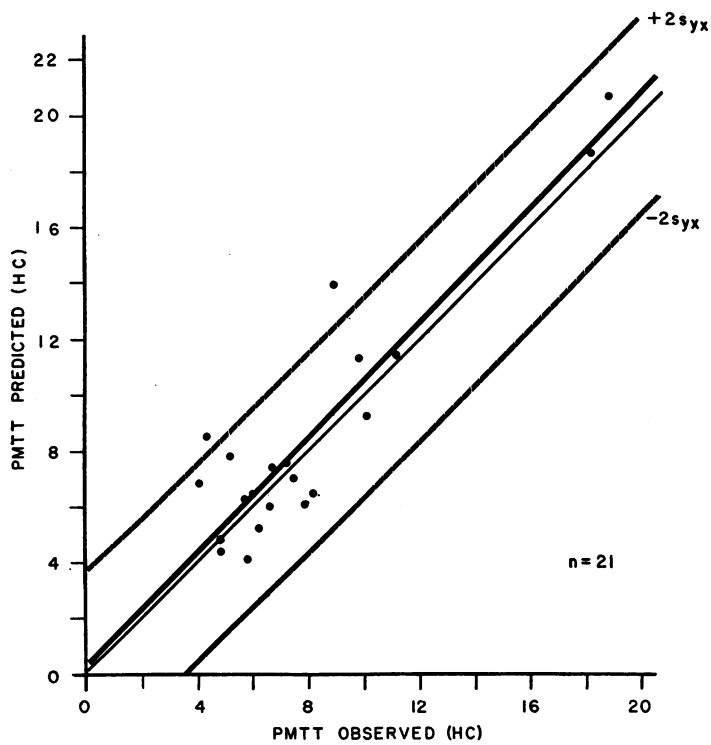

FIGURE 4 Comparison in 21 patients (Group B) of observed and predicted pulmonary mean transit time. PMTT was predicted on the basis of an estimating equation (equation 6 in text) derived from data from a different group of 49 patients (Group A). HC = heart cycle. $s_{y.x}$ = standard error of estimating equation. The heavy solid line is the regression line of predicted on observed values; the fine solid line is the line of identity. The regression line and 19 of 21 points fall within two standard errors of estimate of the line of identity.

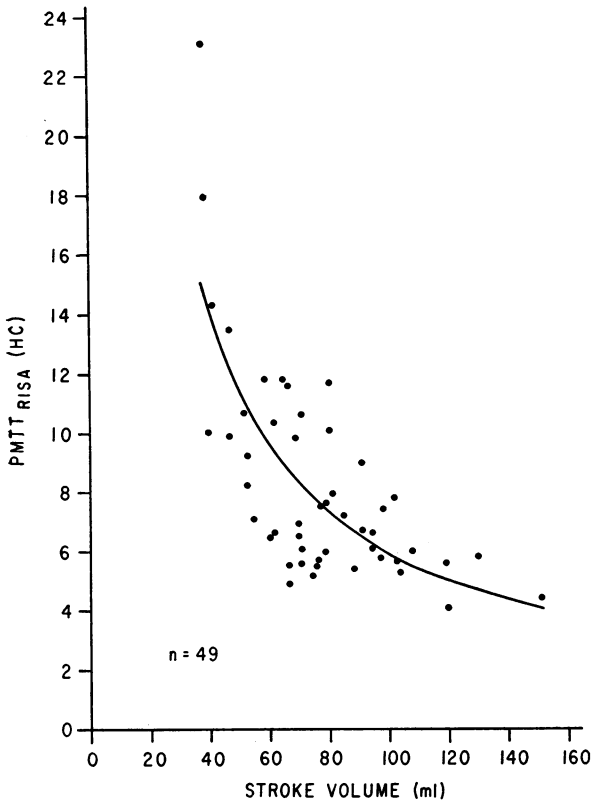

FIGURE 5 Relation of pulmonary mean transit time and stroke volume. The solid line is the regression line, calculated as $PMTT = K(1/SV)$.

average variation of 2.7% about the mean of duplicate values of PBV_{RISA}, the greatest difference between duplicates being 15.4%. Data in the present group yields an average variation of 5.0 ±2.8% about the mean of PBV_{RISA} values, the greatest difference observed being 21.6%. Similar statistics calculated for data published by Yu (15) result in an average variation of 4.2 ±2.1% about the mean of two PBV_{Dye} values in 19 patients; deFreitas, Faraco, Nedel, deAzevedo, and Zaduchliver obtained a value of 3.2 ±2.7% in their patients (11).

Samet et al. (27) in their large series of PBV_{Dye} determinations indicate that 21% of duplicates (18 of 86) were in excess of 20% different from the first determination, whereas in the present series 6% of duplicates (2 of 34) were in excess of 20% different from the first value. Forsberg chose to compare duplicates by a ratio of first to second determinations, and reported a mean value of 1.00 ±0.11 (10). The mean ratio between 34 duplicate $PMTT_{RISA}$ values measured in this laboratory is 0.98 ±0.09.

Since blood flow enters into the calculation of pulmonary blood volume as well as into the statistical analysis of its determinants, the validity of this determination was also evaluated. Cardiac output determination from radiocardiograms has previously been validated by comparison with the Fick method (29). In this laboratory 60 comparisons with Fick determinations again showed no significant difference ($t = 1.558$, $0.2 > P > 0.1$). The RCG and dye dilution measurements of flow were also in agreement. In comparison with previously published data, the standard deviation of the ratio $Q_{RISA} : Q_{Dye}$ is 18%, similar to the figure of 15% found by Dock, Krauss, McGuire, Hyland, Haynes, and Dexter when comparing flow values calculated from the simultaneous injection of two indicators into the pulmonary artery and left atrium (3). The standard deviation of differences between Q_{RISA} and Q_{Dye} is 718 ml, close to the figure of 650 ml obtained by Forsberg (10) utilizing a method similar to that of Dock et al. (3). Duplicate determinations of Q_{RISA} in this laboratory may be expected to fall within 20% of each other (95% confidence). Finally, total blood volume determinations as calculated from the dilution of T-1824 dye and of radio-iodinated human serum albumin showed no systemic differences in the patient studied. Hence the values of blood flow and total blood volume, which enter into the statistical analysis to be discussed, can be presumed to be valid.

Determinants of pulmonary blood volume. Previously published analyses relating PBV to other hemodynamic parameters are, in some degree, contradictory. Whereas some authors observed a positive relation between PBV and stroke volume (1, 5, 9, 10, 14), this relationship cannot be derived from data published by others (4, 6–8) and a negative relationship between these parameters has been published by yet another group (11). Similarly, whereas a positive correlation between left atrial pressure and PBV has been confirmed by some workers (3, 5, 10), it is specifically denied by others (9). Contradictory results regarding the effects of pulmonary vascular resistance on PBV have also been published (1, 3–5, 10).

In contrast, statistical analysis of the data from the present series has resulted in an estimating equation for pulmonary mean transit time, which includes only three independent variables, giving rise to an equation for pulmonary blood volume with only two independent variables. Within the error of the radiocardiographic method, 90% of the observed variability of resting pulmonary blood volume can be ascribed to variation in pulmonary venous pressure and total blood volume.

The simplicity of these equations may be surprising in view of the fact that none of the basic observations is new. The inverse relationship of PMTT and flow was reported by Doyle, Lee, and Kelley (30), and by Dock et al. (3). It is inherent in the definition of mean transit time through a vascular section which exhibits mixing and stationarity, that is, the time required for a

volume of fluid equivalent to the contained volume to pass through the section. Thus, for the lungs:

$$PMTT = \frac{PBV}{SV} \qquad (10)$$

Since in the present series the relationship of PMTT and 1/SV remained statistically significant despite more than twofold differences in PBV, it is apparent that variations in transit time are mediated more by variations in blood flow than by variations in lung blood volume.

An increase in pulmonary blood volume with increasing pulmonary venous pressure was observed by Carlill and Duke (31) and by Sarnoff and Berglund (32) in animal preparations. In man a similar observation was made by Dock et al., (3) McGaff, Roveti, Glassman, and Milnor (5), and by Forsberg (10). The findings in the present series of patients confirm these reports. A graph relating PMTT to P_L in these 49 cases actually has the apperance of a parabola, convex to the pressure axis, indicating that below a certain level P_L has little effect on prolonging PMTT. However, a multiple regression equation parabolic with respect to P_L resulted in an explained variance of PMTT identical to that provided by equation 8 which is linear with respect to P_L. Hence, a linear equation adequately describes the statistical relationship between these two parameters.

Several authors (3, 14, 15) have remarked on a relation between pulmonary blood volume and total blood volume as observed in the present data. However, the major contribution which variations in total blood volume make toward explaining variations in pulmonary blood volume has not been fully appreciated. This may be due to the fact that, although many normal studies have been reported in the literature using the double injection method, there has been little indication for left atrial catheterization in patients with hypervolemia unrelated to heart disease or in patients with primary lung disease. Such studies have been conducted in this laboratory using the RCG method.

Resistance to expansion of pulmonary blood volume has been observed during the administration of plasma expanders but this is presumably due to the rapidity with which the changes are induced (28, 33). In the present series where the increase in total blood volume has come about gradually at some antecedent time and where a steady state is under observation, TBV appears to be the primary determinant of PBV.

The conclusion that only variations in SV, TBV, and P_L need be invoked in order to explain variations in PMTT observed between patients in the present study is inherent in the highly significant correlation between PMTT and these three parameters and in the reproducibility of the RCG technique. Equation 8 explains 75% of the variation of PMTT with a standard error of estimate of 1.8 heart cycles. Since the standard deviation of duplicate $PMTT_{RISA}$ measurements is 1.1 heart cycles which constitutes 60% of the error of estimate of equation 8, then at least 60% of the residual unexplained variance of PMTT in these 49 cases may be ascribed to random errors of the method.

This in effect leaves only 10% residual variance of PMTT justifying the use of an estimating equation which passes through the origin and allows no determinants of PMTT other than the three discussed. This does not preclude that some of the observed variation is in fact due to variation in other hemodynamic parameters but the effect must be small.

An explanation for observed variability of PBV has been sought in differences of vascular distensibility by relating PBV to indices such as pulmonary vascular resistance (PVR) and mean intravascular pressure (MIP). Although each of these factors and several other pressure parameters in the lesser circulation correlate with PMTT in a simple linear regression, none of them produced a significant reduction of variance of PMTT beyond that produced by SV, P_L, and TBV. Because of the intimate relationship between flow, volume, and transit time, the analyses apply equally to PMTT and PBV; moreover, the conclusions have been confirmed by separate calculations of multiple regression equations for PBV.

Certain authors have found the linear relationship of PBV and pulmonary venous pressure to be modified in the presence of increased vascular resistance secondary to long-standing mitral stenosis (3, 5). As illustrated in Fig. 6, no effect of resistance on the relationship of pulmonary blood volume and venous pressure was observed in the present study. These 49 patients include relatively few with mitral stenosis and high resistance; hence the difference between the present and previously published series may lie in the type of patients evaluated.

Alternatively, the difference may lie in the interpretation of data. Elevated vascular resistance and lower than normal pulmonary blood volume are usually considered to be cause and effect. However, the reverse may be true. An elevated pulmonary blood volume must be accommodated in larger or more numerous channels. If the total cross sectional area of vascular channels in the lung is increased, the gradient of pressure across the lungs for any given flow rate will be lower, i.e., a larger pulmonary blood volume will result in a lower pulmonary vascular resistance.

At least some of the differences in pulmonary blood volume reported in patients with elevated left atrial pressure and pulmonary vascular resistance may be explained by differences in total blood volume. The failure

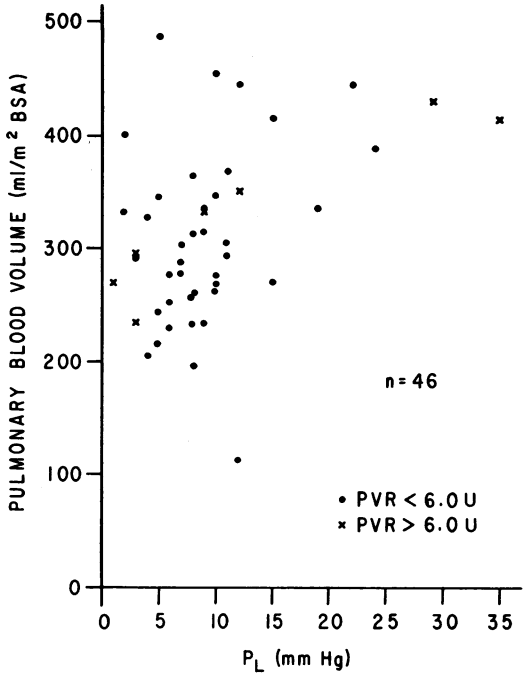

FIGURE 6 Relation of pulmonary blood volume and pulmonary "venous" pressure, P_L, in 46 patients of Group A. Crosses indicate seven patients with pulmonary vascular resistance (PVR) greater than 6.0 U, [U = (mm Hg)/(liters/min per m² BSA)]. For discussion see text.

to specifically consider this factor as a determinant of PBV, and the small residual variance left unexplained by P_L and TBV may account for the contradictory results obtained by other workers. Since data on total blood volume have not been published in previous reports, this possibility cannot be evaluated.

Also contrary to published work is the absence of a significant regression of PBV and SV in Group A when these 49 patients were considered as a single group. If the highest values of PBV were eliminated by omitting data from patients with elevated pulmonary venous pressure (> 12 mm of Hg) and those with elevated total blood volume (> 3.1 liters/m² BSA), a significant regression was observed in the remaining 28 patients. Of these 28, 13 exhibited an elevated PBV(> 300 ml/m² BSA); however, stroke volume was not elevated in these 13 patients being equally distributed about the mean SV for the group of 28. In contrast, total blood volume was elevated above the mean in 10 of the 13 patients with abnormally high pulmonary blood volume. This suggests that in these 13 patients also pulmonary blood volume paralleled total blood volume, and the correlation of PBV and SV was due in large part to the tendency of stroke volume to increase with total blood volume in the absence of myocardial insufficiency.

The implication of the derived estimating equation for PBV, which is linear with respect to pulmonary venous pressure and total blood volume, is that variations in resting pulmonary blood volume are the result of passive distention of the pulmonary bed. With the possible exception of patients with increased pulmonary vascular resistance secondary to mitral stenosis, who were not adequately represented in this series, no evidence of altered vascular distensibility was found in the 70 patients (Groups A and B) studied. From this data it appears that the pulmonary blood volume normally constitutes a rather fixed fraction of total blood volume, the proportion being changed only passively, by an increase in outflow pressure from the pulmonary bed. This concept has been voiced before but has not been adequately quantitated. It is clear that since 90% of the variability of resting pulmonary blood volume can be explained by variation in these two factors the residual effects of other factors, such as vascular compliance, must be small and hence difficult to quantitate and of doubtful significance.

REFERENCES

1. Milnor, W. R., A. D. Jose, and C. J. McGaff. 1960. Pulmonary vascular volume, resistance and compliance in man. *Circulation.* **22:** 130.
2. Fujimoto, K., R. Kunieda, and T. Shiba. 1960. Lung blood volume in acquired valvular disease. *Jap. Heart J.* **1:** 442.
3. Dock, D. S., W. L. Kraus, L. B. McGuire, J. W. Hyland, F. W. Haynes, and L. Dexter. 1961. The pulmonary blood volume in man. *J. Clin. Invest.* **40:** 317.
4. Oakley, C., G. Glick, M. N. Luria, B. F. Schreiner, and P. N. Yu 1962. Some regulatory mechanisms of the human pulmonary vascular bed. *Circulation.* **26:** 917.
5. McGaff, C. J., G. C. Roveti, E. Glassman, and W. R. Milnor. 1963. The pulmonary blood volume in rheumatic heart disease and its alteration by isoproterenol. *Circulation.* **27:** 77.
6. Yu, P. N., G. Glick, B. F. Schreiner, and G. W. Murphy. 1963. Effects of acute hypoxia on the pulmonary vascular bed of patients with acquired heart disease. *Circulation.* **27:** 541.
7. Glick, G., B. F. Schreiner, G. W. Murphy, and P. N. Yu. 1963. Effects of inhalation of 100 per cent oxygen on the pulmonary blood volume in patients with organic heart disease. *Circulation.* **27:** 554.
8. Schreiner, B. F., G. W. Murphy, G. Glick, and P. N. Yu. 1963. Effect of exercise on the pulmonary blood volume in patients with acquired heart disease. *Circulation.* **27:** 559.
9. Vernauskas, E., S. A. Forsberg, J. Widimsky, and S. Paulin. 1963. Pulmonary blood volume and its relation to pulmonary hemodynamics in cardiac patients. *Acta Med. Scand.* **173:** 529.
10. Forsberg, S. A. 1964. Pulmonary blood volume in man. *Acta Med. Scand.* **175**(Suppl): 410.
11. deFreitas, F. M., E. Z. Faraco, N. Nedel, D. F. deAzevedo, and J. Zaduchliver. 1964. Determination of pulmonary blood volume by single intravenous injection of

one indicator in patients with normal and high pulmonary vascular pressures. *Circulation.* **30:** 370.
12. Samet, P., W. H. Bernstein, A. Medow, and S. Levine. 1965. Transseptal left heart dynamics in thirty-two normal subjects. *Dis. Chest.* **47:** 632.
13. Donato, L., C. Giuntini, M. L. Lewis, J. Durand, D. F. Rochester, R. M. Harvey, and A. Cournand. 1962. Quantitative radiocardiography. I. Theoretical considerations. *Circulation.* **26:** 174.
14. Giuntini, C., M. L. Lewis, A. Sales Luis, and R. M. Harvey. 1963. A study of the pulmonary blood volume in man by quantitative radiocardiography. *J. Clin. Invest.* **42:** 1589.
15. Yu, P. N. 1969. Pulmonary Blood Volume in Health and Disease. Lea & Febiger, Philadelphia.
16. Ross, J., Jr., E. Braunwald, and A. G. Morrow. 1960. Left heart catheterization by the transseptal route. A description of the technic and its applications. *Circulation.* **22:** 927.
17. Seldinger, S. I. 1953. Catheter replacement of the needle in percutaneous arteriography. *Acta Radiol.* **39:** 368.
18. Kaltman, A. J., W. H. Herbert, R. J. Conroy, and C. E. Kossmann. 1966. The gradient in pressure across the pulmonary vascular bed in diastole. *Circulation.* **34:** 377.
19. Donato, L., D. F. Rochester, M. L. Lewis, J. Durand, J. O. Parker, and R. M. Harvey. 1962. Quantitative radiocardiography. II. Technic and analysis of curves. *Circulation.* **26:** 183.
20. Veall, N., J. D. Pearson, T. Hanley, and A. E. Lowe. 1954. A method for the determination of cardiac output (preliminary report). *In* Proceedings of the Second Radioisotope Conference, Oxford. Butterworths Scientific and Medical Publications, London. Vol. 1. 183.
21. Hamilton, W. F., J. W. Moore, J. M. Kinsman, and R. G. Spurling. 1932. Studies on the circulation. IV. Further analysis of the injection method, and of changes in hemodynamics under physiological and pathological conditions. *Amer. J. Physiol.* **99:** 534.
22. McNeely, W. F., and M. A. Gravellese. 1954. Measurement of cardiac output by dye dilution technique: use of an "integrated" sample collection in calibration of the photometric instrument. *J. Appl. Physiol.* **7:** 55.
23. Chaplin, H., Jr., and P. L. Mollison. 1952. Correction for plasma trapped in the red cell column of the hematocrit. *Blood.* **7:** 1227.
24. Fudenberg, H., M. Baldini, J. P. Mahoney, and W. Dameshek. 1961. The body hematocrit/venous hematocrit ratio and the "splenic reservoir." *Blood.* **17:** 71.
25. Steel, R. G. D., and J. H. Torrie. 1960. Principles and Procedures of Statistics. McGraw-Hill Book Company, New York.
26. Ezekiel, M. J. B., and K. A. Fox. 1959. Methods of Correlation and Regression Analysis. John Wiley & Sons, Inc. New York.
27. Samet, P., W. H. Bernstein, A. Lopez, and S. Levine. 1966. Methodology of true pulmonary blood volume determination. *Circulation.* **33:** 847.
28. Giuntini, C., A. Maseri, and R. Bianchi. 1966. Pulmonary vascular distensibility and lung compliance as modified by dextran infusion and subsequent atropine injection in normal subjects. *J. Clin. Invest.* **45:** 1770.
29. Lewis, M. L., C. Giuntini, L. Donato, R. M. Harvey, and A. Cournand. 1962. Quantitative radiocardiography. III. Results and validation of theory and method. *Circulation.* **26:** 189.
30. Doyle, J. T., R. A. Lee, and E. B. Kelley. 1952. Observations on the elasticity of the pulmonary vasculature in man. *Amer. Heart J.* **44:** 565.
31. Carlill, S. D., and H. N. Duke. 1956. Pulmonary vascular changes in response to variations in left auricular pressure. *J. Physiol. (London).* **133:** 275.
32. Sarnoff, S. J., and E. Berglund. 1952. Pressure-volume characteristics and stress relaxation in the pulmonary vascular bed of the dog. *Amer. J. Physiol.* **171:** 238.
33. deFreitas, F. M., E. Z. Faraco, D. F. deAzevedo, J. Zaduchliver, and I. Lewin. 1965. Behavior of normal pulmonary circulation during changes of total blood volume in man. *J. Clin. Invest.* **44:** 366.