

## ALTERATIONS IN PULMONARY BLOOD FLOW DISTRIBUTION IN HEART DISEASES WITH PULMONARY HYPERTENSION STUDIED BY RADIOISOTOPE ( $^{131}\text{I}$ -MAA) SCANNING

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### ABSTRACT

Utilizing the  $^{131}\text{I}$ -MAA (macroaggregated albumin labeled with iodine-131) scintillation scanning method, regional pulmonary blood flow distribution was studied in 47 cardiac patients with pulmonary hypertension.

Remarkable increase of blood flow in the upper zones of the lung together with decrease in the lower zones was found in the majority of the patients with mitral valve disease, while in the congenital heart disease with left to right shunt group, elevation of upper/lower ratio of pulmonary blood flow was minimal even in the patients with severe pulmonary hypertension. Upper/lower ratio of pulmonary blood flow showed a good correlation with left atrial pressure and mean pulmonary circulation time but not with pulmonary arterial pressure.

The mechanism underlying these differences of pulmonary circulation pattern in various heart diseases with pulmonary hypertension was discussed and the role of primary factors (perivascular edema and vasoconstriction) was emphasized as the cause of this reversed pattern of pulmonary circulation.

Postoperative studies on the 16 patients with mitral valve disease proved that this abnormal distribution of pulmonary blood flow could be improved in a comparatively short time by successful surgical correction of the disease, whereas in those patients with upper/lower blood flow ratio in an erect position over 2.0, high operative mortality resulted. The surgical significance of the upper/lower pulmonary blood flow ratio measurement in determining the operative risk and curability of the disease was also discussed.

### INTRODUCTION

Among various distressing complications associated with congenital and acquired cardiac diseases, pulmonary hypertension has brought about one of the most annoying problems to the cardiac surgeons in the management of patients during and immediately after cardiac operations.

Since the progress of cardiac surgery in heart-lung machine technique has made the operations possible which require two or even three hours of extracorporeal circulation, the severest cardiac diseases that were hitherto considered

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inoperable have now become the subjects of surgical treatment. The most serious obstacle that a cardiac surgeon must face today is the problem of pulmonary hypertension most commonly associated with these severe cardiac disease, and the further improvement in operative results depends upon the study for clarifying the hemodynamic mechanism and pathological aspects of pulmonary hypertension.

Since Goodwin<sup>1)</sup> described the phenomenon of characteristic narrowing of the arteries in the lower and sometimes middle zones of the lungs in cases of mitral stenosis, the problem of regional pulmonary blood flow in pulmonary hypertensive cardiac diseases has widely attracted the interest of many investigators.

To pursue the hemodynamic aspects of pulmonary hypertension, especially the regional distribution pattern of pulmonary arterial blood flow, various techniques have been devised and applied, such as pulmonary angiography<sup>2)</sup>, differential bronchspirometry<sup>3)</sup> and radioactive gas inhalation method<sup>4)5)</sup>. They have their own merits and demerits but unfortunately their widespread clinical applications have been limited by the lack of quantitativity, potential hazard or discomfort to human body or complexity of techniques and equipments.

In 1951, Cassen *et al.*<sup>6)</sup> and Mayneord *et al.*<sup>7)8)</sup> independently devised an apparatus called scintillation scanner. They administered a radioisotope to human body and, by letting it accumulate in the selected tissues or organs through various mechanisms, succeeded in visualizing those organs in a plane sheet by outer detection of radioactivity. Since then, this method, scintillation scanning, has been applied widely in diagnosing the morphological change of the thyroid gland.

In 1963, Taplin *et al.*<sup>9)</sup> developed a new radioactive pharmaceutical <sup>131</sup>I-MAA (macroaggregated albumin labeled with iodine-131) and Wagner *et al.*<sup>10)</sup>, in the same year, first succeeded in applying this material to the scintillation scanning of the human lung.

Intravenously injected <sup>131</sup>I-MAA particles will be uniformly mixed with blood stream in the right ventricle and, due to their adequate size of aggregation (10-50  $\mu$ ), detained for several hours in the arteriolar capillary bed of the lung in concentration proportional to regional pulmonary blood flow. By moving an external scintillation counter over the thorax, it is possible to gain the quantitative measurement of pulmonary blood flow distribution. This material also offers a useful method for the observation of the various pulmonary circulatory disorders associated with congenital and acquired cardiac diseases.

The object of the present study was to investigate the characteristics of pulmonary circulation in pulmonary hypertensive cardiac diseases, its correlation with pathological changes of the pulmonary vascular bed, its reversibility to normal pattern by successful surgical correction of the cardiac diseases and to

discuss the possibility of determining operative indication and prognostic preestimate of pulmonary hypertensive cardiac diseases by utilizing this  $^{131}\text{I}$ -MAA scintillation scanning method.

#### MATERIALS

Among the patients hospitalized in the First Department of Surgery, University of Nagoya School of Medicine, during the period of February 1966 to January 1968, 39 cases of mitral valve disease, 6 cases of ventricular septal defect with pulmonary hypertension and two cases of patent ductus arteriosus with pulmonary hypertension were selected for this study. Seven cases of aortic valve disease were also studied as the control. In the ventricular septal defect and patent ductus arteriosus group, those were chosen whose systolic pulmonary arterial pressure was over 50 mmHg.

Of 39 cases of mitral valve disease, 7 were mitral stenosis, 5 were mitral insufficiency and 7 were mitral stenosis and insufficiency combined in varying degrees. Seven aortic valve disease patients consisted of 5 aortic insufficiency, one aortic steno-insufficiency and one combination of aortic steno-insufficiency and slight degree of mitral stenosis.

Ages of the mitral valve disease group ranged from 10 yrs. to 46 yrs.; the ventricular septal defect with pulmonary hypertension group from 4 yrs. to 13 yrs.; the patent ductus arteriosus with pulmonary hypertension group 15 yrs. and 24 yrs.; and the aortic valve disease group from 19 yrs. to 30 yrs., respectively.

Out of 26 patients with mitral valve disease who underwent operation, 16 were subjected to the postoperative scanning examination one to seven months after surgery.

The summary of data is tabulated in Tables 1, 2, 3 and 4.

#### METHODS

##### 1. Apparatus

Conventional Shimazu SCC-30 Scintillation Scanner with  $3 \times 2$  inch NaI crystal and a multichannel 37-hole honey-cone collimator with a 5 cm focal point, designed to have 1 cm wide, 70% isoresponse contour at 8.5 cm depth was employed for plane scintigrams in the present study (Fig. 1). With this apparatus, a visual image of the relative distribution of pulmonary blood flow is obtained on a sheet of plane scintigram. Semi quantitative measurement of the distribution is also possible by counting the dots on a scintigram.

In order to determine the more accurate quantitative measurement of regional blood flow by eliminating the error of dot-counting on a scintigram, a "right lung linear scanning method" was devised as illustrated in Fig. 2.

TABLE 1. The summary of data on patients with mitral valve disease (operated)

Patients	Age	Sex	Diag.	U/L		PA (mmHg)	LA (mmHg)	MPCT (sec)	PVR (dynes sec cm <sup>-5</sup> )	CTR (%)	%VC	Activi- tites*	Ope.	Result
				pre	post									
1	A. T.	26	M	MS	2.11	0.86	95/45(80)	36/25(32)	11.2	1204	72	69	III	Comm.
2	F. U.	16	F	MS	1.37		42/15(27)	30/15(21)			57	90	II	Comm.
3	M. T.	34	F	MS	1.00	0.62	50/20(30)	25/12(19)			53	75	II	Comm.
4	T. I.	20	M	MS	4.00		100/45(55)	38/26(30)			70	58	III	Comm.
5	K. T.	37	M	MS	1.43	0.60	44/18(25)	35/12(19)			66	75	II	Comm.
6	K. N.	34	F	MS	0.80		25/5(14)	23/16(12)			48.5	77	II	Comm.
7	H. A.	25	F	MS	0.95	0.40	40/20(30)	35/15(22)			56	72	II	Comm.
8	M. S.	25	F	MS	1.02	0.35	55/24(40)	32/8(17)			47	90	I	Comm.
9	S. S.	46	F	MS	1.30	0.59	65/38(40)	30/16(24)			55	89	II	Comm.
10	T. Y.	38	M	MS	0.75	0.45	26/11(16)	15/12(13)	5.6	62	58	93	II	Comm.
11	M. K.	38	F	MS	1.48	0.75	70/45(62)	35/20(27)	12.2	855	58	60	II	Comm.
12	I. U.	29	M	MS	1.00	0.48	50/24(30)	32/25(22)	5.7	174	60	93	II	Comm.
13	M. Y.	42	F	MS	0.45		42/22(28)	25/5(10)			51	96	II	Comm.
14	K. K.	29	M	MS	0.45	0.32	28/11(18)	18/4(5)			56	88	I	Comm.
15	S. O.	36	M	MS	0.82	0.31	50/18(30)	30/20(26)			52	90	II	Comm.
16	M. S.	33	M	MS	0.75		30/10(25)	18/8(12)	8.0	196	50	87	II	Comm.
17	T. F.	35	F	MS	1.38	0.50	60/28(45)	38/18(24)			68	55	II	Comm.
18	Y. H.	28	F	MS	1.32	1.05	66/30(52)	30/20(21)			59	70	I	Comm.
19	K. K.	10	F	MI	2.32		88/40(56)	60/20(40)			74	52	III	Val.Rep.
20	O. T.	23	M	MI	2.73	1.50	60/18(45)	42/20(28)	15.0	621	64	63	III	Val.Rep.
21	K. K.	21	F	MI	2.20	0.95	40/20(35)	28/20(25)	8.5	231	76	54	II	Val.Rep.
22	E. I.	22	F	MSI	2.27	0.65	65/28(40)	40/22(26)	15.0	436	66	72	III	Val.Rep.
23	H. T.	31	M	MSI	2.64		70/34(40)	42/18(30)			71	70	IV	Val.Rep.
24	Y. I.	35	M	MSI	1.48		60/20(34)	20/6(24)	13.0	307	77	74	III	Val.Rep.
25	M. S.	28	F	MSI	1.20		30/10(22)	30/14(18)	10.0	113	62	47	II	Val.Rep.
26	T. T.	22	F	MS+AI	3.50		60/30(50)	36/22(30)			54	52	III	Val.Rep.+Comm.

\* According to New York Heart Association

TABLE 2. The summary of data on patients with mitral valve disease (non operated)

Patients	Age	Sex	Diag.	U/L	PA (mmHg)	LA (mmHg)	CTR (%)	Activities	
1	F. T.	32	M	MS	1.55	54/30(38)	28/21(19)	60	II
2	N. T.	24	F	MS	1.95	70/32(46)	30/16(21)	62	III
3	H. Y.	23	F	MS	3.05	84/52(65)	45/18(29)	75	II
4	M. T.	25	M	MS	0.95	46/22(30)	30/10(20)	61	II
5	Y. O.	18	F	MS	0.45	28/ 8(12)	16/ 6( 7)	47	I
6	J. S.	18	F	MS	0.45	36/10(17)	25/ 4( 8)	57	I
7	S. K.	24	F	MS	0.60	40/14(21)	22/10(14)	55	I
8	T. H.	35	M	MS	1.82	66/45(52)	38/26(30)	71	II
9	T. O.	21	F	MI	0.80	28/16(18)	24/ 6(14)	61	I
10	E. H.	10	F	MI	1.58	64/34(52)	40/14(37)	79	II
11	M. K.	38	M	MSI	1.10	38/20(30)	26/18(23)	51	II
12	M. F.	38	F	MSI	1.26	48/15(30)	34/20(23)	70	II
13	T. I.	34	F	MSI	0.95	42/24(30)	40/12(20)	69	III

TABLE 3. The summary of data on patients with VSD+PH and PDA+PH

Patients	Age	Sex	Diag.	U/L	PA (mmHg)	RV (mmHg)	Syst. Pr. (mmHg)
1	K. I.	10	F	VSD+PH	0.52	100/40(60)	114/74
2	S. W.	6	M	VSD+PH	0.82	95/38(60)	96/62
3	M. A.	7	M	VSD+PH	0.38	80/44(60)	96/64
4	K. W.	9	M	VSD+PH	0.65	50/20(30)	118/68
5	A. M.	4	F	VSD+PH	0.42	88/48(64)	94/58
6	M. S.	13	M	VSD+PH	0.45	54/ 8(35)	98/62
7	T. I.	24	F	PDA+PH	0.52	52/10(28)	128/58
8	H. S.	15	F	PDA+PH	0.45	60/15(32)	104/40

TABLE 4. The summary of data on patients with aortic valve disease

Patients	Age	Sex	Diag.	U/L	Aortic Pr. (mmHg)	LV (mmHg)	
1	K. K.	19	M	AI	0.50	125/70(100)	125/18(58)
2	H. N.	25	M	AI	0.42	124/60 (86)	120/ 0(44)
3	S. U.	30	M	AI	0.31	140/60(100)	not known
4	T. M.	20	M	AI	0.65	142/ 6 (66)	142/ 0(60)
5	T. H.	28	M	AI	0.80	120/35 (65)	120/0-20(50)
6	M. M.	30	M	ASI	0.38	120/80 (90)	160/20(75)
7	F. I.	25	F	ASI+Ms	0.35	90/60 (95)	155/ 0(80)

A hand made slitted collimator of 8.5 cm high with trapezoid inner space of 4.7×1.5 cm at the top, 3×1 cm at the bottom (Fig. 3), was mounted on Shimazu SCC-15 Scintillation Scanner (2×2 inch NaI crystal), and the detector was moved in a longitudinal direction providing the ratemeter recording of radioactivity variations along a vertical segment of the right lung tissue, from the apex to the base.

## 2. Scanning technique

Lugol's solution was previously administered to block the thyroidal uptake of <sup>131</sup>I-MAA. After assuring the uniformity of colloidal solution of <sup>131</sup>I-MAA by gentle shaking, a dose of 100 to 200 μC was injected intravenously in an

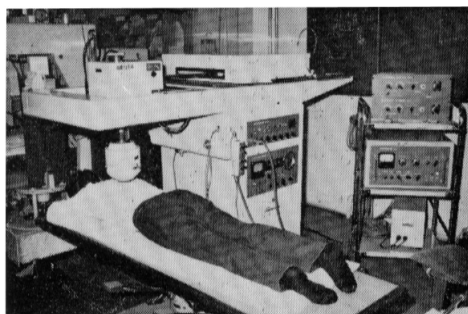


FIG. 1. Shimazu SCC-30 Scintillation Scanner

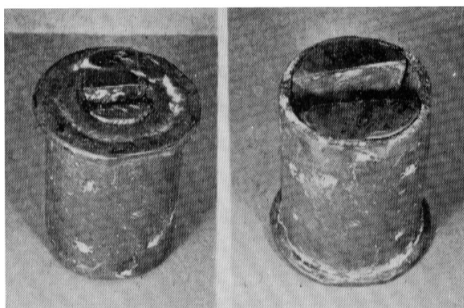


FIG. 3. Slitted collimator devised for right lung linear scanning.

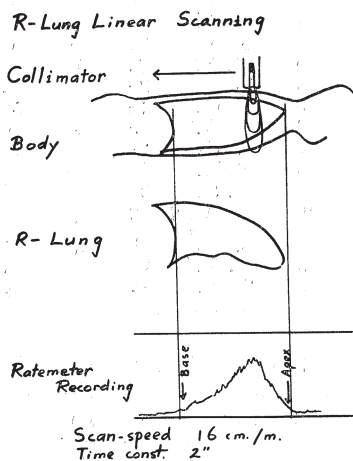


FIG. 2. Right lung linear scanning.

Radioactivity variations along a vertical segment of the right lung from apex to base are transcribed on a ratemeter record.

erect posture. Five minutes after the injection, patient was laid prone and the detector was mounted above his back.

Scanning of the lung was performed with a spacing of 3 mm, at a speed of 60 cm per min. and with adequate ratedown. Right lung linear scanning was carried out simultaneously from the apex to the base of the right lung at a speed of 16 cm per min with a time constant of 2 sec. The 7th cervical vertebral spinous process was chosen as a landmark of anatomical location and its position was transcribed to a scintigram or a ratemeter record. Chest X-ray was used to correct the parallax.

For the purpose of quantifying regional pulmonary blood flow, the ratemeter record obtained from this right lung linear scanning was divided into three equal segments from the apex to the top of the right diaphragmatic leaf. The ratio of concentration of radioactivity between the upper and lower thirds which is parallel to the distribution of arterial pulmonary blood flow, was calculated by planimetric integration of the area beneath the curve (Fig. 4) and was designated "U/L" -upper/lower ratio, following the method described by Friedman *et al.*<sup>11)</sup>

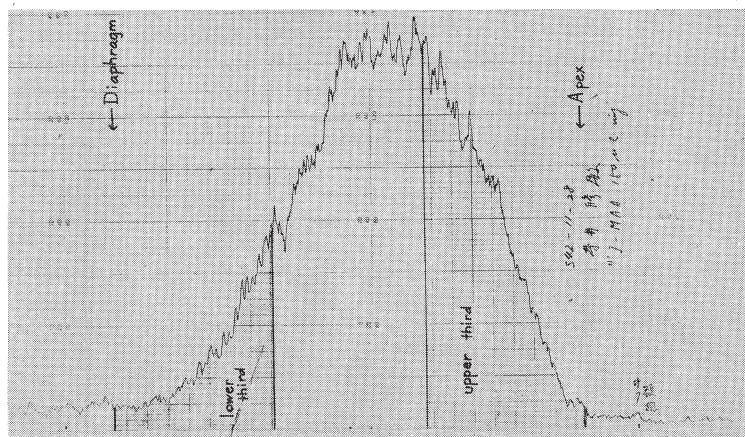


FIG. 4. The ratemeter record of right lung linear scanning was divided into three equal segments from the apex to the diaphragm and the ratio of radioactivity between the upper and lower thirds was calculated by planimetric integration of the area beneath the curve.

In order to avoid the radioactivity variations influenced by the enlarged cardiac silhouette in cardiac patients with pulmonary hypertension, observations and analyses of pulmonary blood flow in the left lung were abandoned.

#### RESULTS

As shown in Fig. 5, the ratio of  $^{131}\text{I}$ -MAA distribution in the upper third of the lung to that in the lower third (U/L) in an erect position was remarkably elevated in the majority of the patients with mitral valve disease, signifying that blood flow of the lower portion of the lung was extremely lessened while that of the upper portion increased. This is quite a reverse of normal pattern of pulmonary circulation in which hydrostatic gradient tends to decrease blood flow in the upper zone of the lung (Normal U/L value in three equal divisions of the erect lung had been calculated to be 0.3 to 0.5, as will be discussed later).

The highest U/L in severest mitral stenosis reached even 4.0, which means that the blood flow of the upper third of the lung is four times greater than that of the lower third against the influence of gravity. U/L in 39 patients with mitral valve disease ranged from 0.45 to 4.00 and averaged 1.47, about three to four times higher than the normal value.

In the ventricular septal defect with pulmonary hypertension group, however, the marked inversion of U/L, often seen in the mitral group, was not found even in the severest case with pulmonary arterial pressure surpassing

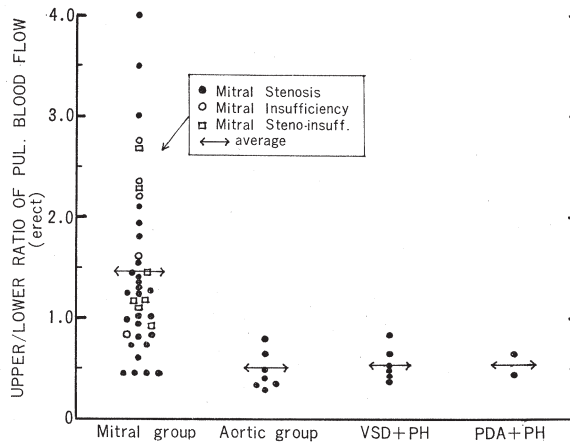


FIG. 5. Upper/lower ratio of pulmonary blood flow in various heart diseases.

Remarkable elevation of U/L was noted in the mitral valve disease group, whereas in the other groups none exceeded the value of 1.0.

100 mmHg. In this group, U/L ranged from 0.38 to 0.82, averaging 0.53, slightly higher than normal.

In two patients with patent ductus arteriosus with pulmonary hypertension U/L was 0.45 and 0.52.

In 7 patients with aortic valve disease, U/L ratio of pulmonary blood flow was also calculated as the control. None surpassed the value of 1.0, with the average of 0.48 ranging from 0.31 to 0.80 (Fig. 5).

Plane scintigram, photoscan, chest X-ray and right lung linear scan of a 23-year-old male with severe mitral insufficiency (Table 1, No. 20) are demonstrated in Figs. 6 A, B, C and D.  $^{131}\text{I}$ -MAA accumulation was remarkably shifted toward the middle and upper regions of the lung and blood flow in the lower zone was decreased. Right lung linear scan also showed the shift of radioactivity peak toward the apex (U/L = 2.27). The lung biopsy of the left lower lobe during the operation (Fig. 6 E) showed significant change of pulmonary vascular bed with cellular intimal proliferation, thickening of the media and fibrosis of the perivascular region. The patient underwent mitral valve replacement with a Kay-Shiley prosthesis but widespread atelectasis in the left lung that occurred after operation required the use of a respirator for two days.

In Figs. 7 A and B are shown scintigram and lung biopsy in a patient of severe mitral stenosis combined with aortic insufficiency (Table 1, No. 26). U/L was 3.50 and pathological changes were remarkable. The patient died 5



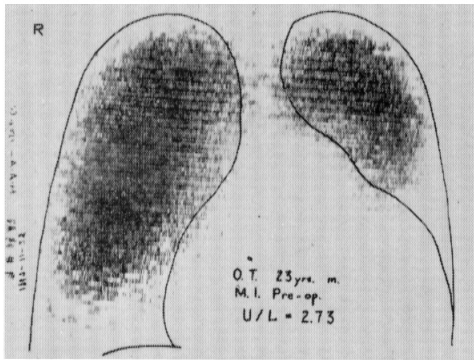


FIG. 6 A

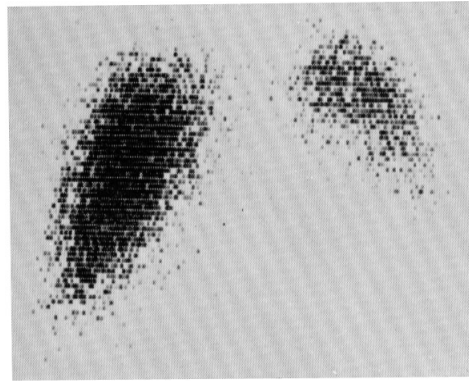


FIG. 6 B

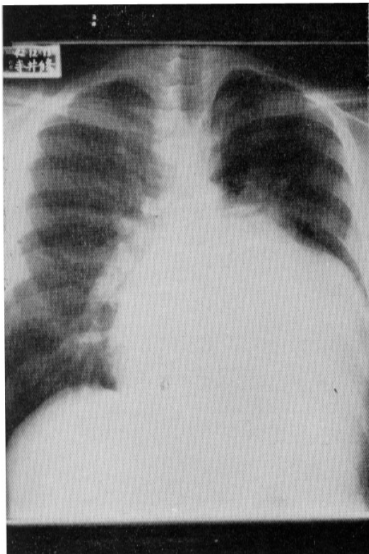


FIG. 6 C

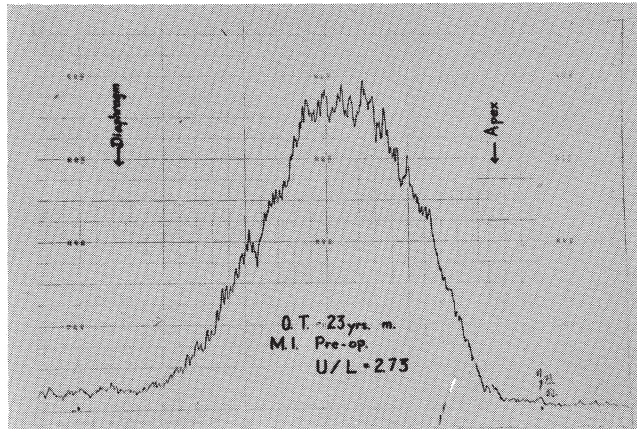


FIG. 6 D

FIG. 6. Scintigram (A), photoscan (B), chest X-ray (C), right lung linear scan (D) and lung biopsy (E) in a 23-year-old male with severe mitral insufficiency (Table 1, No. 20)

Blood flow in the lower zone of the lung was decreased (A) (B), radioactivity peak was shifted toward the apex (D) and cellular intimal proliferation, thickening of the media and fibrosis of perivascular region were found by lung biopsy (E).

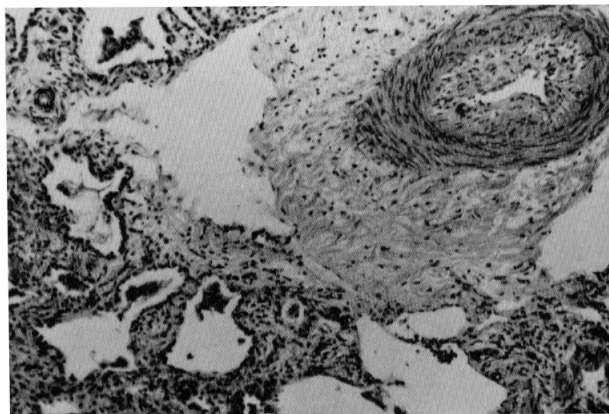


FIG. 6 E (Hx-E  $\times 400$ )

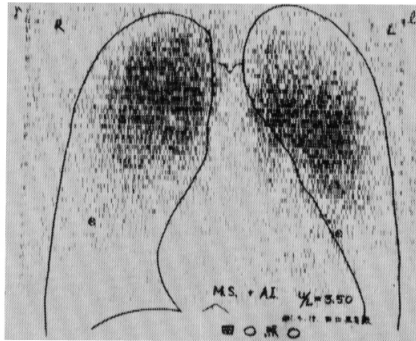


FIG. 7 A

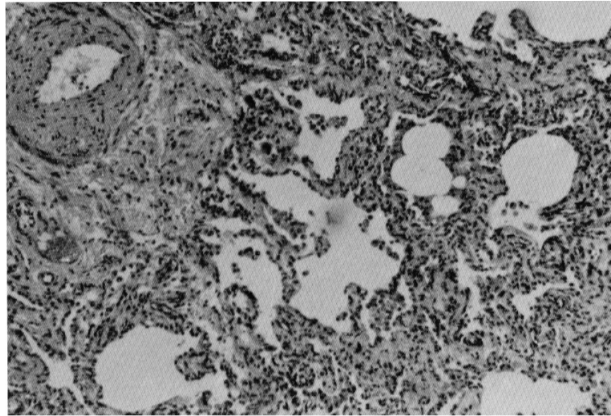
FIG. 7 B (Hx-E  $\times$ 400)

FIG. 7. Scintigram (A) and lung biopsy (B) in severe mitral stenosis combined with aortic insufficiency (Table 1, No. 26)

U/L was elevated to 3.50 (A) and proliferation of the intima and interstitial fibrosis were found by lung biopsy (B).

days after mitral commissurotomy and aortic valve replacement.

The highest U/L in this study (4.00) was recorded in a severe mitral stenosis patient (Table 1, No. 4) whose scintigram and lung biopsy during the operation are shown in Figs. 8 A and B. Narrowing of the vessel with intimal proliferation and fibrosis, thickening of the media and fibrotic changes of alveolar wall were main pathological findings. The patient died 3 days after commissurotomy due to severe pulmonary complications.

Fig. 9 is the montaged right lung linear scan of a moderate mitral stenosis patient (Table 1, No. 7) whose preoperative U/L (0.95) was lowered to 0.40, 4 months after successful commissurotomy. The shift of radioactivity peak toward the bottom of the lung proved increased blood flow to the lower region

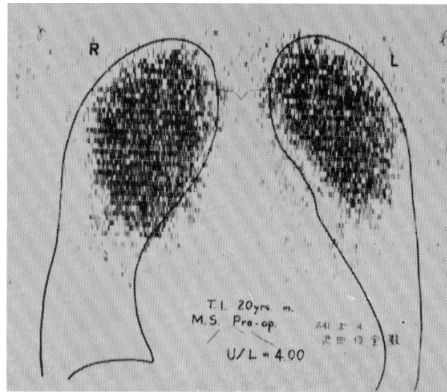


FIG. 8 A

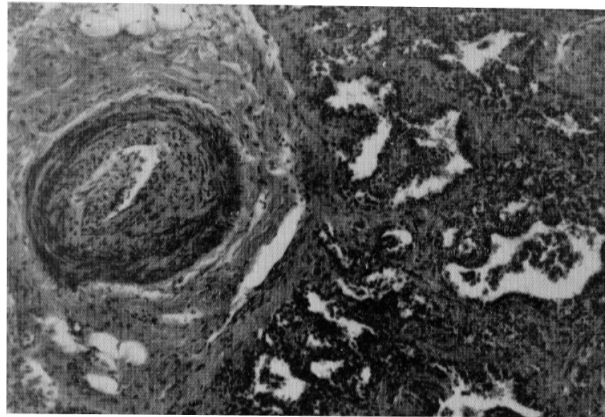


FIG. 8 B (Hx-E  $\times$  400)

FIG. 8. Scintigram (A) and lung biopsy (B) of a 20-year-old male with severe mitral stenosis (Table 1, No. 4)

Accumulation of  $^{131}\text{I}$ -MAA was remarkably shifted toward the upper lung (A) and narrowing of the vessel with intimal proliferation and fibrosis, thickening of the media and fibrotic changes of alveolar wall were seen (B).

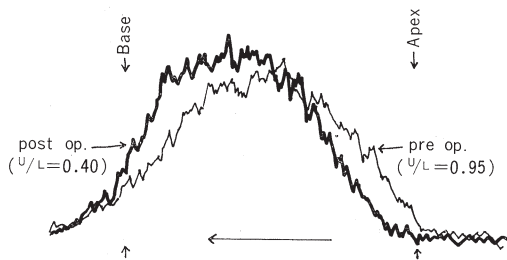


FIG. 9. A montaged right lung linear scan of a moderate mitral stenosis (Table 1, No. 7).

Preoperative U/L (0.95) was lowered to 0.40, 4 months after commissurotomy. Radioactivity peak is shifted to the bottom of the lung, showing the increase of blood flow in the lower region of the lung.

of the lung.

In a case of severe mitral stenosis with mean pulmonary arterial pressure of 80 mmHg and mean left atrial pressure of 32 mmHg (Table 1, No. 1), lung scan was performed twice, 2 months and 4 months after open commissurotomy. Preoperative U/L of 2.11 fell to 1.58 and to 0.86, respectively (Figs. 10 A and B). It is a very suggestive fact that, in such a severe case whose pathological changes of pulmonary vascular bed were far progressed (as shown in Fig. 10 C), pulmonary blood flow disorder can be improved in a comparatively short period of time. The radiocardiogram of the same subject recorded by Takahashi<sup>12)</sup> after intravenous RISA injection well coincided with this finding and showed a remarkable improvement of mean pulmonary circulation time (Fig. 10 D).

In 16 patients with mitral valve disease, lung scan was performed again 1 to 7 months after the operations. Preoperative U/L value, ranging from 0.45 to 2.73 and averaging 1.57, was significantly lowered to the average of 0.67,

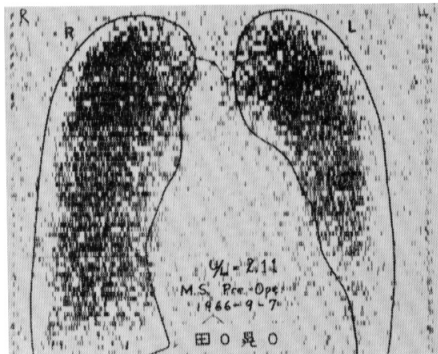


FIG. 10 A

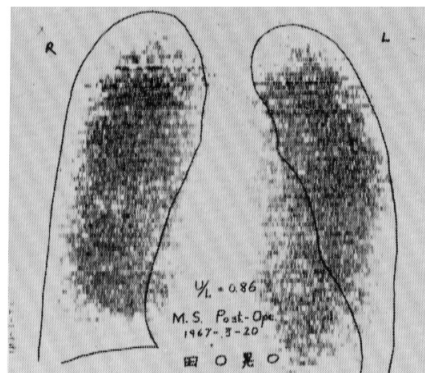


FIG. 10 B

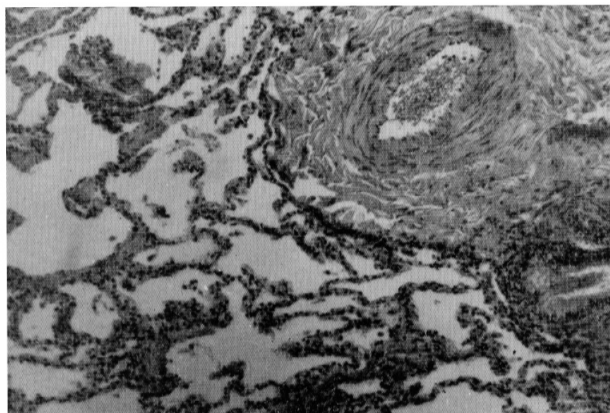


FIG. 10 C (Hx-E  $\times$  400)

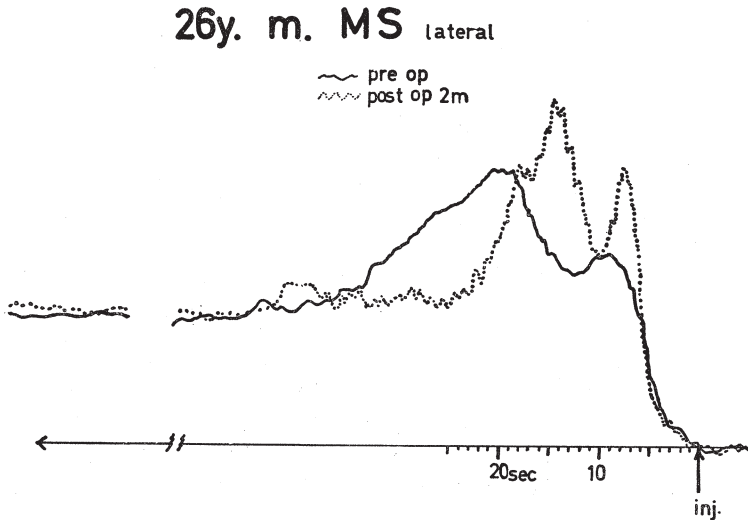


FIG. 10 D

FIG. 10. Preoperative (A) and postoperative (B) scintigram, lung biopsy (C) and radiocardiogram (D) in a 26 year-old male with severe mitral stenosis (Table 1, No. 1)

Postoperative scintigram showed the decrease of blood flow in the upper region of the lung and the increase in the lower lobe, nearing the normal pattern in an erect position (B). Intimal proliferation and media hypertrophy with fibrotic changes of the perivascular region were found by lung biopsy during the operation (C). Postoperative radiocardiogram showed a remarkable improvement in pulmonary circulation pattern with the shortening of mean pulmonary circulation time and sharply divided peaks of the right and left ventricles (D).

ranging from 0.31 to 1.50. Pre- and post-operative changes of U/L are shown in Fig. 11. In the group with U/L over 2.0, however, 4 patients out of 8 died during or within 5 days after operation due mainly to pulmonary complications. In those cases with U/L under 2.0, only 2 operative deaths resulted out of 18.

The correlation between preoperative U/L and mean left atrial pressure was studied in 39 patients with mitral valve disease (Fig. 12). A fairly good correlation was found between the two, but in the cases in which mean left atrial pressure was under 15 mmHg, no remarkable inversion of U/L was met. A steep elevation of U/L started when mean left atrial pressure exceeded 15 mmHg.

The correlation between U/L and mean pulmonary arterial pressure was also studied in 39 patients with mitral valve disease, 6 patients of ventricular septal defect with pulmonary hypertension and 2 patients of patent ductus arteriosus with pulmonary hypertension (Fig. 13). In contrast to the relatively fair correlation between U/L and mean left atrial pressure, mean pulmonary

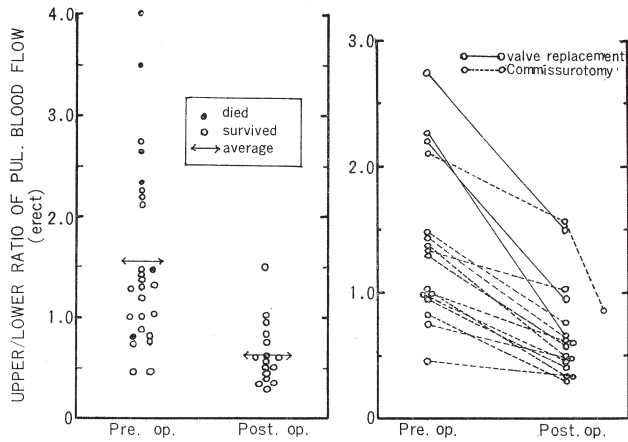


FIG. 11. Postoperative changes of U/L in patients with mitral valve disease.

Preoperative U/L average 1.57 was significantly lowered to 0.67. High operative mortality (4 out of 8) resulted in the group with U/L over 2.0, while in the group with U/L under 2.0, only 2 died out of 18.

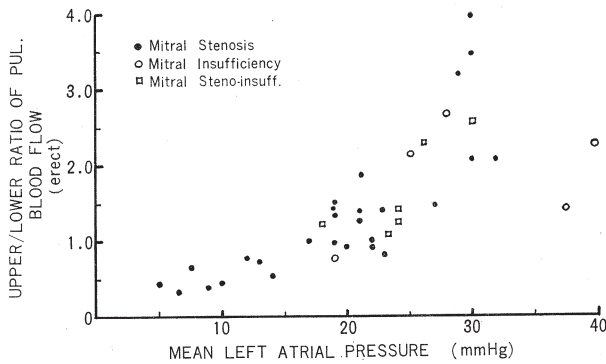


FIG. 12. Relationship between U/L and mean left atrial pressure in mitral valve disease.

U/L ratio showed a good correlation with mean left atrial pressure but in the cases in which mean left atrial pressure was below 15 mmHg, no marked elevation of U/L was found.

arterial pressure showed rather poor correlation with U/L, especially in the groups other than mitral valve disease. This discordance of correlation between the two, namely, U/L with mean left atrial pressure and U/L with mean pulmonary arterial pressure, provokes the speculation about the nature and mechanisms of pulmonary hypertension in various cardiac diseases, which will be discussed later.

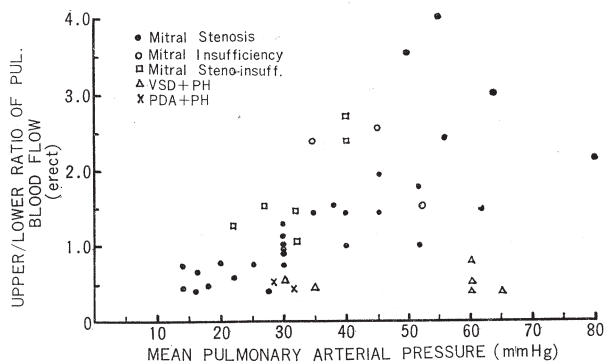


FIG. 13. Relationship between U/L and mean pulmonary arterial pressure in mitral valve disease, VSD+PH and PDA+PH.

U/L did not show so close correlation with mean pulmonary arterial pressure as with mean left atrial pressure. No remarkable elevation of U/L was found among the patients with VSD+PH and PDA+PH, despite their high pulmonary arterial pressure.

Correlation of U/L with MPCT (mean pulmonary circulation time) and PVR (pulmonary vascular resistance) was also studied in some of the patients in whom the radiocardiogram was recorded by Takahashi<sup>12)</sup> utilizing the radioisotope (RISA) dilution method. Both of them showed an excellent correlation with U/N, with one or two exceptions (Figs. 14 and 15).

Correlations of U/L with other factors, CTR (cardio-thoracic ratio), %VC (% vital capacity) and %FEV<sub>1</sub> (% forced expiratory volume at 1 sec) are shown in Figs. 16, 17 and 18. They all showed relatively fair correlation with U/L, implying that clinical severity also can be estimated by calculating U/L in the patients with mitral valve disease.

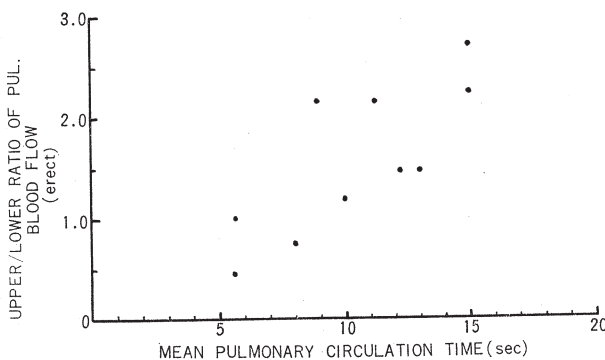


FIG. 14. Relationship between U/L and MPCT

U/L showed an excellent correlation with mean pulmonary circulation time.

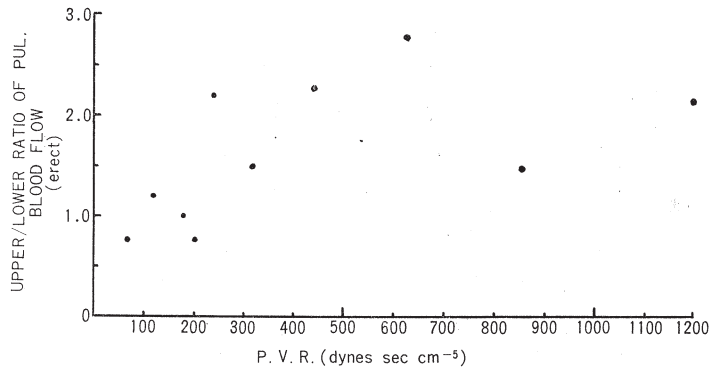


FIG. 15. Relationship between U/L and PVR.

U/L showed an excellent correlation with pulmonary vascular resistance but linearity was lost in the patients whose PVR exceeded 800 dynes sec cm<sup>-5</sup>.

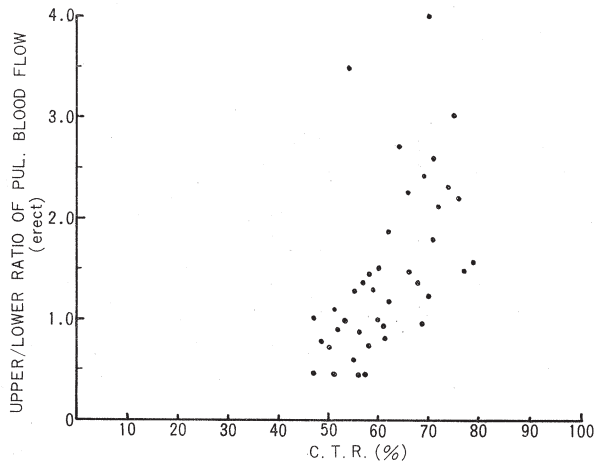


FIG. 16. Relationship between U/L and cardio-thoracic ratio.

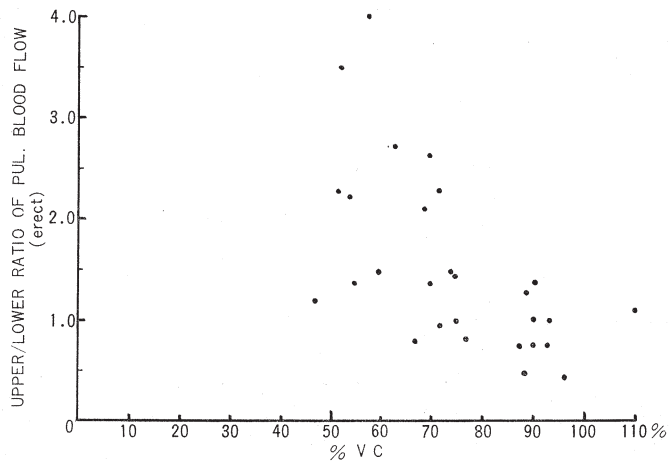


FIG. 17. Relationship between U/L and % vital capacity.



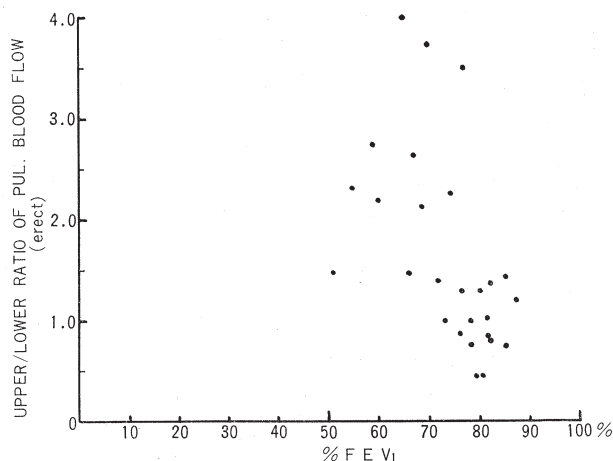


FIG. 18. Relationship between U/L and % forced expiratory volume at 1 second interval

#### DISCUSSION

The problem of pulmonary blood flow distribution in normal subjects has been extensively studied since the report of Martin *et al.*<sup>131</sup> in 1953, in which they first discovered the relatively poor perfusion of the upper lobe of the lung in the erect subjects by proving the significant difference of O<sub>2</sub> and CO<sub>2</sub> concentrations in expired air from upper and lower lobes. This finding was widely supported by many investigators with various methods and techniques, such as lobar bronchspirometry by Mattson and Carlens<sup>3</sup>, radioactive gas (<sup>15</sup>O) by West and Dollery<sup>14,15</sup>, <sup>133</sup>Xe by Ball *et al.*<sup>5</sup>. The reasonable explanation for this phenomenon, shift of blood flow toward the lower lobe of the lung in an erect position, would be that, pulmonary circulation being a relatively low pressure system, uniform distribution of blood flow cannot be maintained against hydrostatic gradient of gravity.

The deviation from this normal pattern of pulmonary blood flow distribution in the patients with mitral stenosis had been suspected by some of the investigators from the findings of chest X-ray<sup>2</sup>, pulmonary angiography<sup>16</sup>, and histological examination of the pulmonary vessels<sup>17</sup>. Their suspect from these findings that the upper lobe of the lung is more abundantly perfused than the lower in the patients with mitral stenosis was first confirmed by Dollery and West<sup>18</sup> who introduced the technique of actual pulmonary blood flow measurement by using radioactive gases (<sup>15</sup>O, <sup>133</sup>Xe).

In 1963, Taplin *et al.*<sup>9</sup> developed a method to produce large aggregates (10-50  $\mu$  in diameter) of human serum albumin and label them with <sup>131</sup>I. This material, referred to as <sup>131</sup>I-MAA, was first applied to scintillation scanning of

human lung by Wagner *et al.*<sup>10)</sup> in the same year, taking advantage of the specificity of this material that these sufficiently large particles lodged in the pulmonary capillary bed in the first passage through the lungs.

Though initially developed for the study of pulmonary embolism<sup>19)20)</sup>, this radioactive pharmaceutical has been widely applied not only to the study of pulmonary circulations but also to various fields of medicine including the study of lung carcinoma<sup>21)22)</sup>, tuberculosis<sup>23)</sup> and circulation study of the brain and kidney<sup>24)25)</sup>.

Ueda *et al.*<sup>26)</sup> improved the technique of <sup>131</sup>I-MAA preparation in 1964 and succeeded in making a product more reproducible and more selective to lung tissues by making the aggregates so uniform in size as to avoid the smaller particles to pass through the pulmonary capillaries and get captured in the liver reticulo-endothelial system. High selectivity (95 to 99% in lung tissues), excellent reproducibility, low radiation hazards (less than 0.1r to the patient in normal dose), low possibility of mechanical obstruction of the pulmonary capillaries and low antigenic activity were discussed and proved in detail elsewhere<sup>27)28)29)</sup>.

To utilize this material in the quantitative study of pulmonary blood flow, a basic principle of conservation of material must be considered. If a certain amount of material ( $Q$ ) flows into a region, some ( $Q_i$ ) will be accumulated in the region, some ( $Q_m$ ) will be metabolized, and the rest ( $Q_e$ ) will flow out of the region. Thus the basic kinetic equation will be<sup>30)</sup>,

$$Q/dt = Q_i/dt + Q_m/dt + Q_e/dt \quad (1)$$

Assuming that the material (<sup>131</sup>I-MAA in this case) is uniformly mixed with pulmonary arterial blood,  $Q/dt$  equals  $F \times C$  where  $F$  = blood flow and  $C$  = concentration of the material. Outflow of <sup>131</sup>I-MAA from the pulmonary capillaries is negligible and uniform distribution of MAA particles in the blood stream was proved by Wagner *et al.*<sup>31)</sup> using <sup>51</sup>Cr labeled red blood cells. So another study by Wagner *et al.*<sup>19)</sup>, which proved the negligibility of MAA metabolism rate during the first hour following injection, has enabled to simplify the equation (1) to

$$F \times C = Q_i/dt \quad (2)$$

which means that the rate of accumulation of the indicator is proportional to blood flow into the region and this forms the theoretical basis of the quantitative measurement of pulmonary blood flow by the <sup>131</sup>I-MAA scintillation scanning method.

On this principle, various quantitative studies on normal pulmonary distribution pattern have been made using <sup>131</sup>I-MAA. Though they were in general

accord that in normal supine subjects blood flow was almost evenly distributed through all the lungfield, the normal value of upper to lower ratio of blood flow in an erect position varied according to the reporters. Friedman *et al.*<sup>11)</sup> calculated U/L in three equal divisions of the lung as  $0.43 \pm 0.08$ , Ball *et al.*<sup>32)</sup> 0.3, Ueda *et al.*<sup>26)</sup> in two equal divisions 0.6 and West and Dollery<sup>14)15)</sup> in 9 equal divisions 0.11, respectively.

Investigations concerning the regional distribution of pulmonary blood flow in the patients with mitral valve disease have also been reported utilizing this material and technique<sup>11)26)33)</sup>. The results of these reports, which almost unanimously agreed that blood flow of the upper region of the lung was notably increased in severe mitral disease, coincided well with the findings of the present study. Their interests in these studies, however, were rather limited to the physiological aspects of specific circulation pattern deviation, and not much has so far been investigated as to the surgical consideration of the problem; that is, what significance this abnormal circulation pattern would bear on evaluating the operative risk and to what extent it could be recovered by successful surgical correction.

To discuss the reversibility of hemodynamic abnormality, the mechanism of this unusual vascular pattern must be taken into consideration first.

A variety of investigations have proved that infusion of hexamethonium<sup>34)35)</sup> or acetylcholine<sup>36)37)</sup> into the pulmonary artery can lower the elevated pulmonary artery pressure in severe mitral stenosis. This fact, along with the evidence of the same effect of 100% oxygen inhalation<sup>38)39)</sup>, is highly suggestive of the vasoconstriction factor taking part in the genesis of pulmonary hypertension.

West and Dollery<sup>40)</sup>, however, noticed in their experiment using isolated dog lung under induced pulmonary hypertension, that infusion of acetylcholine or isoproterenol into the pulmonary artery had no effect on altering the reversed blood flow pattern. Infusion of hypertonic urea into the pulmonary artery, on the contrary, produced a temporary increase of flow to the lower and dependent zone of the same lung. They further went on to prove that histological sections taken from the lower lobe by a rapid freezing method showed thick cuffs of edema around the pulmonary vessels. From these findings, they emphasized the importance of acute interstitial perivascular edema as a cause of the blood flow pattern abnormality.

On the other hand, Kondo<sup>41)</sup> and Sakakibara *et al.*<sup>42)</sup> proved in their detailed study on lung biopsy during the operation that pathological changes of the pulmonary vessels had a good correlation with pulmonary arterial pressure elevation. The present investigation has also proved that, in those cases where U/L ratio of pulmonary blood flow was markedly elevated, the pathological changes in the pulmonary arteries or arterioles were eminent. These evidences suggest that structural changes of the pulmonary vessels also play a part in

the mechanism of blood flow pattern alterations.

It would be a reasonable conclusion derived from these findings that these three factors, constriction of pulmonary arteries and arterioles, interstitial perivascular edema and pathological changes of pulmonary vascular bed, are combined in various degrees according to severity and duration of the disease and determine the abnormal circulation pattern in pulmonary hypertension with mitral valve disease.

A speculated mechanism is, therefore, that initial increase in left atrial pressure is passively transmitted to the pulmonary artery and when the pressure elevation reaches the level of plasma colloid osmotic pressure, edema fluid starts to leak from the pulmonary capillaries into the perivascular space, which, due to the hydrostatic influence of gravity, collects more in the lower and dependent portions of the lung. Continuation of this state will cause the hypoxic reflex vasoconstriction, the elevation of pulmonary vascular resistance and eventually the structural changes of both the pulmonary vessels and alveoli. Decreased blood flow in the lower zones is compensated by the relative increase in the upper and less affected portions of the lung. The fact evidenced in the present study that U/L elevation was found when mean left atrial pressure exceeded 15 mmHg gives support to this hypothesis.

It provokes a discussion of great interest what factor among the three plays a more dominant role in causing the elevation of U/L. As was evidenced in this study, the impressive improvement of U/L was seen in a comparatively short time after the operation even in the severe cases where pathological changes were manifest. This finding implies that the alteration in pulmonary blood flow pattern in mitral valve disease is more dependent on the primary changes caused by left atrial pressure elevation (perivascular edema and vasoconstriction), and that, though the secondary organic changes which follow may persist even after operation, the improvement of pulmonary circulation as a whole can be amply expected if the valve function is perfectly restored by surgical correction.

In the severest cases where U/L ratio of blood flow reaches even 4.0, the situation is different. Perivascular edema reaching its maximum, the structural changes now spread upwards to involve the middle and upper zones, leading to the devastation of the whole lung. High operative mortality in this study (4 out of 8) in the patients whose U/L surpassed 2.0 gives evidence to this conjecture. This finding implies that disturbance of pulmonary blood flow distribution pattern bears a great significance on the risk of a patient with severe pulmonary hypertension in the immediate postoperative period. It is also suggestive of the usefulness of U/L value in determining the operative indication and prognostic preestimate of patients with severe cardiac disease.

Another finding of interest in this investigation is the fact that the left to

right shunt groups showed relatively mild elevation of U/L even in the severest cases with high degree of pulmonary hypertension.

Hyperkinetic factors, not present in mitral valve disease, can account for this difference in pulmonary vascular pattern. Pulmonary hypertension associated with left to right shunt is caused by the increase of blood flow in the pulmonary circulation system and is therefore called pulmonary arterial hypertension or precapillary pulmonary hypertension. In this situation the factor of structural lesions of the pulmonary capillaries plays a more important role in maintaining and increasing the elevated pressure<sup>43)</sup>.

In mitral stenosis, on the contrary, where the disturbance of pulmonary venous drainage is the main cause of pulmonary hypertension (pulmonary venous hypertension or postcapillary pulmonary hypertension), perivascular edema can be more easily developed and hydrostatic gradient more likely affects the lower zones, resulting in the elevation of U/L ratio. Elevated left atrial pressure, therefore, is the determinant of U/L elevation, and the strange absence of correlation of U/L with pulmonary arterial pressure found in this study is thus understood.

A support to this hypothesis is gained from the evidence of Doyle *et al.*<sup>16)</sup> who reported that in rheumatic mitral stenosis pulmonary arterial narrowing was confined to the segmental arteries of the lower zones but that in congenital heart disease there was no difference among the various zones.

U/L ratio among the aortic valve disease patients in this study stayed almost within normal limits but in one case who showed the signs of left heart failure with left ventricular end-diastolic pressure of 20 mmHg, moderate elevation of U/L (0.80) was found. This evidence again indicates that pulmonary venous hypertension, the disturbance of pulmonary venous drainage caused by left atrial pressure elevation, is the determinant of U/L ratio of pulmonary blood flow.

#### SUMMARY

In 39 cases of mitral valve disease, 6 cases of ventricular septal defect with pulmonary hypertension and 2 cases of patent ductus arteriosus with pulmonary hypertension, regional pulmonary blood flow distribution was studied utilizing the method of scintillation scanning after intravenous injection of <sup>131</sup>I-MAA.

1) Remarkable increase of blood flow in the upper zones of the lung accompanied with decrease in the dependent zones was found in the majority of patients with mitral valve disease. Upper to lower ratio of blood flow (U/L) showed a good correlation with left atrial pressure and mean pulmonary circulation time but not with pulmonary arterial pressure.

2) In 16 patients with mitral valve disease, blood flow distribution was studied again after operation, which showed a remarkable recovery from abnormal pulmonary circulation pattern.

3) In patients with congenital heart diseases associated with severe pulmonary hypertension caused by left to right shunt, no marked elevation of upper to lower ratio of pulmonary blood flow was found. Upper to lower ratio of pulmonary blood flow also stayed within normal limits in 7 patients with aortic valve disease studied as the control, except in one patient who showed the signs of left heart failure with left ventricular end-diastolic pressure of 20 mmHg.

4) The mechanism underlying the derangement of pulmonary blood flow distribution was discussed and the role of primary factors (perivascular edema and vasoconstriction) was emphasized as the cause of the reversed pattern of pulmonary circulation.

5) In patients with upper/lower ratio of blood flow in an erect position over 2.0, 4 operative deaths out of 8 resulted, whereas in those with U/L under 2.0, only 2 died out of 18. The surgical significance of upper/lower ratio of pulmonary blood flow in evaluating the operative indication and prognostic preestimate was also discussed.

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