PULMONARY HYPERTENSION IN ACQUIRED VALVULAR CARDIAC DISEASE: EVALUATION BY A SCINTILLATION CAMERA TECHNIQUE

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Diagnosis of pulmonary hypertension is made when the mean pulmonary artery pressure exceeds 20–25/10–15 mm Hg (sys/dias) (*1,2*). There are several causes of increased pulmonary artery pressure. Broadly, they can be divided into increased pressure due either to increased blood flow or to increase in resistance to the flow. In the pulmonary circulation the resistance to flow can be pre- or postpulmonary capillary bed. Increased postcapillary resistance most often results from obstruction to pulmonary venous flow due either to disease of left atrium, left ventricle, or to mitral or aortic valve lesions.

Cardiac catheterization is the procedure most often used to measure hemodynamic alteration due to valvular cardiac disease. Even though catheterization data give useful and definite information, the procedure is potentially hazardous. Kerley and others were able to make a rough estimate of the pulmonary artery pressure by observing the horizontal lines at the costophrenic angle, now popularly called "Kerley B lines" (*3–6*). Radiographic assessment even though simple and nontraumatic is not sufficiently quantitative to be reliable. Ideally then, safe, reliable, quantitative, and nontraumatic techniques are required to assess the hemodynamic changes in cardiac disease.

Introduction of the scintillation camera has afforded a new tool for quantitative studies (*7–9*). Utilizing the fact that pulmonary perfusion in apical and basal regions is pressure dependent (*10–12*). we have devised a scintillation camera technique to assess pulmonary hypertension in acquired valvular cardiac disease. Utilizing this technique, we have studied 27 patients with aortic and mitral valve disease. The brief abstracts of this technique have already been published (*13,14*). The technical details are reported in this communication with special reference to the assessment of pulmonary hypertension in pre- and postsurgical treatment of acquired valvular cardiac disease. The camera technique is very useful in the followup of patients who undergo cardiac surgery for valve replacement.

MATERIALS AND METHODS

Patients were selected from the Cardiology Service of Wadsworth Veterans Administration Hospital. All patients had served in the military service for at least two years. There was no evidence of congenital heart disease at the time of their induction into military service. A total of 27 patients with acquired cardiac disease were studied. All except one were males with an age range of 27 to 79 years (mean 49 years). In one patient with a ventricular septal defect (VSD), the scintillation camera study and cardiac catheterization were repeated postoperatively, thus making 28 total studies (Table 1, Nos. 3 and 26 are the same patient before and after surgery, respectively). Eight normal subjects served as controls. Cardiac catheterization and scintillation camera studies were done during the same week, and there were no clinically recognizable change in the patients' status between the two studies. None of the patients were in cardiac failure at the time of these studies were done.

Of the 27 patients studied, eight had mitral valve disease (three mitral stenosis, three mitral regurgitation, and two had both stenosis and regurgitation). Another eight patients had aortic valve disease (five aortic regurgitation, three patients had both aortic stenosis and regurgitation). There were no patients with only aortic stenosis. Six patients had combined aortic and mitral valve disease (see Table 1). Two

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patients had angina pectoris and one had a ventricular septal defect (acquired after septal myocardial infarction). Pericarditis and cardiomyopathy were present in each patient.

Seven patients had definitive cardiac surgery. Only scintillation camera studies were obtained postoperatively, ranging in time between 1 and 40 weeks following cardiac surgery.

Cardiac catheterization studies. All patients in the present study underwent cardiac catheterization studies in the postabsorptive state. Premedication consisted of Vistaril 50–100 mg administered intramuscularly about 1 hr prior to cardiac catheterization. Right and left heart catherization was performed using conventional techniques. The intracardiac and arterial pressures were recorded by Statham transducer-model 23 Db with zero reference at the midchest level. Mean pressures were determined by electrical integration. In all patients, pulmonary artery wedge and mean pulmonary artery pressures were recorded. Cardiac output was determined using both Fick and indicator-dilution techniques.

Pulmonary vascular resistance (PVR) was calculated by the formula:

$$\text{PVR (mm Hg/liter/min)} = \frac{\text{mean pulmonary artery pressure} - \text{mean pulmonary artery wedge, or left atrial pressure}}{\text{cardiac output (liter/min)}}$$

or

$$\text{PVR (in dynes sec/cm}^{-5}) = \text{PVR (in units)} \times 80$$

Anger scintillation camera studies. The instrument employed in the study was the Anger scintillation camera (Pho/Gamma III Scintillation Camera System from Nuclear-Chicago) (*7–9*).

For each procedure, 300 μCi of ^{131}I-labeled macroaggregates of albumin (^{131}I-MAA, Squibb Albumatope, LS) were injected into an antecubital vein over a period of 2 min. The isotope was injected with the patient in the sitting position, and he remained in this position for 5 min.

Five minutes after injection, the patient was placed in the supine position on a cot mounted on wheels for easy maneuvering. For the anterior view a transverse line was drawn across the chest at the level of

TABLE 1. CARDIAC CATHETERIZATION, ANGER SCINTILLATION CAMERA DATA, AND CLINICAL DIAGNOSIS

No.	Patient	Age	MPA (mm Hg)	PAW (mm Hg)	Cardiac output (L/min)	Cardiac index (L/min/M^2)	PVR (mm Hg/ L/min)	Mean UZ/LZ ratio	Diagnosis
1	BE	59	54	37	2.9	1.5	6.0	1.37	MR + AR
2	MF	45	54	35	4.4	2.6	4.3	1.27	MR + AR + AS
3	BC	46	51	27	2.5	—	1.3	1.47	VSD
4	JW	38	53	25	3.6	1.8	8.0	1.20	MS + MR
5	IJ	45	27	22	3.5	1.9	3.4	1.38	MS + MR
6	NL	45	22	21	4.0	2.2	—	0.88	AS + AR
7	MJ	49	27	22	5.3	2.8	1.0	0.81	Cardiomyopathy
8	PJ	24	12	9	5.7	3.3	1.0	0.52	Pericarditis
9	NH	66	41	30	3.7	2.4	3.0	0.99	AR
10	PE	49	24	15	4.4	2.3	1.3	0.52	AR + AS + MS
11	HJ	41	55	34	—	—	—	1.42	MS
12	FF	49	68	27	6.1	3.1	4.3	0.86	MR
13	SE	50	49	32	6.9	3.3	2.8	1.32	MS
14	BR	79	36	29	3.0	1.76	—	0.66	AR
15	WR	56	22	17	4.3	—	1.0	0.51	MR
16	MM	40	42	39	3.7	—	0.8	1.41	MS + MR + AR
17	BO	60	21	15	4.6	—	2.5	0.74	AR
18	IK	42	18	11	4.7	—	—	1.07	AR
19	SA	56	18	11	4.1	—	2.0	0.69	Angina
20	GC	53	32	32	5.8	—	—	0.80	AR + AS
21	KJ	48	23	16	5.1	2.9	1.0	0.95	AR + AS
22	HE	54	18	15	3.2	1.8	—	0.41	MR
23	WS	42	20	18	3.5	1.2	2.0	0.90	MS
24	BJ	55	28	21	4.5	2.4	1.6	0.43	MR + AR
25	PO	44	30	26	3.6	1.9	1.0	0.88	MS + MR + AR
26	BC	47	26	13	4.3	—	3.0	0.99	VSD
27	CJ	53	36	22	5.6	2.5	2.5	1.27	AR
28	GC	50	21	21	4.3	2.1	2.3	0.45	Angina

MPA = Pulmonary artery mean pressure.
PAW = Pulmonary artery wedge pressure.
PVR = Pulmonary vascular resistance.
MS = Mitral stenosis.
MR = Mitral regurgitation.
AS = Aortic stenosis.
AR = Aortic regurgitation.
VSD = Ventricular septal defect.

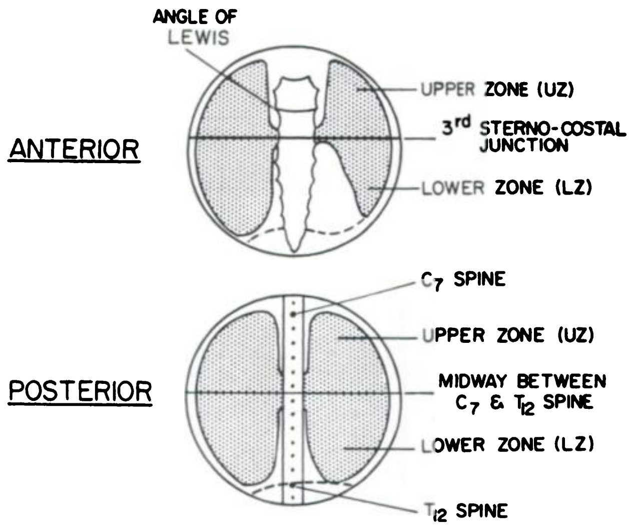

FIG. 1. Schematic diagram of clinical study. Anterior view—transverse line drawn across chest at third sternocostal junction. Scintillation camera crystal splitting line is adjusted to superimpose line. Posterior view—transverse line passes midway between cervical C_7 spine and thoracic T_{12} spine. Scintillation camera crystal splitting line superimposes this line in posterior view. Part of lung above lines is labeled upper zone (UZ) and part below is labeled lower zone (LZ). Ratio of UZ/LZ is obtained for anterior (A) and posterior (P) views. Mean of anterior (A) and posterior (P) ratios is obtained by expression (A + P)/2 which is called mean UZ/LZ ratio.

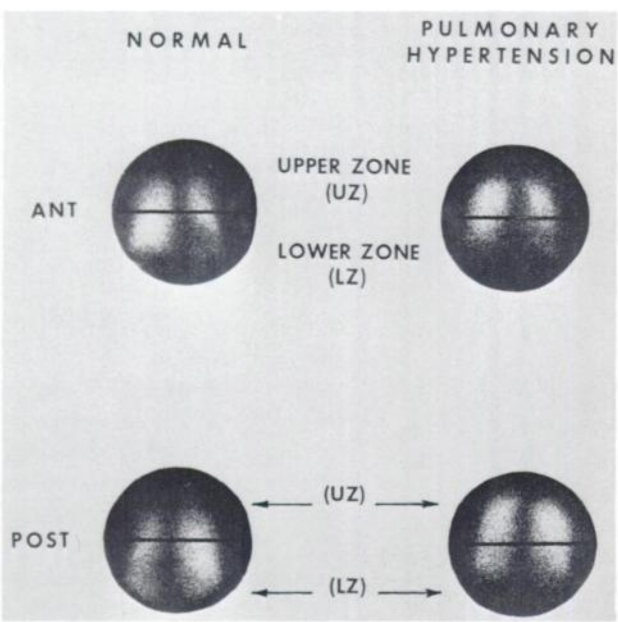

FIG. 2. Anger scintillation camera study in normal subjects and in patients with pulmonary hypertension. In normal subjects (left) most of radioactive material is concentrated over lower zone (LZ) and less activity is seen over upper zone (UZ) in both anterior and posterior views. Apical regions of both lungs show minimal radioactive material concentration. In patients with pulmonary hypertension (right) more radioactive material concentration is noted over upper zone (UZ) and less over lower zone (LZ).

the third sternocostal junction (Fig. 1). The position of the patient was adjusted so that the dividing line of the crystal passed over a transverse line across the chest dividing the lung fields into upper and lower zones. The face of the camera crystal was kept parallel to the ground. By keeping the face of the camera parallel to the ground in both anterior and posterior views, it was hoped to correct for thoracic kyphosis or lordosis. By using the diverging collimator it was possible to include the two lungs completely. The persistence scope was utilized for correct positioning of the patient so that all the borders of the lungs were included in both the views. In the posterior view, the patients were in the prone position. C_7 and T_{12} spines were marked. A transverse line was drawn across the back of the chest between C_7 and T_{12} spines. The patient was positioned so that the dividing line of the crystal was superimposed over this transverse line drawn between C_7 and T_{12} spines. The regions of the lungs above these transverse lines in both anterior and posterior positions were called the upper zones (UZ) and the regions below the transverse lines the lower zones (LZ). The ratio of the counts over the upper zone (UZ) to the lower zone (LZ) was obtained by the expression UZ/LZ. This ratio was obtained for both anterior (A) and posterior (P) views. The mean of these two ratios was calculated as from the expression $\frac{A + P}{2}$ (Fig. 2). This ratio was called mean UZ/LZ ratio. Starting on the day of the scintillation camera study, 5 drops of saturated solution of potassium iodide (SSKI) was given orally twice daily for 3 days to block the thyroidal uptake of ^{131}I.

To demonstrate the plane of the transverse lines in both anterior and posterior views, a thin lead ribbon was placed across the chest at the level of the third sternocostal junction in front and midway between C_7 and T_{12} spines in the back. A 6-ft anteroposterior chest x-ray was taken. It was noted that both lead markers were almost at the same level (Fig. 3), indicating that in both the anterior and posterior views, the plane of section was at the same level.

RESULTS

Table 1 shows the cardiac catheterization data, the type of valvular lesion, and the scintillation camera mean UZ/LZ ratio.

In eight normal subjects the scintillation camera mean UZ/LZ ratio was 0.64 ± 0.12 (range 0.41–0.8). Since the macroaggregate was injected with the patient in the sitting position, the radioactive material was in greater concentration in the lower than in the upper zones (Fig. 2). In three normal subjects the study was repeated within a week. In all three, the ratio obtained in the repeat study was judged to be close enough to the first to attest to

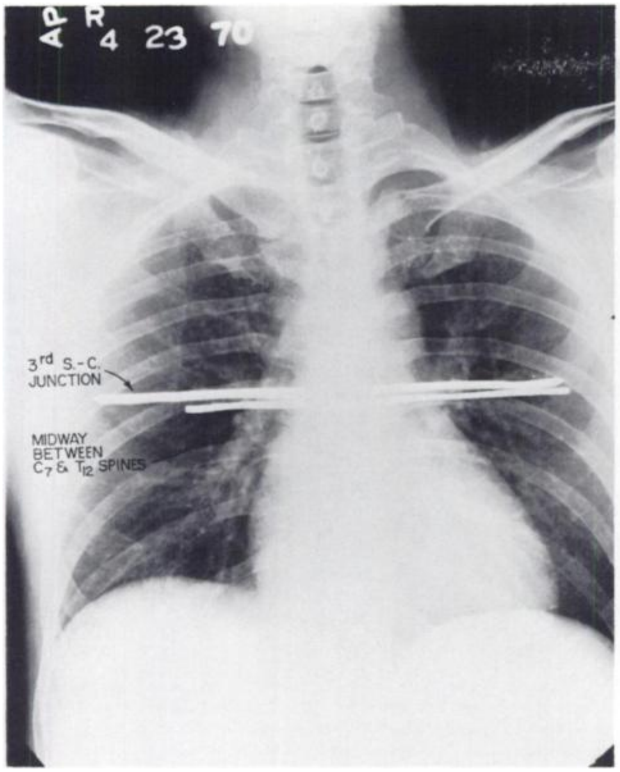

FIG. 3. Six-foot chest x-ray demonstrating identical plane of division of lungs in both anterior and posterior views. Thin lead ribbon is placed, one overlying transverse line at third sternocostal junction anteriorly, and another overlying transverse line midway between cervical C_7 and thoracic T_{12} spines posteriorly. X-ray tube was 6 ft away from subject. Both lines superimpose over one another indicating plane of division of lungs as upper zone (UZ) and lower zone (LZ) is same for both anterior and posterior views.

the reproducibility of the technique. In 27 patients with acquired cardiac disease, mean UZ/LZ ratio was 0.99 ± 0.38 (range 0.41–1.47) (Fig. 4). Unlike the normal subjects, more radioactivity, depending upon the severity of the pulmonary hypertension, was noted in the upper than in the lower zones. The mean UZ/LZ ratio (0.99) was significantly higher in acquired cardiac disease patients than in control subjects (0.64) ($p < 0.001$).

The relationship between the mean UZ/LZ ratio and pulmonary artery wedge and pulmonary artery mean pressure was linear. The correlation coefficient (r) between mean UZ/LZ ratio and pulmonary artery wedge pressure was $r = +0.64$ and was highly significant ($p < 0.001$) (Fig. 5). The correlation between pulmonary artery mean pressure and mean UZ/LZ ratio was $r = +0.63$ and the relationship was highly significant ($p < 0.001$) (Fig. 6). The correlation of mean UZ/LZ ratio and pulmonary vascular resistance was $r = +0.42$ ($p < 0.05$) (Fig. 7). There was negative correlation between mean UZ/LZ ratio and cardiac output $r = -0.34$. This correlation was poor and was not very significant. When the mean UZ/LZ ratio was compared with the cardiac index, the correlation was still poorer, $r = -0.062$, and was not significant. For the group of patients included in the study, the correlation between pulmonary artery wedge and pulmonary artery mean pressure obtained by means of catheterization was good with $r = +0.80$ ($p < 0.001$) (Fig. 8).

It was also evident that the two branches of the pulmonary artery divide in the plane of splitting the camera crystal. The upper zone (UZ) includes mainly the upper lobes and part of the middle lobe supplied by the superior division of the pulmonary artery, lower zone (LZ) includes the lower lobes and the remaining part of the middle lobe (on the right side) and lingular segment (on the left side) that are supplied by the inferior division of the two pulmonary arteries (Fig. 3).

Figure 9 shows the pre- and postoperative mean UZ/LZ ratio in seven patients who had cardiac valve replacement surgery. Usually it takes 4 to 5 weeks before there is any reduction of UZ/LZ ratio. By

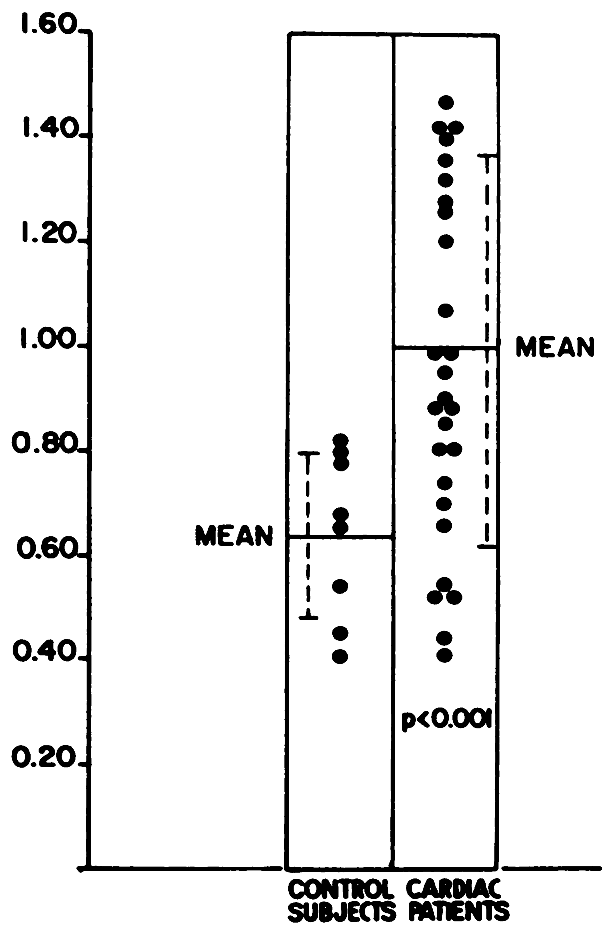

FIG. 4. Scintillation camera mean UZ/LZ ratio of control subjects and in patients with acquired cardiac disease. Mean UZ/LZ ratio for eight control subjects without cardiac-valvular disease is 0.64 ± 0.12 (range 0.41–0.82). Mean UZ/LZ ratio for patients with acquired cardiac disease is 0.99 ± 0.38 (range 0.41–1.47). Difference between mean is highly significant $p < 0.001$.

about 6 months after surgery, the UZ/LZ ratio returns to normal range. The mean UZ/LZ ratio was correlated with clinical improvement. The return of mean UZ/LZ ratio was associated with good surgical benefit and clinical recovery.

DISCUSSION

Of several causes of pulmonary hypertension, the one which concerns the physician most is valvular cardiac disease, especially mitral and aortic valvular disease. These cardiac valvular diseases are amenable to surgery and pulmonary hypertension can be cured if treated by prosthetic valve replacement of the diseased valve. At present, cardiac catheterization is the only definitive procedure which gives the quantitative data on the severity of hemodynamic changes associated with valvular cardiac disease. As mentioned earlier, this procedure is not without complications and is potentially hazardous. After the replacement of the cardiac valves, the hemodynamic alterations are assessed mainly clinically. The clinical evaluation is subjective. Frequent catheterization is not resorted to for the followup because of its associated complications. The scintillation camera technique described here appears to offer a safe and quantitative procedure needed for pre- and postoperative assessment of valvular cardiac disease.

When the pulmonary venous pressure is increased either because of mitral or aortic valvular disease (stenosis or regurgitation, or both), the pressure is transmitted back to the pulmonary capillary bed and finally is reflected in increased pulmonary artery mean and pulmonary artery wedge pressure. The increased pressure in the pulmonary artery overcomes the effect of gravity and results in reversal of flow to the apical and basal regions. Intravenously injected macroaggregated human serum albumin labeled with radioactive ^{131}I reflects the regional pulmonary blood flow (*15*). This is seen very clearly in Fig. 2. By this technique, in addition to obtaining the ratio of the upper zone to the lower zone, the activity is seen visually, confirming quantitative data obtained.

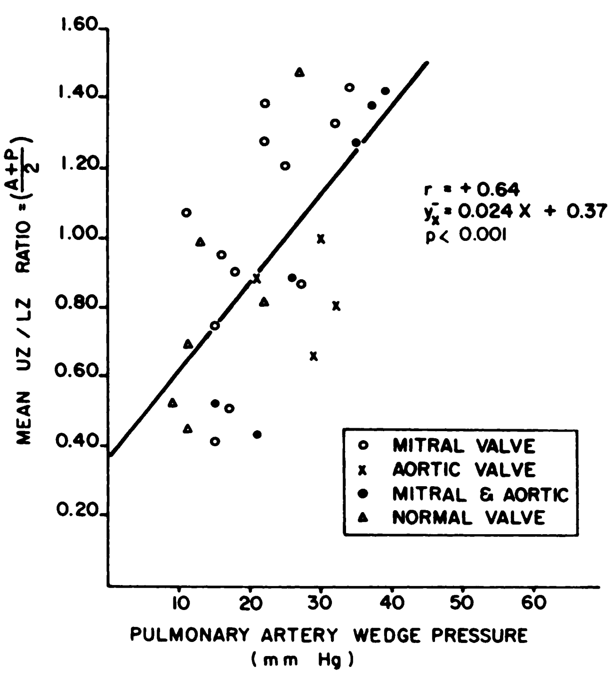

FIG. 5. Correlation of pulmonary artery wedge pressure and Anger scintillation camera mean UZ/LZ ratio. Pulmonary artery wedge pressure on x-axis and Anger scintillation camera mean UZ/LZ ratio on y-axis. Correlation coefficient (r) = +0.64. Correlation is highly significant with $p < 0.001$. Solid line represents regression line.

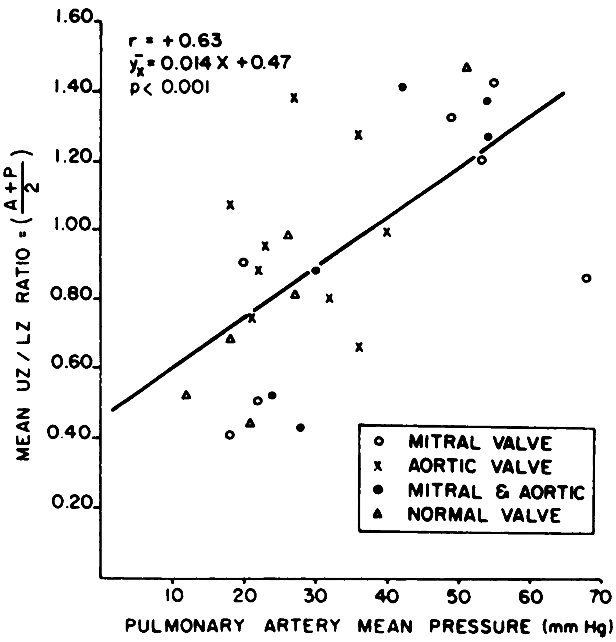

FIG. 6. Correlation of pulmonary artery mean pressure and Anger scintillation camera mean UZ/LZ ratio. Pulmonary artery mean pressure on x-axis and Anger scintillation camera mean UZ/LZ ratio on y-axis. Correlation coefficient (r) = +0.63. Solid line is regression line. Correlation is highly significant with $p < 0.001$.

In both anterior and posterior views, the transverse line divides the lung parenchyma at the same plane as evidenced in Fig. 3. The upper zone (UZ) includes the upper lobe and part of the upper part of the middle lobe. The lower zone (LZ) includes the lower lobe and the remaining part of the middle lobe on the right and lingular lobe of the left side.

There is clear separation of the mean UZ/LZ ratio of the normal people and those with pulmonary hypertension. The mean UZ/LZ ratio is related linearly to pulmonary artery wedge and pulmonary artery mean pressure (Figs. 5 and 6). There is close correlation of scintillation camera mean UZ/LZ ratio with pulmonary artery wedge (r = 0.64) and pulmonary artery mean pressure (r = 0.63). It is possible then after obtaining the scintillation camera mean UZ/LZ ratio to calculate with confidence ($p < 0.001$) the pulmonary artery wedge and pulmonary artery mean pressure. Friedman and Braunwald studied the regional pulmonary blood flow with a conventional rectilinear scanner. They studied patients with only mitral valve disease (*16*). The reason for not including the patients with aortic valve disease was not mentioned in their study. Friedman and Braunwald obtained the ratio of the count over upper one-third of the lung to the lower one-third. The ratio correlated well with left atrial pressure ($r = 0.91$). Correlation with mean pulmonary artery pressure was only 0.68. The higher correlation obtained with left atrial pressure in their study is probably due to the selection of patients as they included only mitral valve disease and totally excluded the patients with aortic valve disease. The reversal of pulmonary blood flow is probably dependent upon the pressure increase in the pulmonary artery irrespective of the cause, whether it is mitral or aortic valve disease. Hence, we have included patients with all types of acquired cardiac disease. This provides the basis for application of the scintillation camera technique in assessing pulmonary artery mean and pulmonary artery wedge pressures in a wide variety of clinical settings. In this study the variation of pulmonary artery mean pressure and pulmonary artery wedge pressure obtained during cardiac catheterization is seen in Fig. 8. The correlation coefficient between these two parameters measured directly during catheterization is 0.80.

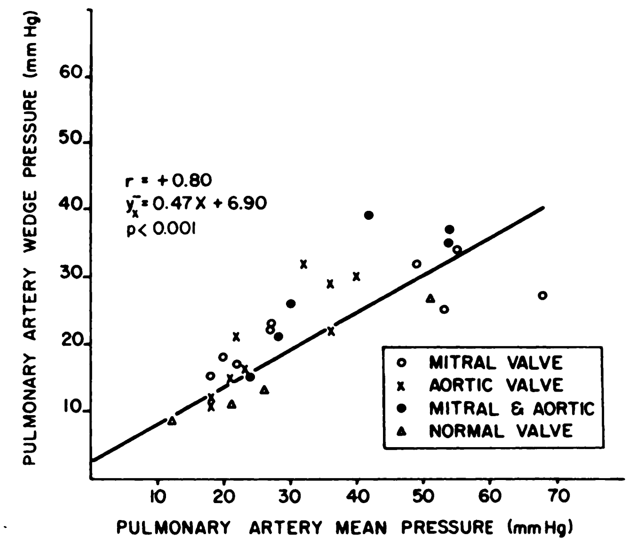

FIG. 8. Correlation of pulmonary artery mean and pulmonary artery wedge pressure obtained during cardiac catheterization. For group of patients studied, pulmonary artery mean pressure is on x-axis and pulmonary artery wedge pressure on y-axis. Correlation between pressures is good $p < 0.001$ and correlation coefficient $(r) = +0.80$. Solid line is regression line.

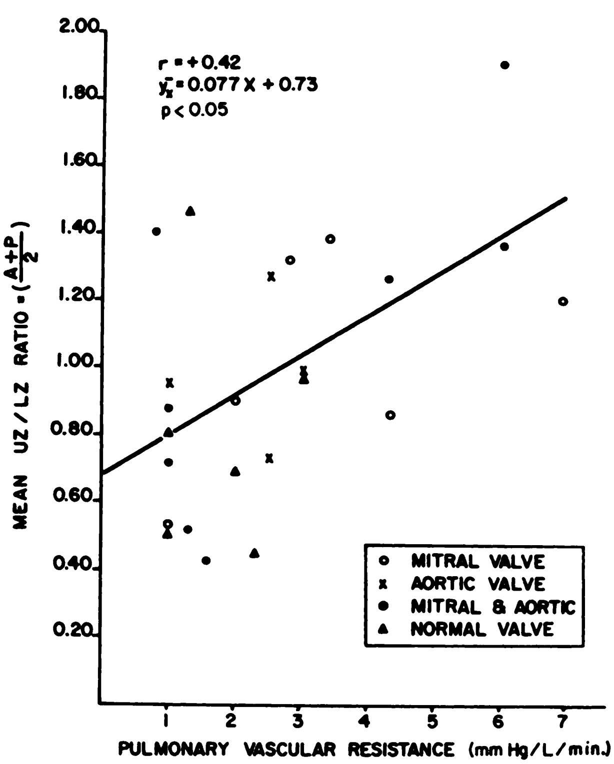

FIG. 7. Correlation of pulmonary vascular resistance and Anger scintillation camera mean UZ/LZ ratio. Pulmonary vascular resistance (mm Hg/liter/min) is on x-axis and Anger scintillation camera mean UZ/LZ ratio is on y-axis. Correlation coefficient $(r) = +0.42$ and is significant ($p < 0.05$). Solid line represents regression line.

Cardiac valve replacement and postoperative followup. Seven patients had cardiac valvular surgery. The type of valve lesion and mode of surgical therapy are seen in Fig. 9. During the first 3–4 weeks following surgery, there is no appreciable change in scintillation camera mean UZ/LZ ratio. This is probably due to the immediate postoperative status during which time these patients may have postoperative atelectasis, etc. The mean UZ/LZ ratio returns to a normal range 24–40 weeks after surgery. In every case the return of the mean UZ/LZ ratio is associated with good surgical benefits as assessed clinically. Three patients (D, E, and F in Fig. 9) were lost to followup for late studies. Patients were followed postoperatively by only the scintillation camera study. As these patients were doing well clinically, it was felt unethical to subject them to a potentially hazardous procedure like cardiac catheterization. One patient with centricular septal defect (VSD) (Patient Nos. 3 and 26 in Table 1) had preoperative mean UZ/LZ ratio of 1.47. His preoperative pulmonary artery mean and wedge pressure were 51 and 27 mm Hg, respectively. After the correction of VSD, 6 weeks later the mean UZ/LZ ratio had decreased to 0.99. The cardiac catheterization showed the reduction of pulmonary artery mean and pulmonary

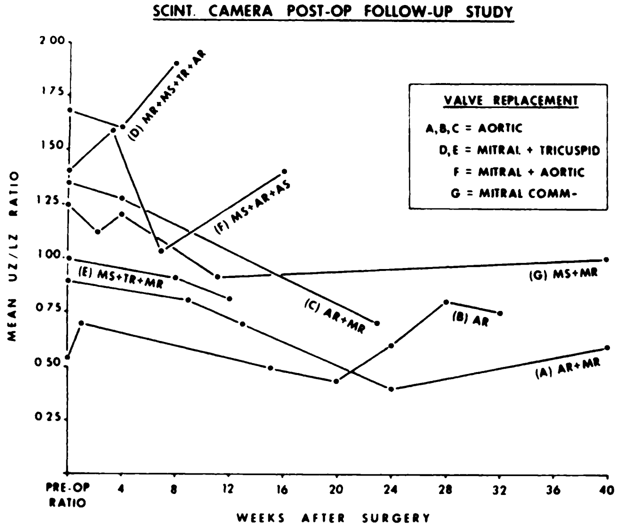

FIG. 9. Pre- and postoperative mean UZ/LZ ratios. Note reduction of mean UZ/LZ ratio to normal range after cardiac valve replacement. No appreciable change in mean UZ/LZ ratio during first 4–5 weeks following surgery. Mean UZ/LZ ratio returns to normal range after 16–24 weeks. Reduction of mean UZ/LZ ratio is associated with good clinical recovery.

artery wedge pressure to 26 and 13 mm Hg, respectively.

The pulmonary vascular changes observed in acquired cardiac valvular disease are reversible if the cause is removed. This is established by the fact that the mean UZ/LZ ratio returns to the normal range after cardiac valve replacement or repair.

Potential application. The scintillation camera technique may be of practical value in the clinical assessment of patients with acquired cardiac valvular disease. Many hospitals and clinics are now using the scintillation camera as a standard instrument in their nuclear medicine departments. The scintillation camera technique is far simpler than the technique that employs a rectilinear scanner (*16*). In each view the counts are taken for 200 sec. Within this time 50,000–100,000 counts are accumulated. In each case, the total study time is not more than 10–15 min. Any anatomical variation due to thoracic kyphosis will be corrected by taking an anterior and a posterior view.

Initially, we started with ^{131}I-labeled human serum albumin and therefore, we continued to use it throughout the present study. However, ^{99m}Tc-labeled albumin or sulfur colloid macroaggregates can replace the ^{131}I-labeled compound and perhaps be an even better agent. By using a larger amount of ^{99m}Tc-labeled compound, the lungs are better visualized. Instead of 200 sec, only 45–60-sec counts are adequate. Use of ^{99m}Tc obviates the need for supersaturated potassium iodide solution after the study.

The close correlation of the mean UZ/LZ ratio and the pulmonary artery mean and wedge pressure serves to estimate the severity of hemodynamic changes in cardiac valvular disease. The scintillation camera technique may serve as a screening procedure before cardiac catheterization. For the postoperative followup of patients when there is no indication for a major procedure like cardiac catheterization, the scintillation camera technique may be employed to follow the clinical course of patients subjected to surgery.

CONCLUSION

Pulmonary hypertension in acquired valvular cardiac disease has been assessed in 27 patients by a scintillation camera technique. A mean UZ/LZ ratio was obtained by dividing the counts from upper half of the lung field by the counts over the lower half. The mean UZ/LZ ratio correlates well with pulmonary artery mean and wedge pressure. After corrective surgery of the cardiac valve, the mean UZ/LZ ratio decreases and returns to normal range in patients judged clinically to have good surgical benefits.

The procedure is simple, nontraumatic, and more quantitative than the conventional radiographic procedure and less hazardous than cardiac catheterization. The pulmonary artery mean and wedge pressure can be estimated by obtaining the scintillation camera mean UZ/LZ ratio.

The scintillation camera technique is useful in the postoperative followup of cardiac surgery patients and may be useful as a screening procedure before cardiac catheterization.

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