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Research Article

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Regional Lung Function in Patients with Mitral Stenosis Studied with Xenon^{133} during Air and Oxygen Breathing *

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In a normal man sitting upright, pulmonary blood flow per unit volume of lung is several times greater in the lower zones of the lungs than in the upper (1, 2). Dollery and West (3) have shown that in patients with mitral stenosis this pattern is often reversed and that the upper zones may have several times the blood flow per unit volume of the lower zones. Two explanations for this finding have been suggested. West, Dollery, and Heard (4) have shown that a similar reversal of flow pattern can be produced in an isolated dog lung by sustained elevation of the pulmonary vein pressure, causing perivascular edema in the dependent portion. They suggested that a similar process may cause the increased vascular resistance in the lower zones in patients with mitral stenosis. Another theory proposes that vascular engorgement and edema in the lung bases cause a local loss of compliance or an increase in airway resistance, and the resultant underventilation and hypoxia could cause vasoconstriction in these regions (5). This is consistent with the observations that oxygen breathing can reduce vascular resistance in some cases of mitral stenosis (6–8) and that infusion of acetylcholine into the pulmonary artery may simultaneously lower pulmonary arterial pressure and reduce arterial oxygen saturation (5, 9, 10). The fall in arterial saturation was attributed to the relief of hypoxic vasoconstriction in underventilated lung units (9).

New techniques based on the inhalation or intravenous injection of radioactive gas to study the distribution of ventilation and blood flow in the lung might provide some evidence in favor of one or the other of these theories. Dollery and West (3) using such a method found that the abnormality of blood flow distribution tended to be more marked in pulmonary hypertensive patients. No comparison has been made between the blood flow pattern and left atrial pressure or pulmonary vascular resistance, however, and these measurements might be more relevant. Apart from two single reports (2, 11), there have been no observations of regional ventilation in mitral stenosis. If selective reduction in the ventilation of the lower zones were the cause of regional hypoxia, as suggested above, it should be detectable by this technique. Furthermore, if lower zone hypoxia were initiating vasoconstriction, this should be relieved by oxygen breathing, and the flow distribution should return towards normal.

We have studied 15 cases of mitral valve disease by the xenon^{133} technique of Ball, Stewart, Newsham, and Bates (2) and have attempted to relate the blood flow distribution to the regional distribution of ventilation and to hemodynamic observations made at cardiac catheterization. The influence of oxygen breathing on pulmonary hemodynamics and on blood flow distribution was also studied.

Methods

Patient selection. Fifteen patients have been studied (Table I). In eight of these, mitral stenosis was the only valvular abnormality, and in 14 it was the dominant lesion. Clinically the mitral valve disease was considered moderately severe to very severe, and all but three subsequently underwent a mitral valvotomy. One patient (No. 13) had moderate left lower lobe bronchiectasis. Routine pulmonary function tests were done by methods

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TABLE I

*Clinical and routine pulmonary function data**

Patient	Age	Sex	Height	BSA	Clinical diagnosis	Lung function test (per cent predicted value)					
						VC	FRC	RV	MMF	ME	Dco
			cm	m^2							
1	44	F	157	1.68	MS	76	196	296	42	62	101
2	46	M	169	1.65	MS	76	114	145	100	111	88
3	33	F	145	1.35	MS						
4	31	M	177	1.92	MS, MI	96	113	132	67	86	88
5	40	M	173	1.73	MS, MI, TI	53	94	128	18	85	65
6	34	F	159	1.25	MS	79	103	128	78	88	54
7	43	F	157	1.51	MS	65	110	160	54	65	84
8	45	F	161	1.62	MS						
9	40	F	162	1.60	MI, MS	75	95	118	130	93	
10	28	F	155	1.35	MS, MI	76	102	116	81	101	72
11	55	M	175	1.95	MS, MI, AI	75	63	68	143	114	164
12	53	F	155	1.63	MS	71	92	120	30	73	153
13	24	F	158	1.50	MS†	39	86	145	54	77	84
14	48	F	159	1.38	MS, TI	56	68	79	68	98	54
15	36	F	152	1.45	MS, MI	83	76	93	88	90	84

* MS = mitral stenosis; MI = mitral insufficiency; AI = aortic insufficiency; TI = tricuspid insufficiency; VC = vital capacity; FRC = functional residual capacity; RV = residual volume; MMF = maximal mid-expiratory flow rate; ME = mixing efficiency; Dco = steady-state diffusing capacity at rest.
† Left lower lobe bronchiectasis.

described elsewhere (12–14) on all but two (see Table I) and showed abnormalities similar to those previously described in this condition (15).

Hemodynamic data. Cardiac catheterization in the supine posture was carried out in all but one of the patients (Table II). The cardiac output was measured by the direct Fick method, oxygen consumption being determined by analysis of expired air collected for 2 minutes. In 11 patients, observations were repeated after 100% oxygen had been breathed for 20 to 30 minutes. Since oxygen consumption cannot be measured by expired gas analysis during oxygen breathing, it was necessary to measure the oxygen uptake from a closed circuit spirometer system. This measurement was not made in some of the patients, in whom it was assumed that the oxygen consumption after 25 minutes of oxygen breathing was the same as on air, an assumption supported by the observations of Bateman, Davidson, Donald, and Harris in patients with mitral stenosis (9). During oxygen breathing the oxygen content of blood samples

TABLE II

*Hemodynamic data**

Patient	Air						Oxygen					
	Pressure						Pressure					
	PAs	PAd	PAm	PCm	$\dot{Q}c/m^2$	PVR	PAs	PAd	PAm	PCm	$\dot{Q}c/m^2$	PVR
	mm Hg				*L/min*	*dyne-sec-cm⁻⁵*	*mm Hg*				*L/min*	*dyne-sec-cm⁻⁵*
1	54	24	28	14	3.4	192	42	20	28	18	2.7	168
2	65	35	50	30	3.2	300	60	34	42	26	2.8	248
3	62	22	38	20	2.6	410	65	25	36	20	3.4	298
4	45	20	36	22	3.2	192	43	22	29	25	2.3	71
5	130	60	80	27	1.2	2,020	94	45	55		1.4	
6	51	25	33	18	2.0	480	47	19	28	13	2.2	544
8	25	15	17	11	1.8	220	22	12	15	12		
9	50	28	31	14†	2.6		42	20	28		2.9	
10	83	37	60	25†	4.5	266						
11	44	22	32	21	3.5	98						
12	52	27	35	17	3.2	294	43	20	31	17	2.6	268
13	47	23	36	19	3.1	295	29	14	22	16	5.0	64
14	80	36	57	18	1.2	2,504	70	55	57	18	1.5	1,502
15	75			17†								

* PAs = pulmonary arterial systolic; PAd = pulmonary arterial diastolic; PAm = pulmonary arterial mean pressure; PCm = pulmonary capillary "wedge" pressure; $\dot{Q}c/m^2$ = cardiac index; PVR = (PAm − PCm) × 80/$\dot{Q}c$, pulmonary vascular resistance.
† Left atrial mean pressure.

was measured by the method of Van Slyke and Neill (16) and during air breathing by the spectrophotometric method of Nahas (17). Mean pressures were obtained by electrical integration with an end-hole catheter lying in the pulmonary artery, and in the pulmonary capillary "wedge" position.

Xenon studies. The procedure and apparatus employed have been described elsewhere (2) The patients sat upright [1] in a specially constructed chair, and six collimated scintillation detectors were placed over the posterior chest. Their position was located as described by Ball and associates (2) with the aid of a 6-foot posterior-anterior film of the chest taken at full inspiration. The fields covered by these detectors have been designated "upper," "middle," and "lower" zones on each side. Another detector continuously recorded the activity of the inspired gas. The pulses from the scintillation detectors and a volume tracing from the spirometer were recorded on a multichannel magnetic tape, and the information from any four channels could be played back simultaneously through rate meters to a direct-writing recorder.

Regional blood flow was measured by injecting about 0.5 mc of xenon dissolved in saline through a polyethylene catheter previously placed in an antecubital vein. The xenon was then rapidly flushed in with approximately 15 ml of normal saline. As the injection was made, the patient was instructed to breathe in slowly to full inspiratory capacity and to hold his breath with the glottis open while the count rate was continuously recorded over each lung zone. Although there was no way of ascertaining that the patient did not close his glottis on a given breath hold, several practice runs were done in an attempt to avoid it.

The regional distribution of a single breath of inspired gas was determined by the patient inhaling from the end of a normal expiration to full inspiratory capacity from a spirometer circuit containing 0.3 to 0.5 mc of xenon per L of air (see below for an explanation of the calculations).

The dynamic index of ventilation (18) was determined by the patient rebreathing at his normal depth and frequency from the circuit until no further change in the regional concentration of radioactive xenon took place. The rate of increase in concentration over each lung zone during this period was an index of regional ventilation. When equilibration was complete, the regional chest count rate was recorded while the patient held his breath at full inspiration. This permitted the ratio of chest count rate to local xenon concentration (assumed at equilibration to be equal to the spirometer circuit concentration) to be computed for each region of the lung at this lung volume (total lung capacity), thereby correcting for differences in the geometry and volume of the counter fields. The single breath and perfusion studies were then repeated in an identical fashion after the patient had breathed oxygen for at least 20 minutes, the spirometer circuit being filled with oxygen containing 0.3 to 0.5 mc per L of xenon.

The perfusion studies were performed in duplicate on room air and oxygen in all patients. If the duplicates, either during air or oxygen breathing, failed to agree within 10% of the mean, the values were not used in the subsequent analysis of the effect of oxygen. The single breath studies were also done in duplicate except where indicated in Table IV, and all results have been included in the analysis of the effect of oxygen breathing on this measurement.

Analysis of data. The blood flow distribution in the lung can be obtained from the ratio of the concentration of xenon in any two zones. After an intravenous injection of X_L mc of xenon, the quantity of xenon in the counter field is given by: $F_{Ax} \cdot V_x = X_L \cdot (\dot{Q}_x/\dot{Q}c)$, where F_{Ax}, V_x, and $\dot{Q}_x$ are the concentration of xenon, the volume, and the blood flow, respectively in the field x, and $\dot{Q}c$ is the pulmonary capillary blood flow. Similarly, in the counter field y, $F_{Ay} \cdot V_y = X_L \cdot (\dot{Q}_y/\dot{Q}c)$. Therefore, the ratio, $(F_{Ax}/F_{Ay}) = (\dot{Q}_x/V_x)/(\dot{Q}_y/V_y)$, or the ratio of the concentration of injected xenon in two counter fields, is equal to the ratio of the blood flow per unit volume to these two areas. Hereafter the symbols $\dot{Q}_U/\dot{Q}_M$, $\dot{Q}_M/\dot{Q}_L$, and $\dot{Q}_U/\dot{Q}_L$ will be used to describe the ratios of flow per unit lung volume in any two lung zones as indicated by the subscripts, U (upper), M (middle), and L (lower).

It can similarly be shown that after a single breath of xenon $(F_{Ax}/F_{Ay}) = (\Delta V_x/V_x)/(\Delta V_y/V_y)$, where $\Delta V_x/V_x$ and $\Delta V_y/V_y$ are the increase in volume per unit lung volume in regions x and y respectively. The ratios of ventilation per unit lung volume in any two lung zones will be referred to by the symbols $\Delta V_U/\Delta V_M$, $\Delta V_M/\Delta V_L$, and $\Delta V_U/\Delta V_L$.

Bentivoglio and associates from this laboratory (18) have described a method for comparing the 90% "wash-in time" (t90) for each lung zone with the predicted time for the whole lung. The t90 was the time required for the count rate to reach 90% of its value at equilibration. The predicted time is determined from the tidal volume and respiratory frequency by a calculation similar to that used for the "helium mixing efficiency" (19). It is necessary to make a correction for the xenon in the chest wall, and this was done by asking the patient to hyperventilate after he was switched out of the spirometer circuit until the chest counters recorded a constant value. This count rate was then assumed to represent the chest wall count at the end of the equilibration, and it was assumed to have increased at a constant rate during the period of equilibration, from the initial background count rate.

The ventilation per volume of a lung zone is inversely related to its wash-in time, and to compare any two lung zones x and y the dynamic ventilation ratio $(\tilde{V}_x/\tilde{V}_y)$ was defined as the reciprocal of the ratio of their 90% wash-in time, that is, $\tilde{V}_x/\tilde{V}_y = t90_y/t90_x$.

[1] Ideally the xenon and hemodynamic studies should have been done in the same posture. However, studies by Dollery and West (3) and previous studies in our laboratory had been performed with subjects in the upright posture.

TABLE III

*Perfusion ratio**

	Air						Oxygen					
	Right			Left			Right			Left		
Patient	$\dot{Q}_U/\dot{Q}_M$	$\dot{Q}_M/\dot{Q}_L$	$\dot{Q}_U/\dot{Q}_L$	$\dot{Q}_U/\dot{Q}_M$	$\dot{Q}_M/\dot{Q}_L$	$\dot{Q}_U/\dot{Q}_L$	$\dot{Q}_U/\dot{Q}_M$	$\dot{Q}_M/\dot{Q}_L$	$\dot{Q}_U/\dot{Q}_L$	$\dot{Q}_U/\dot{Q}_M$	$\dot{Q}_M/\dot{Q}_L$	$\dot{Q}_U/\dot{Q}_L$
1	0.87	1.26	1.09	0.74	1.44	1.06	†					
2	1.10	2.93	3.13			3.20	0.95	2.58	2.44			2.73
3	1.01	3.35	3.39	0.68	1.78	1.20	0.89	2.87	2.54	0.69	1.62	1.13
4	0.77	1.32	1.02	0.97	1.22	1.18	0.66	1.17	0.77	0.72	1.08	0.78
5	1.21	1.40	1.70	0.83	1.33	1.10	1.03	1.06	1.09	0.70	1.00	0.70
6	1.13	3.39	3.84	0.99	2.40	2.37	0.87	3.07	2.66	0.90	2.22	1.99
7	1.19	1.76	2.08	0.90	1.75	1.58	0.93	1.57	1.45	0.71	1.53	1.08
8	0.60	0.79	0.47	0.50	0.85	0.42	0.54	0.50	0.27	0.54	0.53	0.28
9	1.03	1.01	1.03	0.69	1.02	0.70	†					
10	1.28	2.19	2.80	0.88	1.54	1.36	†					
11	0.66	0.82	0.55	0.72	0.67	0.48	0.69	0.87	0.61	0.61	0.84	0.51
12	0.76	1.14	0.86	0.73	0.94	0.68	†					
13	0.83	1.13	0.94	1.41	2.09	2.95	0.82	1.10	0.90	1.17	2.00	2.34
14	0.66	2.86	1.88	0.84	1.97	1.65	†					
15	0.74	1.10	0.81	0.79	1.30	1.03	†					

* $\dot{Q}_U$, $\dot{Q}_M$, and $\dot{Q}_L$ = flow per unit lung volume in the upper, middle, and lower zones, respectively.
† Duplicate determinations failed to agree within 10%.

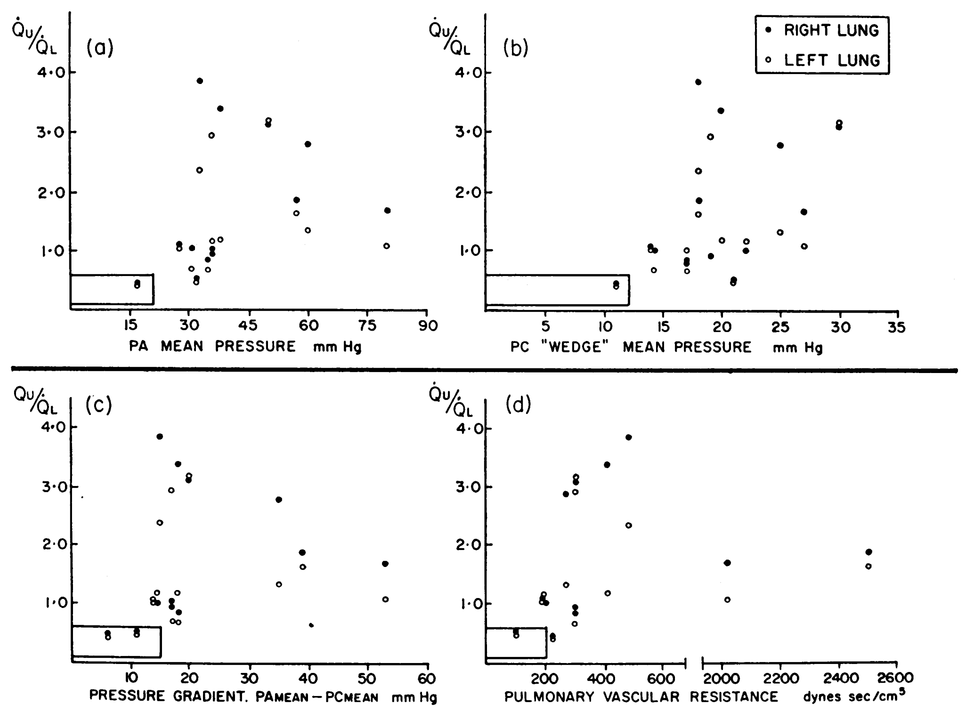

FIG. 1. RELATIONSHIP BETWEEN THE RATIO OF UPPER TO LOWER ZONE BLOOD FLOW PER UNIT VOLUME AND HEMODYNAMIC DATA. The rectangles enclose approximate normal values. There is significant correlation only in 1-b ($r = +0.45$, $p = < 0.02$).

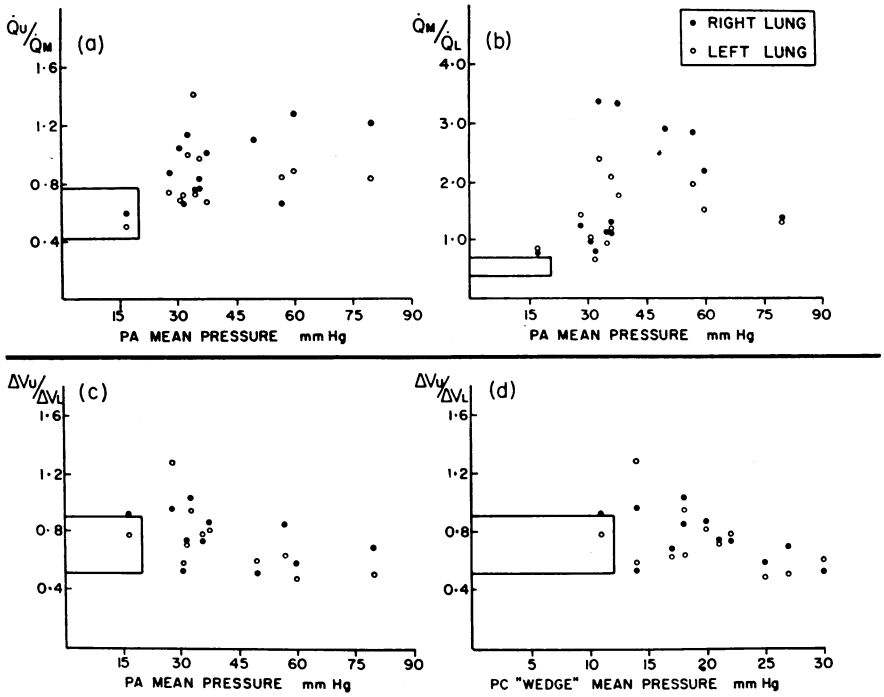

FIG. 2. RELATIONSHIP BETWEEN PULMONARY ARTERIAL PRESSURE AND UPPER TO MIDDLE ZONE BLOOD FLOW RATIO (A) AND MIDDLE TO LOWER ZONE RATIO (B); RELATIONSHIP BETWEEN UPPER TO LOWER ZONE SINGLE BREATH VENTILATION RATIO AND PULMONARY ARTERIAL PRESSURE (C) AND "WEDGE PRESSURE" (D). The rectangles enclose approximate normal values. There is significant correlation only in (c) ($r = -0.51$, $p = < 0.02$) and (d) ($r = 0.46$, $p = < 0.05$).

Results and Discussion

The routine lung function tests and hemodynamic observations during air and oxygen breathing are shown in Tables I and II. The pulmonary arterial pressure and cardiac output varied over a wide range, which makes the changes in calculated pulmonary vascular resistance on oxygen breathing difficult to interpret. However, in six of the 12 cases where this information was available, there was a significant fall in the mean pulmonary arterial pressure. The wedge pressure showed no consistent change.

Distribution of pulmonary blood flow. The ratio of perfusion per unit lung volume of upper zone to that in the lower zone ($\dot{Q}_U/\dot{Q}_L$) studied by an identical technique in 22 normal subjects in the seated posture was 0.280 (± SD 0.102) for the right lung and 0.314 (± 0.128) for the left lung.[2] The values for the upper, middle, and lower zones of the patients studied are shown in Table III. As compared to the normal values, the proportion of flow passing through the upper zones of the lung was increased although the magnitude of the change from normal varied greatly from patient to patient.

Figure 1-a shows the upper to lower zone flow ratio ($\dot{Q}_U/\dot{Q}_L$) plotted against the mean pulmonary arterial pressure. If the whole group was considered, no significant correlation was found ($r = + 0.28$, $p = < 0.2$). However, if the three cases with the pulmonary arterial pressure greater than 50 mm Hg were excluded, then $\dot{Q}_U/\dot{Q}_L$ was found to increase significantly with increasing pulmonary arterial pressure ($r = +.57$, $p = < 0.01$). The greatest disturbance in flow distribution was observed in patients with mild to moderate pulmonary hypertension. When pulmonary hypertension was very severe, the preponderance of flow per unit volume through the upper lung zones was no longer apparent, and perfusion was fairly uniform throughout

[2] Calculated from data of Ball and associates (2) plus five additional observations.

the lung. The same pattern was observed when the ratio of middle to lower zone flow per unit volume ($\dot{Q}_M/\dot{Q}_L$) was plotted against the pulmonary arterial pressure (Figure 2-b), but was less apparent when upper to middle zone flow ratio ($\dot{Q}_U/\dot{Q}_M$) was plotted against the pulmonary arterial pressure (Figure 2-b). $\dot{Q}_U/\dot{Q}_L$ was found to increase significantly with increasing wedge pressure in the whole group ($r = +0.45$, $p = < 0.02$) (Figure 1-b).

Because of the uncertainties in measurement of cardiac output mentioned above, blood flow ratios were compared both to the pulmonary artery to left atrial pressure gradient (Figure 1-c) and to the calculated pulmonary vascular resistance (Figure 1-d). When the ratios were related to either parameter, it appeared that maximal disturbance of flow pattern occurred when the vascular resistance was slightly elevated and that when elevation of resistance was marked there was again a reduction in flow to the upper zones relative to the lower.

The increase in the relative perfusion per unit volume of the upper parts of the lung in mitral disease, shown here by the radioactive xenon technique, is consistent with the findings of Dollery and West (3), who observed the rate of disappearance of soluble radioactive gases. Like these authors, we found that the degree of reversal of the normal perfusion gradient tends to become more marked as the pulmonary arterial pressure increases. However, it appears from our data that with very marked elevation of pulmonary arterial pressure and vascular resistance, perfusion of upper zones relative to lower decreases to an intermediate value.

The severity of mitral valve disease can be related to the elevation of left atrial pressure, but elevation of the pulmonary vascular resistance is probably dependent on both the severity and the duration of the condition. These data suggest that whatever factors initially operate to cause a regional elevation of vascular resistance at the lung bases, with the passage of time they affect the upper zones as well. At this stage there is a marked increase in total as distinct from basal zone vascular resistance and a return of the distribution of flow towards normal.

Distribution of a single breath. The average normal distribution ratio of a single inspiratory capacity breath ($\Delta V_U/\Delta V_L$) in 22 subjects quoted above is 0.745 ($\pm$ SD 0.083) for the right lung and 0.649 ($\pm$ SD 0.065) for the left lung. By comparison with these values it can be seen that the distribution of a single breath in most of the patients with mitral disease was within the normal range (Table IV, Figure 2-c, d). However, there was a statistically significant

TABLE IV

Ventilation data

	Single breath distribution ratio												Dynamic ventilation ratio					
	Air						Oxygen						Air					
	Right			Left			Right			Left			Right			Left		
Patient	$\Delta V_U/\Delta V_M$	$\Delta V_M/\Delta V_L$	$\Delta V_U/\Delta V_L$	$\Delta V_U/\Delta V_M$	$\Delta V_M/\Delta V_L$	$\Delta V_U/\Delta V_L$	$\Delta V_U/\Delta V_M$	$\Delta V_M/\Delta V_L$	$\Delta V_U/\Delta V_L$	$\Delta V_U/\Delta V_M$	$\Delta V_M/\Delta V_L$	$\Delta V_U/\Delta V_L$	$\tilde{V}_U/\tilde{V}_M$	$\tilde{V}_M/\tilde{V}_L$	$\tilde{V}_U/\tilde{V}_L$	$\tilde{V}_U/\tilde{V}_M$	$\tilde{V}_M/\tilde{V}_L$	$\tilde{V}_U/\tilde{V}_L$
1	0.97	1.01	0.97	1.44	0.90	1.29	0.98	0.89	0.86	1.09	0.90	0.98						
2	0.70	0.76	0.53	0.71	0.86	0.61							0.76	0.67	0.51	0.89	0.63	0.56
3†	0.90	0.97	0.87	0.99	0.81	0.81	0.85	0.94	0.80	0.71	0.77	0.64	1.03	1.13	1.16	1.12	0.91	1.02
4	0.79	0.94	0.74	0.97	0.81	0.78	0.82	0.87	0.71	0.76	0.74	0.56	0.81	1.60	1.29	0.44	1.01	0.45
5	0.98	0.72	0.70	0.70	0.72	0.51	0.86	0.71	0.61	0.79	0.72	0.57	2.60	0.77	2.00	0.74	1.14	0.85
6†	0.98	1.06	1.04	0.99	0.96	0.95	0.91	0.87	0.80	0.99	0.94	0.93	0.82	0.96	0.79	1.46	0.94	1.38
7	0.88	0.82	0.71	0.98	0.75	0.72	0.75	0.67	0.49	0.71	0.70	0.50						
8	1.01	0.91	0.93	0.93	0.83	0.78	0.77	0.89	0.69	0.77	0.82	0.63						
9	0.69	0.79	0.54	0.77	0.76	0.59	0.69	0.77	0.53	0.67	0.77	0.52	0.69	0.94	0.65	0.73	0.78	0.57
10	0.73	0.81	0.59	0.73	0.68	0.49	0.83	0.81	0.67	0.69	0.73	0.50	0.79	0.92	0.73	0.65	0.49	0.32
11	0.87	0.85	0.74	0.88	0.80	0.71	0.87	0.76	0.66	0.81	0.81	0.65	0.68	0.79	0.54	0.76	0.96	0.73
13													0.95	1.54	1.47	0.92	2.49	2.18
14†	0.88	0.98	0.86	1.05	0.61	0.64												
15†	0.74	0.93	0.69	0.77	0.81	0.63												

* V_U, V_M, and V_L = ventilation per unit lung volume in the upper, middle, and lower zones, respectively.
† Single breath measurements not done in duplicate.

negative correlation when $\Delta V_U/\Delta V_L$ was related to the mean pulmonary arterial pressure ($r = -0.51$, $p = < 0.02$) or to the mean wedge pressure ($r = -0.46$, $p = < 0.05$).

In view of the striking disturbances of distribution of perfusion reported above, the near normal distribution of the single breath in most subjects was surprising. If, as pointed out by Bentivoglio and associates (20), the single breath distribution is largely determined by regional lung compliance, it can be concluded that the relative compliance in upper and lower zones in most patients was in the normal range in spite of marked elevations of pulmonary venous pressure. It has been shown by Borst and associates (21) that acute elevation of pulmonary venous pressure in the absence of pulmonary edema causes only slight changes in the pulmonary compliance, and Cook and associates (22) have demonstrated that compliance changes following experimental elevations of the pulmonary venous pressure can be related almost entirely to the presence of edema fluid in air spaces. Pulmonary edema of this degree was probably not present in the patients studied here although interstitial and perivascular edema may well have been present. It appears that the disturbance of perfusion gradient observed in these patients was unrelated to any change in regional lung compliance.

Dynamic ventilation. Almost without exception the t90 was longer than predicted in all lung zones, an observation that accords with the impaired inert gas distribution observed in many of the patients (Table I). Bentivoglio and associates (18) found in ten normal subjects an average "dynamic ventilation ratio" ($\tilde{V}_U/\tilde{V}_L$) of 0.6 (range, 0.35 to 1.0). In some of our patients this ratio was abnormally increased, indicating

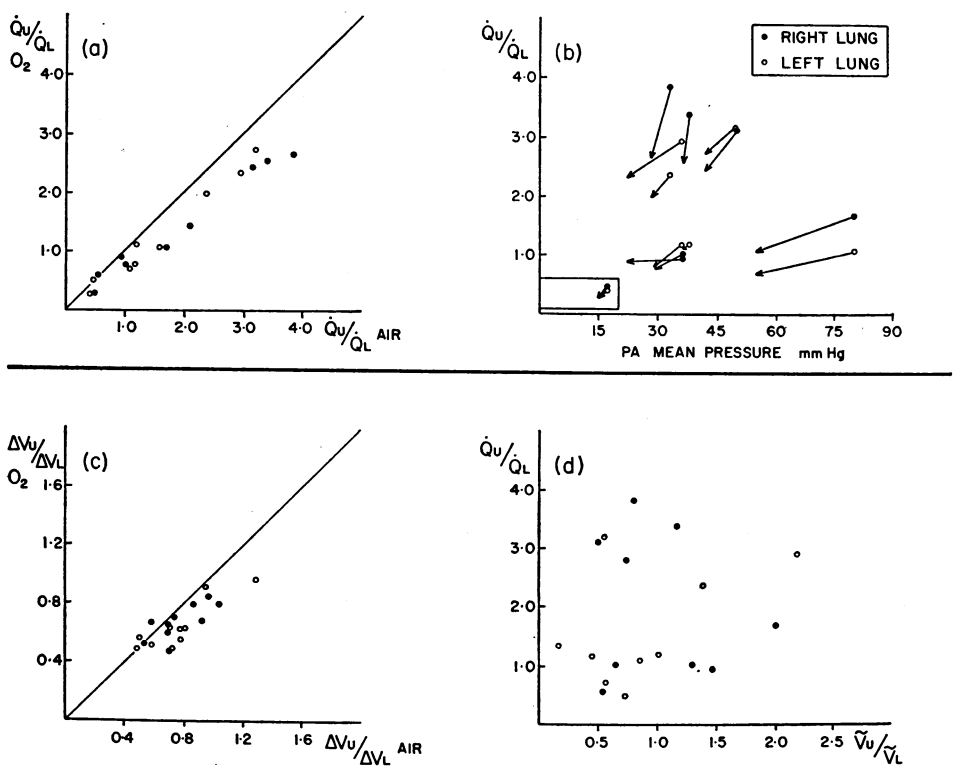

FIG. 3. (A) UPPER TO LOWER ZONE BLOOD FLOW RATIO DURING OXYGEN AND AIR BREATHING AND THE LINE OF IDENTITY ($P = < 0.001$). (B) RELATIONSHIP BETWEEN CHANGE IN UPPER TO LOWER ZONE BLOOD FLOW RATIO AND PULMONARY ARTERIAL MEAN PRESSURE DURING AIR (OPEN AND CLOSED CIRCLES) AND OXYGEN BREATHING (ARROW HEADS). (C) UPPER TO LOWER ZONE SINGLE BREATH VENTILATION RATIO DURING OXYGEN AND AIR BREATHING AND THE LINE OF IDENTITY ($P = < 0.001$). (D) RELATIONSHIP BETWEEN UPPER TO LOWER ZONE BLOOD FLOW RATIO AND UPPER TO LOWER ZONE DYNAMIC VENTILATION RATIO ($\tilde{V}_U/\tilde{V}_L$).

that the lower zone was poorly ventilated in relation to the upper zone during quiet breathing. However, the ratio of dynamic ventilation of upper and lower zones did not seem to be correlated with the pulmonary arterial mean pressure ($r = +0.10$, $p = < 0.8$) or wedge pressure ($r = -0.12$, $p = < 0.7$, nor was there any correlation between $\dot{Q}_U/\dot{Q}_L$ and the dynamic ventilation ratio ($r = +0.16$, $p = < 0.6$) (Figure 3-d). These findings, together with the abnormally high mixing indexes based on whole lung helium equilibration studies (Table I), indicate that the distribution of inspired air was abnormal throughout the lung and that this impairment was sometimes greatest in the lower zones. To conclude that there was regional hypoxia, however, it is necessary to demonstrate reduction of ventilation in relation to perfusion, and regional $\dot{V}/\dot{Q}$ ratios cannot be computed by the present technique (20). It seems extremely unlikely, however, that underventilation of the lower zones could have been the prime cause of the flow shifts observed, as these were in some instances marked in the presence of normal $\dot{V}_U/\dot{V}_L$ ratios (Figure 3-d).

Effect of oxygen inhalation. The inhalation of oxygen almost invariably resulted in some shift of perfusion to the lower zones from the upper (Table III and Figure 3-a). The mean reduction of $\dot{Q}_U/\dot{Q}_L$ was, however, small, averaging 21.8% ($p = < 0.001$), and there was no close correlation between the decrease in $\dot{Q}_U/\dot{Q}_L$ and the fall in pulmonary arterial pressure after oxygen breathing (Figure 3-d). Oxygen breathing also caused a greater proportion of a single breath of inspired xenon to pass into the lower zones, the mean fall in $\Delta V_U/\Delta V_L$ being 12.5% ($p = < 0.001$) (Figure 3-c).

It cannot be deduced from these changes that oxygen breathing caused a selective vasodilation of previously hypoxic lower zones, although they are consistent with such an explanation. Reduction of pulmonary arterial pressure due to any cause such as fall in cardiac output (23) or diffuse vasodilation throughout the lung will result in relatively greater perfusion of the more dependent zones. A reduction in cardiac output due to oxygen breathing is unlikely (7, 9, and Table II). Diffuse vasodilation throughout the lung, however, cannot be excluded, as oxygen breathing did cause some reduction in pulmonary arterial pressure in many patients (Table I). Whether vasodilation was diffuse or confined to the lower zones, the flow shifts observed were small, and it is unlikely that hypoxia was important in maintaining the increased resistance of the lower zone vessels at this stage.

Conclusions. These data show more clearly than any previously published the changes occurring in the pattern of flow distribution in patients with mitral disease and show their relationship to the changes in hemodynamics and in regional ventilation. In early cases there is a shift of blood flow from the lower to the upper zones of the lung, the degree of which correlates roughly with the severity of the condition as judged by the elevation of pulmonary venous pressure. In more advanced cases where the pulmonary vascular resistance is markedly elevated, the increase in perfusion of the upper zones relative to the lower is not so pronounced, suggesting that the factors causing vascular narrowing are operating throughout the lung. By contrast with these marked changes in the distribution of blood flow, regional compliance is not greatly affected. The abnormal distribution of ventilation during quiet breathing and the increase in perfusion of the lower zones following oxygen administration are consistent with the hypothesis that hypoxic vasoconstriction in the lower zones may have played some part in the flow shift and elevation of pulmonary vascular resistance observed. However, reduced perfusion of the lower zones was sometimes marked in the absence of relative underventilation of the lower zones, and the redistribution of perfusion that followed oxygen breathing was small. Therefore, it appears unlikely that vasoconstriction in the lower zones resulting from hypoxia was the principal cause of their reduced perfusion.

On the other hand, our observations are consistent with the suggestion of West and others (4) that perivascular edema of the lower zones initiated the redistribution of flow to the upper zones. The absence of regional compliance changes is not inconsistent with this and merely reflects the absence of edema fluid in the air compartment. With progressive elevation of the pulmonary venous pressure, perivascular edema may also appear in the upper zones, and the

over-all pulmonary vascular resistance will become markedly elevated, but the flow distribution will return towards normal. Although this explanation accords with our observations, it does not explain the medial hypertrophy and intimal proliferation that occur in precapillary vessels and are also most marked in the lower zones (24). The presence of perivascular edema and reduced flow must initiate these changes in some manner as yet unknown.

Summary

The distribution of blood flow and ventilation in the lung was studied with xenon^{133} in 15 patients with mitral valve disease, and the results were related to hemodynamic observations made at cardiac catheterization.

In comparison to normal subjects there was an increase in the ratio of upper to lower zone blood flow per unit volume, and this increase tended to be greater in the presence of higher pulmonary venous pressure. The relative increase in upper zone blood flow was less in the presence of extreme pulmonary hypertension with marked elevation of pulmonary vascular resistance than it was in cases of moderate pulmonary hypertension.

The distribution of a single breath of inspired gas was minimally disturbed in these patients, indicating the absence of marked disturbances of regional compliance.

The equilibration time for inspired gas during quiet normal breathing was delayed in all zones and sometimes showed selective delay in the lower zones.

Oxygen breathing caused a small increase in the perfusion of lower zones relative to upper and a similar but smaller increase in the proportion of a single breath passing to the lower zones. The effect of oxygen on perfusion distribution, however, was not greatest in those instances where the disturbance of ventilation was most marked, nor was it related to the fall in pulmonary arterial pressure observed after oxygen breathing at cardiac catheterization. Relative hypoxia of the lower zones therefore does not seem to have been the principal cause of the abnormal blood flow distribution.

These observations are consistent with the hypothesis that an elevation of vascular resistance occurring first in the lower zones and then throughout the lungs in mitral disease is initiated by perivascular edema resulting from elevated pulmonary venous pressure.

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