Regional pulmonary blood flow in mitral disease studied by xenon radiospirometry

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Regional lung perfusion was measured in the sitting position by 4 external detectors after intravenous injection of ^{133}Xe in 24 patients with mitral valve disease and in 8 people with no cardiopulmonary disease acting as normal controls. Right- and left-sided heart catheterization was carried out on the patients on the following day. Mitral valve stenosis was found in 9, mitral valve regurgitation in 8, and both stenosis and regurgitation in the remaining 7.

Regional lung perfusion in the normal people fell linearly from the basal to the apical sections of the lungs. The perfusion distribution in patients with mitral valve disease and a pulmonary capillary vein (PCV) pressure lower than 15 mmHg (2.0 kPa) did not differ significantly from that of the controls. A redistribution of the regional perfusion, with an increase in the apical perfusion and a fall in the basal perfusion of the lungs, was seen in patients with a raised PCV pressure. The hyperperfusion of the apical lung sections correlated with the mean pressure in the pulmonary artery ($r=+0.795$, $P<0.001$), while the basal hypoperfusion correlated with the PCV pressure ($r=+0.842$, $P<0.001$). The PCV pressure can be predicted with an exactitude of ± 7 mmHg (0.9 kPa) (95% confidence limits). Neither the cardiac index nor the pulmonary vascular resistance correlated with the changes in perfusion.

Xenon radiospirometry is a rapid and reliable method for evaluating PCV pressure before or after operation in patients with mitral valve disease.

In normal people gravity causes a basal hyperperfusion of the lungs, so that the pulmonary blood flow is greater at the bottom than at the top. Other factors influence the pulmonary blood flow (Jordan, 1965). Basal vascular resistance, measured in the sitting position, decreases when oxygen is breathed (Dawson, Kaneko, and McGregor, 1965) and perivascular oedema (Kazemi *et al.*, 1970) and organic vascular disease can also affect the pulmonary vessels (Olsen, 1966). These factors change the pattern of lung perfusion in patients with mitral valve disease (MVD) (Ball *et al.*, 1962) and may completely invert it.

These perfusion distribution patterns have been studied by means of radioactive gases such as $^{15}\text{O}_2$, $^{13}\text{CO}_2$ (Dollery and West, 1960), and ^{133}Xe (Ball *et al.*, 1962; Jebavy *et al.*, 1970), and by scanning after the injection of radioactive-labelled albumin aggregate (Friedman and Braunwald, 1966; Giuntini *et al.*, 1974). With ^{133}Xe measure-

ments of regional blood flow can be repeated and expressed in terms of alveolar perfusion. The technique has therefore been used for studying the perfusion distribution in patients with mitral valve disease, and from this, with the patient in the sitting position, a picture of the pressure in the pulmonary circulation may be obtained.

Patients and methods

Twenty-four patients with mitral valve disease were studied. By means of right and left heart catheterization the cardiac output was measured by the method of Fick and also a left ventriculogram taken. Nine of the patients had mitral stenosis, 8 had mitral valve insufficiency, while the remaining 7 had both stenosis and regurgitation. The cardiac catheterization data are shown in the Table.

The patients were subjected to regional radiospirometry the day before heart catheterization. ^{133}Xe dissolved in isotonic saline was injected into a cubital vein of the left arm and the radioactivity in the right lung was measured by 4 scintillation detectors placed posteriorly

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TABLE Clinical, cardiac catheterization, and lung perfusion data in 24 patients with mitral valve disease

Case No.	Age (yr)	Sex	PCV pressure (mmHg)	Mean AP (mmHg)	PVR ($\text{dyn s}^{-1} \text{cm}^{-5}$)	Cardiac index ($\text{l min}^{-1} \text{m}^{-2}$)	Perfusion index (flow/alveolus)*				Diagnosis
							1	2	3	4	
1	45	M	3	15	196	2.70	0.546	0.676	1.005	1.330	R
2	58	F	5	16	125	2.10	0.433	0.710	1.150	1.455	R
3	47	F	6	15	176	2.70	0.554	0.794	1.089	1.284	R
4	58	M	8	16	130	2.20	0.622	0.750	1.028	1.269	R
5	64	F	9	16	82	4.34	0.492	0.759	1.061	1.478	R
6	56	F	12	16	84	2.10	0.776	0.930	1.083	1.118	S
7	37	F	14	20	40	4.70	0.714	0.867	1.204	1.073	R
8	53	F	14	20	160	1.80	0.782	0.937	1.109	1.033	S+R
9	37	F	14	21	73	5.10	0.977	1.057	1.015	0.947	R
10	59	F	16	22	55	1.60	0.761	1.000	1.091	1.011	S
11	60	F	16	17	142	1.60	0.960	1.035	1.078	0.920	S
12	49	F	17	25	71	2.70	0.676	0.978	1.050	1.084	S
13	40	M	17	27	144	3.40	0.825	1.113	1.137	0.842	S+R
14	38	F	17	34	384	2.10	0.906	1.062	1.037	0.899	S+R
15	48	F	20	24	35	1.40	0.863	0.964	1.112	0.995	S+R
16	62	M	20	32	180	2.70	0.949	1.010	0.929	1.072	R
17	45	F	21	30	136	2.80	0.907	1.022	0.984	1.021	S+R
18	61	F	22	30	108	2.60	1.266	1.080	0.929	0.771	S
19	51	F	22	29	267	1.30	1.181	1.053	1.093	0.737	S
20	67	M	24	30	138	1.98	1.062	0.957	1.094	0.917	S+R
21	61	F	25	32	175	2.10	1.127	1.353	0.909	0.855	S
22	36	F	25	40	260	2.80	1.291	1.318	0.996	0.625	S
23	46	F	26	32	160	1.90	0.909	1.059	1.083	0.901	S
24	62	F	26	32	88	3.00	1.071	1.149	1.026	0.760	S
Mean 51.7			16.6	24.6	142	2.57	0.860	0.985	1.054	1.016	
$\pm$ SD ± 9.7			± 6.9	± 7.4	± 80	± 0.99	± 0.237	± 0.169	± 0.072	± 0.221	

*Numbers refer to detectors (see Fig. 1).

PCV=pulmonary capillary venous pressure. AP=aortic pressure. PVR=pulmonary vascular resistance.

S=mitral stenosis. R=mitral regurgitation.

Conversion from Traditional Units to SI Units: 1 mmHg $\approx$ 0.133 kPa.

FIG. 1 Positioning of external scintillation detectors vertically over posterior surface of right lung with 18 cm between centres of upper and lower detector. Internal diameter of each collimator=4 cm.

vertically above each other (Fig. 1). The upper edge of the apical detector corresponded to a line between the superior margin of the right clavicle and the upper margin of the scapula during maximum inspiration (total lung capacity (TLC)). Perfusion measurements were carried out at TLC, where the difference in perfusion between the top and bottom of the lungs is most pronounced (Anthonisen and Milic-Emili, 1966; Hughes *et al.*, 1968; Lilja, 1972). The detectors had a crystal diameter of 5 cm and a 10-cm long cylindrical collimator. The distance between the centre of the apical and basal detectors was 18 cm in all the investigations. Each detector was connected to a ratemeter with a time constant of 2 seconds and a discrimination level of 81 KeV (Meditronic). The output of the ratemeter was registered on a 4-channel linear writer with a paper speed of 50 mm/s.

After an injection of 0.7 mCi ^{133}Xe the patient inspired to TLC and the breath was then held with the glottis open, in order to eliminate activity from the extra-pulmonary circulation (right heart and pulmonary arteries), until the output of the ratemeter reached plateau levels (Fig. 2).

The procedure was repeated three times and the mean

FIG. 2 Regional ratemeter readings of pulmonary blood flow from 4 detectors in a subject without cardio-pulmonary disease recorded at maximum inspiration (TLC). Heights of perfusion h_1 , h_2 , h_3 , and h_4 correspond to detectors 1, 2, 3, and 4 in Fig. 1.

of the three readings used for the calculations. After this the patient breathed into a closed system consisting of a 5-litre rubber bag full of oxygen connected to a CO_2 absorber. After a stable rebreathing level had been reached the patient inspired again to TLC and continued to do so until the ratemeter output was constant (Fig. 3). At least three measurements were made during inspiration to TLC and the mean regional rebreathing height (Fig. 3) was used for the calculations.

Eight men volunteers, whose mean ($\pm$ SD) age was

FIG. 3 Regional ratemeter readings of ^{133}Xe activity on rebreathing into closed system with CO_2 absorber. TLC = plateaus on three inspirations to TLC. r_{regional} = expression of amount of alveolar air within field of individual detector.

21.2 ± 2.0 who had no signs of heart or pulmonary disease and whose lung function was normal were subjected to regional radiospirrometry by the same technique as described above. The intra-individual coefficient of variation was within 5 per cent.

Calculations

About 95 per cent of the radioactivity of intravenously injected ^{133}Xe diffuses to the alveolar air during the first

passage through the pulmonary circulation (West, 1964). Since ^{133}Xe is uniformly mixed in the right ventricle the amount supplied to each alveolus is proportional to the alveolar blood flow. The height of perfusion 'h' (Fig. 2) is, therefore, proportional to the regional blood flow. Further, the maximum radioactivity registered during breath holding is proportional to the amount of lung tissue within the field covered by the detector and is dependent on the sensitivity of the detector as well as the dose of ^{133}Xe injected. If the perfusion height registered by each detector is expressed as a percentage of the sum of the four perfusion heights then dosage independence is obtained, as follows:

$$h_n\% = h_n \times 100 / (h_1 + h_2 + h_3 + h_4)$$

where $n=1, 2, 3$, or 4, corresponding to the numbering of the detectors in Fig. 1. If the registered activity of each detector after rebreathing and inspiration to TLC (Fig. 3) is expressed as a percentage of the total rebreathing activity then a dosage independent expression of the amount of lung tissue within the field of each detector is obtained as follows:

$$r_n\% = r_n \times 100 / (r_1 + r_2 + r_3 + r_4)$$

where $n=1, 2, 3$, or 4.

The ratio (P_n) of the perfusion height in per cent ($h_n\%$) and the rebreathing height in per cent ($r_n\%$) ($h_n\% / r_n\% = P_n$) is therefore dependent only on the regional perfusion. This ratio P_n is termed the perfusion index. Since the size of the alveoli of the apex and base of the lung is the same at maximum inspiration (TLC) (Milic-Emili *et al.*, 1966) r_n per cent is proportional to the number of alveoli, and therefore the perfusion index can be given as flow per alveolus. With increasing perfusion of the apical region the ratio P_1/P_3 will increase and is thus an expression of apical hyperperfusion. Similarly, the expression $P_1 + P_2 + P_3/P_4$ will increase with decreasing basal perfusion and will thus be an expression of the basal hypoperfusion. These indices of perfusion were chosen being most suitable for correlation with the haemodynamic measurements.

Results

The perfusion indices in the patients with mitral valve disease are shown in the Table and Fig. 4.

In the normal subjects the regional perfusion fell linearly from the base to the apex of the lungs (Fig. 4). A mean bottom/top perfusion ratio (P_4/P_1) of 2.7 was measured. If the 24 patients with mitral valve disease are separated into three according to their PCV pressure the pattern of regional perfusion is significantly different. Apical blood flow increases with increasing PCV pressure while basal perfusion decreases (Fig. 4).

In the 9 patients with mitral valve disease and normal (< 15 mmHg) PCV pressure at rest (group B) the regional perfusion index was not significantly different from that of the normal subjects (group A). The perfusion indices obtained from detector 3

FIG. 4 Regional perfusion indices (flow/alveolus) at TLC in normal subjects (A) and in patients with mitral valve disease (B, C, D). Group B=9 patients with mean AP 17.2 ± 2.4 (1 SD) mmHg (2.3 ± 0.3 kPa) and PCV $= 9.4 \pm 4.3$ mmHg (1.2 ± 0.5 kPa). Group C=10 patients with mean AP 27.0 ± 5.1 mmHg (3.6 ± 0.7 kPa) and PCV $= 18.8 \pm 2.4$ mmHg (2.5 ± 0.3 kPa). Group D=5 patients with mean AP 33.2 ± 3.9 mmHg (4.4 ± 0.5 kPa) and PCV $= 25.2 \pm 0.8$ mmHg (3.3 ± 0.1 kPa). Increased apical perfusion and decreased basal flow occurs with increasing pressures in pulmonary artery and in PCV. Note: all perfusion indices corresponding to detector 3 are independent of measured pressure. Perfusion indices are given ± 2 SEM.

were independent of pressure variations. Apical (P_1/P_3) and basal perfusion ($P_1+P_2+P_3/P_4$) correlated with the pulmonary circulation pressures ($P < 0.001$).

Regression analysis of the relation between PCV pressure and the basal hypoperfusion enables PCV to be predicted with an exactitude of ± 7 mmHg (0.9 kPa) (95% confidence limits). There was no correlation between cardiac output, cardiac index, or pulmonary vascular resistance and perfusion levels.

Discussion

In a person in a sitting position lung perfusion is greatest in the basal region because of the higher hydrostatic pressure. We have measured a bottom-top perfusion ratio of 2.7 in normal subjects. That agrees with the results of other radioactive-gas studies (Dawson *et al.*, 1965; Anthonisen and Milic-Emili, 1966; Lilja, 1972) and scannings after

the injection of radioactive labelled albumin aggregate (MAA) (Friedman and Braunwald, 1966).

The mean pressure in the pulmonary artery (PA), measured in cm H₂O, corresponds to the height of the lungs, and for this reason the perfusion pressure is lowest in the apical part. A rise in PA pressure should therefore increase apical perfusion. We confirmed this in our study (Fig. 5). Hypoperfusion of the basal region has been observed with increased PCV pressure (Fig. 6). Such an increase in

FIG. 5 Apical hyperperfusion. P_1/P_3 related to mean ($\pm$ SD) pressure in pulmonary artery in 24 patients with mitral valve disease. Correlation coefficient: $r = +0.782$ ($P < 0.001$).

FIG. 6 Basal hypoperfusion. $P_1+P_2+P_3/P_4$ related to mean ($\pm$ SD) PCV pressure in 24 patients with mitral valve disease. Correlation coefficient: $r = +0.824$ ($P < 0.001$).

FIG. 7 Apical hyperperfusion. P_1/P_3 related to pulmonary vascular resistance in 24 patients. Correlation coefficient: $r = +0.297$ (not significant).

FIG. 8 Basal hypoperfusion. $(P_1 + P_2 + P_3)/P_4$ related to pulmonary vascular resistance in 24 patients. Correlation coefficient: $r = +0.340$ (not significant).

the basal vascular resistance may be caused by interstitial oedema resulting from a rise in PCV pressure (West, Dollery, and Heard, 1965). Morphological (Olsen, 1966) and functional studies (Steiner, 1958; West *et al.*, 1965) of patients with mitral valve disease (Ball *et al.*, 1962) and of patients with left-sided heart congestion (Kazemi *et al.*,

1970) have confirmed this.

This basal hypoperfusion is partly reversible—as may be seen in patients with mitral valve disease after oxygen treatment (Dawson *et al.*, 1965) and in the decrease in pulmonary vascular resistance after infusion of acetylcholine into the pulmonary artery (Bateman *et al.*, 1962)—whether or not it is caused by the abolition of vasoconstrictive reflexes as a reaction to a raised PCV pressure or by vasoconstriction resulting from hypoxia (McGregor *et al.*, 1953; Dawson *et al.*, 1965; Bergofsky, Haas, and Porcelli, 1968). Normalization of the pulmonary vascular resistance has not been observed either in these studies or in haemodynamic studies after mitral valve surgery (Zener *et al.*, 1972). This is in agreement with the intimal thickening and perivascular fibrosis of the basal vessels found at necropsy in patients with mitral valve disease (Olsen, 1966).

The reduction in basal perfusion that occurs with age first becomes noticeable after the age of 65 (Holland *et al.*, 1968). This is in agreement with the fact that the perfusion distribution in patients with mitral valve disease with normal PA and PCV pressures does not differ significantly from that of normal subjects, despite the difference in average age (Fig. 4).

Friedman and Braunwald (1966) and Giuntini *et al.* (1974) found a positive correlation between pulmonary vascular resistance (PVR) and perfusion distribution in the lungs, but Jebavy *et al.* (1970) and Pain *et al.* (1972) were unable to do so. This correlation is seen only when radioactive MAA has been used. As the resistance of the pulmonary circulation is low compared with that of the systemic circulation an increase in the basal regional resistance, expressed by a reduction in basal perfusion, would not be expected to influence the total PVR. If the patients are grouped according to the upper normal limit of the basal perfusion (mean value of $(P_1 + P_2 + P_3)/P_4$ (+2 SEM) = 2.2) and with normal PVR ($< 200 \text{ dyn s}^{-1} \text{ cm}^{-5}$) 80 per cent of the patients with normal PVR have reduced basal perfusion and increased apical perfusion (Fig. 7 and 8) without any increase in PVR. The increase in vascular resistance thus results only in a redistribution of the blood to the apical section.

The PVR in patients above the regression line (Fig. 6) is greater than in patients below it ($P < 0.02$, t test). Thus an increase in PVR is seen simultaneously with a reduction in basal perfusion but independent of the PCV pressure. There must therefore be factors other than the PCV pressure level that bring about the increased PVR. Such a factor could be the effect on the pulmonary blood vessels of a long-standing disease.

The lack of correlation between perfusion distribution and PVR when measured by the ^{133}Xe technique compared with the good correlation found when using radioactive MAA could result from physiological differences in the two methods. Tracer MAA is distributed only to the vascular phase while ^{133}Xe is distributed to both the vascular and air phases. Since ventilation and perfusion are complementary (Liljestrand, 1958) this explanation seems improbable. On the other hand, the discrepancy could result from a difference in the patients studied. Friedman and Braunwald (1966) found no correlation between PVR and perfusion distribution with normal PVR values. This is in agreement with our results. Since a correlation has been found between the results with radioactive MAA and ^{133}Xe used on the same patient (Jebavy *et al.*, 1970) probably the lack of correlation between PVR and perfusion distribution is not due to differences in the methods but is a difference in the patients.

With a raised PCV pressure the mean pulmonary artery (PA) pressure will be correspondingly increased. This will occur up to a PCV pressure of 25 mmHg (3.3 kPa), after which the mean PA pressure increases more than the PCV pressure (excessive pulmonary hypertension (Walston *et al.*, 1973)). All our patients had a PCV pressure of 25 mmHg (3.3 kPa) or less, so that the basal perfusion reduction caused by the moderately increased PCV pressure merely resulted in a redistribution of the blood to the apical lung section with an unchanged PVR. When compensatory changes in the blood flow, which occur at a PCV pressure greater than 25 mmHg (3.3 kPa), become so extensive that they involve the apical section an increase in the PVR and a simultaneous normalization of perfusion distribution can first be observed (Friedman and Braunwald, 1966). The regional pulmonary blood flow can be determined partly by radioactive-labelled MAA (Friedman and Braunwald, 1966) and partly by radioactive gases, for example ^{133}Xe (Ball *et al.*, 1962).

When calculating the regional blood flow the regional count rate must be transformed to flow/ml lung tissue or flow/alveolus. This is done by a geometrical correction, when using the scanning technique, based on measurement of the lung dimensions on the x-ray picture of the thorax (Giuntini *et al.*, 1974). With the ^{133}Xe technique the volume correction is simple, since the re-breathing level is an expression of the amount of lung tissue in the fields of each detector. Perfusion measurements may also be repeated when using ^{133}Xe since the radioactivity expires within minutes. The half life of the tracer most often used, ^{131}I -MAA, is three hours (Giuntini *et al.*, 1974), which

makes repeated measurements impracticable.

The upper/lower (U/L) perfusion ratio is used in most investigations as an expression of the pulmonary blood flow distribution (Friedman and Braunwald, 1966; Giuntini *et al.*, 1974). U/L will be higher both when the apical perfusion is increased and when the basal perfusion is decreased. We used two distribution ratios, one for apical hyperperfusion (P_1/P_3) and another for basal hypoperfusion ($(P_1+P_2+P_3)/P_4$). P_3 constitutes part of the expression for the apical perfusion, as this index has been found to be independent of the measured pressure. $P_1+P_2+P_3/P_4$ was used to express the basal hypoperfusion as it gave a better correlation to the PCV pressure ($r=0.821$) than was the case with P_3/P_4 ($r=0.631$). This discrimination between the apical and basal perfusion is of little importance so long as the PCV pressure is less than 25 mmHg (3.3 kPa) (passive pulmonary hypertension), but this discrimination would be more physiologically correct in cases where the PA pressure increases more than the PCV pressure.

One of the difficulties of quantitatively measuring the regional perfusion distribution is the determination of the basal lung limits. With increased pulmonary venous pressure the range of maximum perfusion is displaced towards the apical region (Hughes *et al.*, 1969), which makes it even more difficult to determine the basal limits. Our four fixed detectors gave a constant hydrostatic pressure difference between the detectors. The volume correction made from the re-breathing level compensated somewhat for the differences in detector positioning in relation to the base of the lung in calculating the relative perfusion. Thus our correlation coefficients were better than those found when there were varying distances between the detectors (for example, U/L) (Dawson *et al.*, 1965; Jebavy *et al.*, 1970; Pain *et al.*, 1972).

Friedman and Braunwald (1966) found a correlation coefficient of 0.91 for the regression between PCV pressure and U/L in 35 patients, despite the fact that small changes in the cardiac output of patients with mitral valve disease may cause considerable fluctuations in the PCV pressure. Our correlation coefficient, $r=0.821$, was not significantly different from that found by Friedman and Braunwald (1966) ($P>0.05$). The exactitude with which the PCV pressure can be predicted is ± 7 mmHg (0.9 kPa) (95% confidence limits), which is comparable with that of ± 5 mmHg (0.7 kPa) (95% confidence limits) found by Friedman and Braunwald (1966). When there are pathological changes in vessel the walls in the lower zones (Olsen, 1966) the perfusion distribution will not be reliable in predicting changes in the left atrial pressure.

Conclusion

The radioactive-xenon method of determining regional pulmonary perfusion in patients with mitral valve disease has been found to be reliable and rapid and may, in contrast to scanning after injection of MAA, be repeated. The volume correction is also simple compared with the scanning technique and the results are immediately available in terms of flow per alveolus. Since it is possible to predict the PCV pressure with an exactitude of ± 7 mmHg (0.9 kPa) from the perfusion distribution (95% confidence limits), and since neither extensive intervention nor particular co-operation from the patient are necessary the method can be recommended for the evaluation of patients with suspected mitral valve disease in whom frequent heart catheterization should be avoided—for example, after corrective surgery on the mitral valve.

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