Regional Uptake of Radioactive Oxygen, Carbon Monoxide and Carbon Dioxide in the Lungs of Patients with Mitral Stenosis

By C. T. DOLLERY, M.B., M.R.C.P., AND J. B. WEST, M.D.

The inhalation of radioactive oxygen (O\textsubscript{15}) with external chest counting allows the measurement of regional ventilation and oxygen uptake in the lung.\textsuperscript{1} The subject inhales a measured volume of air containing a minute amount of oxygen-15 and holds his breath for 10 to 15 seconds. The initial peak counting rate is determined by the ventilation of the core of lung tissue between the counters, and the subsequent fall of counts during apnea is related to the oxygen uptake. By combining oxygen-15 with carbon to form labeled carbon monoxide, the transfer of which is diffusion limited, measurements of regional diffusing capacity per unit of lung volume can be made.\textsuperscript{2} Oxygen-15-labeled carbon dioxide, which diffuses very rapidly, allows measurement of regional blood flow per unit lung volume.\textsuperscript{3} The present paper reports the results obtained by applying these techniques to patients with mitral stenosis and the conclusions drawn about the regional distribution of pulmonary blood flow in this disease.

Methods

Oxygen-15 was prepared by deuteron bombardment of nitrogen molecules in the Medical Research Council cyclotron at Hammersmith Hospital. The target gas, 3 per cent of oxygen in nitrogen, was circulated through the bombardment box and passed rapidly to the adjoining laboratory using a continuous flow system. This gas was diluted in a secondary system so that the final radioactivity was about 5 mc./L of air. The radioactivity was monitored continuously in a re-entrant ionization chamber. For oxygen measurements this gas was used unaltered, but by use of 2 furnaces all the oxygen could be converted to either carbon monoxide or dioxide as desired. Carbon monoxide was made by passing the radioactive gas from the cyclotron over heated charcoal at 900 C, and removing the small proportion of carbon dioxide in a sodalime absorber. Carbon dioxide was made by passing the oxygen-15 over heated charcoal at 450 C, and converting residual monoxide to dioxide by passing the mixture over copper oxide at 900 C. The completeness of chemical conversion was checked frequently using a mass spectrometer to measure oxygen and carbon dioxide and an infrared analyzer to measure carbon monoxide. Oxygen-15 has a half-life of only 2 minutes and the maximum radiation dose to the blood or to any part of the body for 6 breaths of 1 L each was calculated to be less than 400 millirads. This dose is comparable with that given to the lung by a lateral chest radiograph, and is slightly greater than the weekly dose allowed to radiation workers.

The patient was seated in a chair so that the chest was in a vertical position, thus allowing a study of the influence of the gravitational hydrostatic pressure difference on the circulation at the apex and base of the lung. The counters were arranged so that 1 pair was positioned anteriorly and posteriorly over each lung at a different vertical level on each side. The radioactive gas was inhaled from a plastic bag attached to a respiratory valve box, and after emptying the bag with a single rapid inspiration, the patient held his breath for 10 to 15 seconds. The counting rates of the left and right pairs of counters were displayed on 2 pen recorders. Most measurements were made using parallel counting, but some were made with the counters arranged for coincidence counting. Parallel measurements gave higher counting rates with less statistical fluctuation, whereas coincidence counting allowed excellent spatial resolution, but counting rates were lower and the statistical fluctuation greater. The counting positions were referred to the ribs and intercostal spaces in the mid-clavicular line, and the left second interspace and the right fourth interspace were the positions most frequently used. It was necessary to avoid the left fourth interspace because the heart often lay within the counting field and labeled blood within it interfered with the clearance curve.

Oxygen-15 clearance is so nearly linear that, after a background correction, the clearance rate could be expressed as percentage fall per second of initial activity. Carbon monoxide and dioxide
Table 1
Mean Radioactive Oxygen and Carbon Monoxide Clearance Rates in Per Cent per Second at the Second and Fourth Intercostal Spaces in Patients with Mitral Stenosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Oxygen-15 clearance rates</th>
<th>Ratio of clearance rates</th>
<th>Carbon monoxide clearance rates</th>
<th>Ratio of clearance rates</th>
<th>Pulmonary artery pressure</th>
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<tbody>
<tr>
<td></td>
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<td>fourth space</td>
<td>2nd/4th space</td>
<td>second space</td>
<td>fourth space</td>
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<td>1</td>
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<td>2.5</td>
<td>0.64</td>
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<td>3.25</td>
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<td>4</td>
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<td>1.1</td>
<td>1.27</td>
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<td>1.7</td>
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<td>0.61</td>
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<td>0.64</td>
<td>3.8</td>
<td>3.3</td>
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</table>

Table 2
Mean Radioactive Oxygen and Carbon Dioxide Clearance Rates in Per Cent per Second at the Second and Fourth Intercostal Spaces in Patients with Mitral Stenosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Oxygen-15 clearance rates</th>
<th>Ratio of clearance rates</th>
<th>Carbon dioxide clearance rates</th>
<th>Ratio of clearance rates</th>
<th>Pulmonary artery pressure</th>
</tr>
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<td>second space</td>
<td>fourth space</td>
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<td>16.0</td>
<td>5.5</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>13.9</td>
<td>2.3</td>
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<td>17</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>9.1</td>
<td>5.1</td>
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were removed exponentially, and the curves from the pen recorders were replotted on a semilogarithmic graph after correction for background radiation and radioactive decay. The slope of this line in per cent/second of the instantaneous activity has been defined as the clearance rate for these gases.

Initially, measurements were made on a mixed group of 10 patients who had mitral stenosis of varying degrees of severity. Later, 7 additional patients with severe mitral stenosis, and with clinical and radiological evidence of pulmonary hypertension and right ventricular hypertrophy were selected for carbon dioxide clearance measurements.

Results

The results in tables 1 and 2 show the clearance rates per unit volume at the second and fourth intercostal spaces and the ratio of the second to the fourth space clearance rates. Since the observed clearance rates are dependent on lung volume, the ratio of clearance rates at second and fourth interspaces has been used for comparisons between groups. The logarithm of this ratio has been used to achieve a normal distribution for statistical analysis. In table 3 are shown the geometric means of the ratio of the clearance rates for normal subjects and the 2 groups of patients with mitral stenosis, and the significance of the separation of the means for patients from normals.

Radioactive Oxygen

Radioactive oxygen clearance rates were measured first in a group of 10 patients with mitral stenosis of varying degrees of severity (table 1) and later in a second group of 5 patients with severe mitral stenosis selected for the studies with radioactive carbon dioxide (table 2). In most patients, the ratio of clearance rates was higher than the normal mean.
Oxygen-15 clearance rates at the second and fourth intercostal spaces; 15 patients with mitral stenosis compared with 6 normal subjects. A figure of 0.45 indicating a relatively higher apical blood flow in the patients with mitral stenosis (fig. 1). The first group of patients had a mean ratio of second/fourth space clearance rates of 0.96 and the second group a mean ratio of 1.38; in both groups, the difference from the normals was statistically significant. High values of the ratio of second/fourth space clearance rates were particularly noticeable among the patients with the highest pulmonary artery pressures. Nine patients had a higher oxygen-15 clearance rate at the second than the fourth interspace, and of these, 6 had a pulmonary artery systolic pressure of 60 mm. Hg or higher. Six of the patients studied with oxygen-15 had a clearance rate ratio of less than unity and only 1 of them had a measured pulmonary artery systolic pressure over 60 mm. Hg. Three of these patients had not had a cardiac catheterization because a short diastolic murmur with a late opening snap without clinical, radiological or electrocardiographic evidence of pulmonary hypertension suggested that the mitral stenosis was mild.

Radioactive Carbon Monoxide Measurements

Measurements with carbon monoxide were made only in the first group of patients (table 1; fig. 2). The mean ratio of clearance rates in normals was 0.59 and in patients 1.03 (table 3). This difference is significant. Although 8 of the 10 patients had fourth space clearance rates below the mean normal, 5 of them had a higher clearance rate at the second space than the mean normal for this position, so that the diffusing capacity of the whole lung would probably be normal. Three patients had clearance rates at both second and fourth spaces below the mean normal, and in them the whole lung diffusing capacity may have been low.

Radioactive Carbon Dioxide Measurements

When labeled carbon dioxide became available, measurements were made in 7 patients (fig. 3), all of whom had clinical, radiological and electrocardiographic evidence of severe mitral stenosis with pulmonary hypertension (figs. 4A, 4B, and 5). In this group, the ratio of second to fourth space clearance rates was
NORMAL MITRAL STENOSIS

Counting position: Intercostal space

Figure 3
Carbon dioxide clearance rate at the second and fourth intercostal space; 7 patients with mitral stenosis and severe pulmonary hypertension compared with 5 normal subjects.

2.32, compared with the normal ratio of 0.30. This difference is highly significant. All 7 patients in the severe group had had a cardiac catheterization, and in all except 1 the pulmonary artery pressure was high. The low value found in this patient was surprising because she was severely incapacitated; there was a strong parasternal lift and on auscultation a close opening snap with a rumbling murmur throughout diastole which suggested tight mitral stenosis. Radiographically the lung fields showed basal interstitial edema and attenuation of the pulmonary vessels in the lower zones. These findings supported a diagnosis of severe mitral stenosis with pulmonary hypertension, and the low pressure found with the cardiac catheter was unexpected and is unexplained.

Discussion
The rate of fall of radioactivity in the field of the counters is determined by 2 factors: the rate of transfer into the pulmonary capillary and the rate of removal of the labeled blood from the counting field. It is possible to set out in a formal manner the factors which affect the removal of the radioactive gases from the alveolar gas into the blood, but the measured clearance rate depends upon the removal of radioactivity from the counting field, and thus on how fast the blood leaves the lungs. If the rate of removal were slow compared with the transfer of carbon dioxide from alveolar gas to blood, there would be a plateau on the records before the downstroke. The absence of this plateau is reliable evidence of fast removal of radioactive gas from the counting field. A further possible objection is that although some radioactive blood leaves the counting field very early, the rest is more gradually removed, either because the blood drains at different rates from different areas of the same field, or because the contents of the field are gradually washed out. Evidence against this is that most of the clearance curves are initially linear when plotted on semilogarithmic paper. They become curved when recirculation of radioactive blood occurs after some 10 seconds.

Oxygen-15 is not an ideal gas for measuring flow because it has a relatively slow uptake which makes the measurement of the slope imprecise. The transfer of oxygen-15 from alveoli to blood has been examined in detail, and in general the clearance rate is proportional to blood flow per unit of lung volume. In normal subjects, there is a small alveolar end-capillary gradient at rest and when the diffusing capacity of the lung is reduced, the diffusion barrier may bring about an appreciable lowering of clearance rate. Carbon dioxide does not suffer from this disadvantage.

Table 3
Geometric Means of Ratios of Second to Fourth Interspace Clearance Rates for Normal Subjects and Patients with Mitral Stenosis and Significance of Separation of the Means for Patients from Normals

<table>
<thead>
<tr>
<th>Radioactive gas</th>
<th>Mean clearance rate ratios</th>
<th>Second/fourth interspace</th>
<th>Mitral stenosis</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>0.45</td>
<td>0.96 p&lt;0.01</td>
<td>1.38 p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>0.59</td>
<td>1.03 p&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>0.30</td>
<td>2.32 p&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
as it is very diffusible and the uptake is rapid and proportional to the blood flow per unit of lung volume. It may seem incongruous that carbon dioxide labeled with oxygen-15 should be taken up rapidly in the lung, while a net excretion of ordinary carbon dioxide is taking place. The reason is that as the blood is passing along the pulmonary capillary, molecules of carbon dioxide are continually passing in both directions across the alveolar membrane. The rate at which carbon dioxide leaves the alveolar gas depends upon its partial pressure, while the rate at which it leaves the blood is proportional to its local tension. Thus, the over-all transfer depends on the difference between the partial pressure in blood and alveolar gas. Since blood arriving in the lungs contains no radioactive carbon dioxide, any partial pressure of this gas in the alveoli will insure its rapid absorption.

Since carbon monoxide becomes firmly bound to hemoglobin, it exerts no significant "back pressure," and transfer across the alveolar membrane is limited by the diffusing characteristics of the lung. This is also the case for the labeled carbon monoxide, so that the clearance rate is proportional to the diffusion per unit of lung volume.

The first group of 10 patients was studied with both oxygen-15 and carbon monoxide so that estimates of regional flow and diffusing characteristics could be made. This group was taken at random from patients with mitral stenosis representing all grades of severity. Direct comparison of the clearance rates at the 2 levels shows that 4 patients had a higher oxygen-15 clearance at the second space than at the fourth and the remaining 6 a higher clearance at the fourth than the second. The
carbon monoxide clearance rates in the same group showed 5 patients with higher clearances at the second space than the fourth, and 5 with the reverse situation. This contrasts with the normal second space clearance rate which is lower than the fourth space clearance rate in the sitting position at rest, in the ratio 0.45:1 for oxygen-15 and 0.59:1 for labeled carbon monoxide. The lower clearance rates near the lung apex in the vertical chest position in normals may be the result of gravity effect on the hydrostatic pressure, reducing perfusion. As the pulmonary artery pressure is raised in many patients with mitral stenosis, the effect of the hydrostatic pressure influence would be proportionately less. This could account for a change towards more uniform perfusion, but would not explain the apparent reversal of the normal ratio in severe cases. The most marked increase in second space clearance rates occurred in those patients with the highest pulmonary artery pressures. Since it was realized that the oxygen slopes may be influenced by regional changes in diffusion, it was decided to investigate a further group of patients with severe mitral stenosis by using labeled carbon dioxide in which the clearance rate is faster and dependent purely on perfusion. The second group of 7 cases all showed a higher carbon dioxide clearance rate at the second interspace than at the fourth in the ratio 2.32:1. Five of these patients were also studied with oxygen-15 and this showed a ratio of second to fourth interspace clearance rates of 1.38:1. In some patients, the reversal of the ratio observed with labeled carbon dioxide was more marked than with oxygen-15. The difference between the ratio obtained with the 2 gases requires further study, but may possibly depend upon reduced oxygen transfer caused by regional changes in diffusion. Determined by the carbon dioxide clearance rate, the blood flow at the level of the second interspace was up to 6 times higher than at the fourth interspace. Such changes in perfusion are remarkable and must depend upon intense vasoconstriction of the lower zone vessels or on organic narrowing, or both.

While oxygen-15 and carbon dioxide clearance rates are dependent on regional perfusion per unit of lung volume, the clearance rate of carbon monoxide is a measure of the diffusion per unit of lung volume. The high carbon monoxide clearance rate at the second interspace in some patients is of the same order as was found in normal subjects after exercise, this suggests that the raised pulmonary artery pressure has the same effect in opening the remaining apical capillaries as does exercise in normals. In some patients, the fourth space clearance rate was low without an increase at the second space. These patients may have had a low whole lung diffusing capacity, described in some patients with mitral stenosis.

The clearance rate measurements show that the normal distribution of blood flow and diffusing properties per unit lung volume tends to be reversed in patients with severe mitral stenosis. Theoretically, this could be caused by diminution in the regional blood flow or by increases in the regional lung volume. There is convincing evidence, however, that regional pulmonary vessel changes parallel the severity of mitral stenosis. Doyle et al. observed that arterial narrowing in patients with mitral stenosis complicated by pulmonary hypertension was most marked at the base and in the midzones, whereas the upper zone arteries were often normal. Steiner showed with pul-
PULMONARY UPTAKE OF RADIOACTIVE GASES

Pulmonary angiograms that the upper zone pulmonary veins were grossly dilated and the lower zone veins normal or narrow in patients with mitral stenosis and very high pulmonary artery pressures. Harrison examined lungs (post mortem) from patients with mitral stenosis and confirmed the dilatation of the arteries in the upper zone and constriction of those in the lower. He showed that the narrowing of the lower zone arteries was usually regular and even, although focal narrowing also occurred. Our results demonstrate that these changes in the radiological and pathological appearances of the vessels are associated with substantial changes in the partition of blood flow.

The changes in the lower zone vessels in mitral stenosis are difficult to explain. The hydrostatic pressure difference is small in comparison with the high arterial pressure reached in severe cases, and it is difficult to believe that it alone can be responsible for the preponderance of vascular changes in the lower zone. Changes in the pulmonary venous pressure may also play an important part. Whatever the cause may be the changes are sufficient in some cases to reduce the lower zone perfusion to a fraction of the normal and increase it in the upper zone to values near those seen in the normal lower zone.

Summary

Using radioactive oxygen ($^{18}$O) and carbon monoxide with external counting over the chest, it is possible to measure perfusion and diffusion per unit of lung volume. Patients with mitral stenosis, particularly those with high pulmonary artery pressures, may show a higher blood flow through the upper zone of the lung than the lower. This distribution of blood flow is the reverse of that found in normal subjects. The observed changes in blood flow are consistent with the radiological and pathological changes in the pulmonary vascular tree in mitral stenosis.

Acknowledgment

We should like to thank the staff of the M.R.C. cyclotron for the use of their facilities, Mr. P. Buckingham for valuable technical assistance, and Dr. P. Hugh-Jones and Professor J. McMichaels, F.R.S., for interest and support.

Summario in Interlingua

Per medio del uso de radioactiva oxygeno ($^{18}$O) e mono- o bioxydo de carbon, con contation externe supra le thorace, il es possibile mensurar perfusion e diffusion per unitate de volumine pulmonar. Patientes con stenosis mitral—particularly in le presentia de alte pressiones pulmonoarterial—monstra frequentemente un plus intense fluxo de sanguine in le zone superior del pulmon que in le zone inferior. Iste distribution es le contrario de lo que es incontrate in subjectos normal. Le observe alteraciones es congrue con le alteraciones radiologic e pathologic in le vascularatura pulmonar de patientes con stenosis mitral.

References


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