Pulmonary vascular dilatation and diffusion-dependent impairment of gas exchange in liver cirrhosis


ABSTRACT: To test the hypothesis that diffusion-limitation for oxygen is due to abnormal vascular dilatation and significantly contributes to the arterial hypoxaemia of liver cirrhosis requires an experimental approach that detects both diffusion-limitation for oxygen and the presence of abnormal dilatation of pulmonary vessels exposed to alveolar gas.

We therefore studied the gas exchange of a 64 year old man with alcoholic liver cirrhosis and severe resting arterial hypoxaemia (arterial oxygen tension \( P_{a,O_2} \) 7.5 kPa) whilst breathing air and 100\% O\(_2\) using conventional blood gas (CBG) analysis, the multiple inert gas elimination technique (MIGET) and whole body scintigraphy (WBS) following the i.v. administration of radiolabelled boli of macroaggregates with a minimum diameter of 15 µM.

During air breathing, there was a consistently positive difference between the arterial oxygen tension predicted by MIGET and that actually measured (P-M \( P_{a,O_2} \), average 0.9 kPa). During \( O_2 \) breathing, P-M \( P_{a,O_2} \) became negative, (average -12.2 kPa), and shunt estimated by the \( O_2 \) method (% of \( Q' \)) was consistently less than that measured by MIGET. Whereas both \( O_2 \) method and MIGET estimates of shunt never exceeded 25\%, the WBS shunt was 40\%, indicating that a substantial fraction of cardiac output flowed through abnormally dilated pulmonary vessels, some of which were exposed to alveolar gas and, hence, participated in gas exchange.

Although our observations pertain to one subject, we believe they provide the most convincing in vivo evidence to date that abnormal dilatation of interalveolar vessels may, per se, result in a significant diffusion impairment for \( O_2 \). Furthermore, in view of the consistently negative P-M \( P_{a,O_2} \) observed during oxygen breathing, we speculate that such abnormal vascular dilatation may also have produced a significant diffusive impairment of one or more of the less soluble inert gases used in the MIGET analysis.


Patients with significant arterial hypoxaemia and liver cirrhosis are known to have extensive pulmonary vascular dilatation, which is largely interalveolar in location [1–3]. It has been postulated that blood flowing through such dilated interalveolar vessels may not fully equilibrate with alveolar gas because of the increased distance between the alveolar-capillary membrane and red blood cells, resulting in a diffusive impairment to oxygen uptake [4, 5]. This mechanism has been proposed to explain why, when such patients breathe 100\% oxygen, there is typically both a marked increase in arterial oxygen tension \( P_{a,O_2} \) and a substantial negative discrepancy between functional and "anatomical" shunt fractions as quantified by the conventional oxygen method and radionuclide macroaggregate technique, respectively [4–8]. These observations, whilst collectively indicative of abnormal interalveolar vascular dilatation, are not sufficiently specific to validate the actual presence of diffusion-limitation for oxygen. Thus, significant inequality of alveolar ventilation-perfusion ratios \( V'\lambda/Q' \) could equally explain a marked improvement in arterial \( P_{a,O_2} \) with 100\% oxygen breathing. Indeed, recent studies using the multiple inert gas elimination technique (MIGET), an analysis which can indirectly detect oxygen diffusion-limitation, have attributed the arterial hypoxaemia in patients with liver cirrhosis to \( V'\lambda/Q' \) inequality and intrapulmonary shunting [9–11]. However, none of these MIGET studies has provided any direct evidence of actual pulmonary vascular dilatation; and, hence, they do not, by themselves, invalidate the specific hypothesis that diffusion-limitation for oxygen can occur as a direct consequence of abnormal dilatation of interalveolar vessels.

To adequately test the above hypothesis requires an experimental approach that has the power to simultaneously...
detect both diffusion-limitation for oxygen and the presence of abnormal dilatation of pulmonary vessels exposed to alveolar gas. Since the MIGET analysis and radiotrace macroaggregate technique, respectively, fulfill these criteria, we utilized both methods to assess the pulmonary gas exchange of a 64 year old man with alcoholic liver disease and severe arterial hypoxaemia, whilst breathing air and 100% oxygen.

Subject and methods

A 64 year old retired forestry worker presented with a 5 year history of progressive exertional dyspnoea. He admitted to an alcohol consumption of 60 gm·day⁻¹ for 30 yrs, and a 30 pack-year smoking history. Examination revealed a moderately obese man with gross finger clubbing and extensive spider naevi, who became cyanosed on mild exertion. Examination of his respiratory and cardiovascular systems was normal. His liver was enlarged, with a span of 16 cm, but there was no clinical evidence of splenomegaly or abdominal ascites. Chest radiographic image appeared completely normal. Liver scan revealed an enlarged liver with generalized poor and patchy uptake. Routine liver function tests revealed a mildly reduced serum albumin of 33 g·L⁻¹ (normal 35–45 g·L⁻¹) and mildly increased total bilirubin of 35–45 g·L⁻¹ (normal 0.34–1.02 mL·min⁻¹·kg), and liver biopsy showed a histological picture consistent with inactive alcoholic cirrhosis. Pulmonary function tests revealed mild airflow obstruction with a forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) of 70 and 79%, respectively, and an FEV₁/FVC ratio of 69%. Lung volumes measured by body plethysmography were also slightly reduced with total lung capacity (TLC) and vital capacity (VC) both 78% pred. Transfer factor for carbon monoxide, measured by the single-breath helium method, was markedly impaired (0.17 mL·min⁻¹·kg, normal range 0.34–1.02 mL·min⁻¹·kg), and liver biopsy showed a histological picture consistent with inactive alcoholic cirrhosis. Pulmonary function tests revealed mild airflow obstruction with a forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) of 70 and 79% predicted, respectively, and an FEV₁/FVC ratio of 69%. Lung volumes measured by body plethysmography were also slightly reduced with total lung capacity (TLC) and vital capacity (VC) both 78% pred. Transfer factor for carbon monoxide, measured by the single-breath helium method, was markedly impaired (34% pred). Arterial blood gas determination breathing room air showed $P_{a,CO_2}$ 7.3 kPa, arterial carbon dioxide tension ($P_a,CO_2$) 3.1 kPa and pH 7.45. A contrast bubble echocardiogram using a transoesophageal lead showed normal biventricular size and function with no evidence of an intracardiac shunt. However, delayed echocardiography was observed in the left heart chambers approximately three cardiac cycles after its detection in the right heart chambers, consistent with the presence of intrapulmonary shunt [7].

The patient was then studied on three consecutive days. On days 1 and 3, 135 MBq of $^{99m}$Tc-labelled albumen macroaggregates (mean size=20 µm, range 15–50 µm) were injected into an antecubital vein, while the patient was sitting erect breathing air and while breathing 100% $O_2$ for 30 min, respectively. After 5 min, the subject then adopted the supine posture and whole body scintigraphy was performed over the subsequent 15 min using a large field of view gamma camera linked to a dedicated micro-delta nuclear medicine computer (Siemens). Counts were collected from anterior and posterior images of the lungs, abdomen and legs, as well as right and left lateral images of the head and anterior images of the arms. For each image, counts were collected for 1 min, and where two views were involved, these counts were averaged. Counts emanating from the thyroid gland were excluded from the analysis. The percentage of radiolabelled macroaggregates shunted from pulmonary to systemic circulation was calculated by the equation proposed by Gates et al. [12]:

$$\frac{\text{total body counts-total lung counts}}{\text{total body counts}} \times 100 = \% \text{ right-to-left shunt}$$

This is a quantitative measure of the percentage of cardiac output flowing through vessels >15 µm in diameter. This method has been documented to give estimates of shunt that closely correspond with those measured by the classical $O_2$ method, both in pulmonary disease with known large arterio-venous (A-V) malformations [13] and in intracardiac right-left (R-L) shunts [12]. Using the same batch of macroaggregates, whole body scintiscans were performed on two patients with suspected pulmonary emboli on days 1 and 3, and the calculated shunt estimates were 3 and 4%, respectively. On both study days, radiopharmaceutical analysis found >97% of $^{99m}$Tc was bound to the albumen macroaggregates.

On day 2, gas exchange was studied using conventional blood gas analysis and the MIGET. The latter analysis has been described in detail by Wagner and co-workers [14], and our application of it has been published [15]. Six inert gases (acetone, diethyl ether, enflurane, cyclopropane, ethane and sulphur hexafluoride (SF₆) dissolved in normal saline) were infused intravenously, and mixed venous and arterial blood was sampled from indwelling pulmonary and radial arterial catheters. The subject wore a noseclips and breathed through a mouthpiece. Blood and expired gas were sampled whilst the subject, in the seated posture, breathed air (three runs), and 100% $O_2$ for 30 min (2 runs). One run was also obtained in the supine posture whilst breathing 100% $O_2$. Cardiac output was measured from the mass balance characteristics of the inert gases. Haemoglobin and haematocrit were measured, as was the partial pressure of $O_2$ required to achieve 50% saturation of arterial blood ($P_{SO_2}$). Oxygen tension ($P_O_2$) and carbon dioxide tension ($P_{CO_2}$) were measured from both arterial and mixed venous samples using a Corning 178 automatic pH/blood gas system. This system was automatically calibrated throughout the study period with serial one and two point calibrations every 15 and 60 min, respectively ($P_{O_2}$ range 0–11.5 kPa). Under these operating conditions, the Corning 178 has been documented to show only a small degree of imprecision, even at relatively high $P_{O_2}$ (95% confidence limits = $\pm$2.4 kPa at a $P_{a,CO_2}$ of 50.3 kPa; manufacturer’s instructions, Corning 178). As a further check, we subsequently tested the individual accuracies of both gas electrodes, previously calibrated as above, with blood equilibrated for 40 min with a gas mixture containing 40.3% $O_2$ and 6.0% $CO_2$, the concentrations of which were validated by standard electro-chemical and Haldane techniques, respectively. Predicted $P_{O_2}$ for the equilibrated blood was 38.5 kPa.
This compared with duplicate $P_O_2$ measurements obtained from each electrode of 38.1, 38.3 kPa and 38.0, 38.8 kPa, respectively. Mixed venous and arterial contents for both gases were derived. Venous admixture ($% Q'$) was calculated both during air and 100% O$_2$ breathing by the standard equation (table 1 and fig 1).

$$Q'/Q' = Ci,O_2 - Ca,O_2 / Ci,O_2 - CV,O_2$$

where $Ci$, $Ca$ and $CV$ equal the oxygen content of ideal, arterial and mixed-venous blood, respectively. The partial pressures of the inert gases were measured for the arterial, mixed venous and expired gas samples, their retentions and excretions were derived, and the distribution of ventilation-perfusion as a function of ventilation-perfusion ratio ($V'A/Q'$) were determined. From MIGET we obtained the inert gas shunt and predicted $P_a,O_2$ on air and oxygen, and the predicted venous admixture on air.

### Results

During air breathing, the predicted $P_a,O_2$ was consistently greater than measured $P_a,O_2$ (P-M $P_a,O_2$) with an average difference of 0.9 kPa (table 1). Despite a moderate degree of $V'A/Q'$ inequality, as quantified by the indices log SDQ' and log SDV', only a negligible quantity of $Q'$ perfused low $V'A/Q'<0.1$ (table 1). Partitioning of the total venous admixture predicted by MIGET into that due to $V'A/Q'$ inequality and pure shunt revealed equivalent contributions from each mechanism. However, consistent with the positive P-M $P_a,O_2$, the predicted venous admixture was substantially less than that actually measured (42% vs 59% of $Q'$, respectively; (table 1 and fig 1). During O$_2$ breathing, there was little change in the measured degree of $V'A/Q'$ inequality. However, the P-M $P_a,O_2$ was negative in both runs.
(average = -12.2 kPa), and the MIGET estimate of shunt was greater than that measured by the O$_2$ method (25 vs 18% of $Q'$, respectively). Similar discrepancies were also apparent in the single run performed in the supine posture (table 1). During air and 100% O$_2$ breathing, the radio-labelled macroaggregates of shunt were 41 and 40% of $Q'$, respectively, considerably exceeding that measured by MIGET on air and by MIGET and O$_2$ methods on 100% O$_2$ (table 1).

### Discussion

Both in vivo angiography and postmortem studies of patients with liver disease and arterial hypoxaemia have consistently documented the presence of extensive pulmonary vascular dilatation, which is limited mainly to those vessels exposed to alveolar gas [1–3, 7]. As observed in our current subject, these patients typically show a substantial increase in $P_{a,O2}$ on breathing 100% oxygen, and measurements of intrapulmonary "anatomical" shunt using the radionuclide macroaggregate technique substantially exceed functional estimates of shunt as measured by the O$_2$ method [2, 7, 8]. Taken together, these observations have been interpreted as convincing evidence that diffusion-limitation of O$_2$ due to alveolar vascular dilatation is a significant contributory mechanism to the arterial hypoxaemia associated with liver disease [2, 5, 7].

On the other hand, AGUSTI et al. [11] have argued that only studies utilising the MIGET analysis can satisfactorily examine the potential role of diffusion-limitation in the overall pulmonary gas exchange of such patients, and have concluded that, even in the presence of moderate arterial hypoxaemia, the role of diffusion-limitation appears negligible. However, only two studies, each involving six subjects, have specifically used the MIGET analysis to assess gas exchange in patients with liver disease and moderate to severe arterial hypoxaemia ($P_{a,O2}$ <9.3 kPa) [10, 16]. In both patient groups, as in our subject, there were significant differences between $P_{a,O2}$ predicted by MIGET and $P_{a,O2}$ actually measured (P-M $P_{a,O2}$, 0.7 and 1.3 kPa, respectively). The authors of both studies proposed postpulmonary shunting as the most likely explanation for the observed P-M $P_{a,O2}$ differences. However, such a mechanism would not explain the complete abolition of the P-M $P_{a,O2}$ when breathing 100% O$_2$, as observed by EDELL et al. [10] and in our current subject. Moreover, physiological postpulmonary shunting would appear insufficient to account for the observed P-M $P_{a,O2}$ differences, particularly at $P_{a,O2}$<8.0 kPa. Similarly, portopulmonary anastomosis have only rarely been identified [1] and, when present, carry only small quantities of blood which is relatively O$_2$ rich [17]. We, therefore, believe that the consistent P-M $P_{a,O2}$ differences observed in our subject and those of EDELL et al. [10] and CASTAING and MANIER [16] are most likely to represent a significant diffusion impairment for O$_2$ occurring at the alveolo-capillary level. In our subject, such diffusion-limitation contributed equally with right-left shunting and $V_A/Q'$ inequality to the overall impairment of O$_2$ gas exchange when quantified in terms of venous admixture (fig. 1). Whereas the MIGET analysis can indirectly detect the presence of diffusion-limitation and quantify its relative contribution to arterial hypoxaemia, it cannot, alone, identify the presence of abnormal vascular dilatation. Similarly, the radionuclide macroaggregate (RM) estimate of intrapulmonary shunt, whilst providing anatomical evidence of abnormal pulmonary vascular dilatation, cannot quantify the contribution that such an abnormality may functionally have on overall gas exchange. In our subject, both MIGET and O$_2$ estimates of shunt are considerably less than that estimated by the RM method (table 1), indicating that a substantial fraction of the injected radionuclide macroaggregates must have passed from the pulmonary to systemic circulations via dilated vascular channels which are exposed to alveolar gas and participate in gas exchange. Otherwise, there should have been no observed differences between functional estimates of shunt (i.e. MIGET and O$_2$ methods) and that measured by the RM method. It therefore seems reasonable to conclude that the observed diffusion-limitation for O$_2$ is most likely to be a consequence of the demonstrated alveolar vascular dilatation.

Theoretical and in vitro studies provide substantial evidence for significant diffusion-limitation to O$_2$ uptake in blood flowing in vessels larger than 20 µm. The flow profile in such vessels is parabolic and, because of sheer forces, red blood cells (RBC) tend to move away from the vessel wall resulting in a radial distribution of haematorcit [18]. Thus, for blood flowing in the centre, as opposed to that flowing along the wall, not only is there a greater overall alveolo-capillary distance for O$_2$ molecules to diffuse, but its transit time is effectively shortened and it contains a greater concentration of potential O$_2$ carrying RBC. Furthermore, the diffusivity of oxygen within this increased "alveolar-capillary distance" is likely to be substantially reduced by intervening high resistance plasma layers [19, 20].

An intriguing observation of the current study is that in all three oxygen runs the measured $P_{a,O2}$ values were consistently greater than those predicted by the MIGET analysis (table 1). Similarly, in two of the three patients with liver disease and arterial hypoxaemia recently reported by EDELL et al. [10], the measured $P_{a,O2}$ values were greater than those predicted by MIGET during O$_2$ breathing. These findings contrast with previously published studies using the MIGET analysis in both normal and patient groups breathing 100% O$_2$, in whom the measured $P_{a,O2}$ values were invariably substantially less than those predicted by MIGET [14, 21, 22]. In our own laboratory, using essentially the same experimental protocol and technical equipment as in the current study, we have never previously observed the measured $P_{a,O2}$ to exceed that predicted by MIGET in a large number of both normal subjects and patients with varying lung disorders when breathing 100% O$_2$ [23]. Indeed, inevitable leaks in the O$_2$ delivery system, deterioration of the arterial blood samples prior to analysis, and insensitivity of the MIGET analysis to detect physiological postpulmonary shunt should all conspire to produce a positive P-M $P_{a,O2}$ during 100% O$_2$ breathing [14, 21]. Particularly in view of our
limited data base, experimental error could explain our observation, the most likely sources being in the actual measurement of $P_aO_2$ and/or in the MIGET analysis. It would seem unlikely that there were significant errors in our $P_aO_2$ measurements (see Methods). The greater shunt estimate as measured by MIGET compared with the $O_2$ method, raises the possibility that the former may have been overestimated either as a consequence of MIGET’s known inability to separate pure shunt ($V'/Q'=0$) from very low $V'/Q'$ units ($V'/Q'<0.005$) or, because of fitting error in the recovered distributions. Neither of these possibilities appear likely since for the three oxygen runs the maximum observed % of $Q'$ going to $V'/Q'$ units <0.1 was 1.6%, and the goodness of fit of the recovered distributions, as quantified by the residual sum of squares, was excellent for all runs and comparable during air and $O_2$ breathing (table 1).

An alternative explanation is that the inert gas $SF_6$, the second heaviest of the six inert gases and the gas exchange characteristics of which are the principal determinant of the MIGET shunt, was also partially diffusion-limited. Such diffusion-limitation would presumably still be less than that for $O_2$ during air breathing, hence still permitting our observation of a positive P-M $P_aO_2$. However, during 100% $O_2$ breathing, the corresponding sixfold increase in the alveolo-capillary $O_2$ gradient may have been sufficient to specifically reduce the diffusion-limitation for $O_2$, such that it actually became less than that for $SF_6$. This would be consistent with the observed greater MIGET estimate of shunt compared with that estimated by the $O_2$ method and the corresponding negative P-M $P_aO_2$ (table 1). Breathing 100% $O_2$, by releasing hypoxic vasoconstriction, may also have resulted in a further increase in the diameter of those intra-alveolar vessels already abnormally dilated, thus further predisposing $SF_6$ to diffusion-limitation. This would neatly explain the increase in MIGET shunt observed during $O_2$ breathing (table 1). The alternative explanation of oxygen-induced atelectasis would appear distinctly unlikely, as there was neither evidence of any units with very low $V'/Q'$ ratios during air breathing nor any apparent loss of units with low $V'/Q'$ ratios during $O_2$ breathing.

The commonly held belief that inert gases are not diffusion-limited is based on a theoretical analysis of alveolocapillary gas equilibration, which predicts that both in health and disease, diffusion-limitation of individual MIGET inert gases should be readily detectable by consideration of the respective retentions (R) and blood-gas partition coefficients (i.e. $\lambda$) of all six gases [14, 21, 27]. The theoretical basis for such an approach is that, in a homogeneous gas-exchanging lung in which there is complete alveolo-capillary inert gas equilibration, the inverse of individual gas R and $\lambda$ values (and corresponding logarithmic transformations $ln(1-R/R)$ and $ln(1/\lambda)$) are linearly related [14, 26]. Thus, a gas which is diffusion-limited will diverge from the linear relationship determined by the other five diffusion-independent gases. However, such relationships become increasingly nonlinear with increasing degrees of simulated $V'/Q'$ inequality [26] and shunt (Crawford et al. unpublished observations) with the most poorly soluble gases diverging most (fig. 2a).

Since we are proposing that any diffusion-limitation is occurring within the blood phase, wherein the solubility of a given inert gas is the primary determinant of its ability to achieve intravascular equilibration, any relative diffusion-limitation would be most likely to occur (and hence most likely to be detectable) between the two least soluble MIGET inert gases, i.e. $SF_6$ and ethane. Thus, if there is significant diffusion limitation for $SF_6$, one would predict that its retention should be relatively greater than that of ethane. However, as already pointed out above, the greater the shunt the more $SF_6$ will be retained relative to ethane, without the need to invoke diffusion-limitation specific for $SF_6$ (fig. 2a). In the oxygen runs, we have two estimates of shunt: that determined by MIGET ($Q'/Q'=25$%) and that by the classical oxygen method ($Q'/Q'=18$%). The measured retention of $SF_6$, relative to that of ethane ($SF_6/EtHr$) has, for the three $O_2$ runs, a mean value of 0.77 (range 0.75–0.84). In contrast, a simulation, utilizing a modified version of the lognor programme of West, and which assumes inert gas diffusion equilibration [22], predicts, for the same input variables $V_A$, $Q'$, ventilation-perfusion inequality and shunt as quantified by the MIGET analysis as $SF_6/EtHr$ of
The same simulation, but with a shunt value of 18% (corresponding to that estimated by the oxygen method), predicts an even smaller SF6/EthR of 0.64. Thus, at least within the range of shunt values estimated experimentally, the measured retention of SF6 is relatively greater than that of ethane when compared with simulations that do not allow for possible inert gas diffusion-limitation (fig. 2b).

When the individual raw measured retentions for SF6 and ethane are compared with those predicted from the curve fitting procedure utilizing the retention values of all six inert gases, in five of the six experimental runs the retention of SF6 estimated from the curve fit is less than that actually measured, whereas the opposite is the case for ethane (fig. 3). This consistent dispersion of the two least soluble inert gases implies there is an additional factor determining the relative retention characteristics of these two gases which is not influencing the other more soluble gases. This is exactly what might be predicted in the event of a specific diffusion-limitation for SF6 relative to ethane.

In the context of the current study, diffusion-limitation for SF6 would have resulted in an increase in its retention relative to excretion, which the MIGET analysis, since it assumes inert gas equilibration, would have attributed to $V'/Q'$ inequality and/or shunt. Thus, the degree of $V'/Q'$ inequality and/or shunt would have been overestimated and that due to $O_2$ diffusion limitation underestimated. Similarly, even the $O_2$ method can only be regarded as a true quantification of intrapulmonary shunt if, in fact, 100% $O_2$ is sufficient to completely overcome any underlying $O_2$ diffusion-limitation. However, even this assumption may be questioned in the presence of severe alveolo-capillary diffusion-limitation [28, 29].

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References


