Quantification of right-to-left shunt with $^{99m}$Tc-labelled albumin macroaggregates and 100% oxygen in patients with hereditary haemorrhagic telangiectasia

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ABSTRACT

Pulmonary arteriovenous malformations (PAVMs) are often associated with hereditary haemorrhagic telangiectasia (HHT). The quantification of right-to-left shunts in patients with PAVMs is important in diagnosis and follow up. Traditionally, this shunt is measured by the 100% oxygen method, in which the value for the arteriovenous difference in oxygen content, $C_{aO_2} - C_{vO_2}$ (where $C_{aO_2}$ is the oxygen content of arterial blood and $C_{vO_2}$ is the oxygen content of mixed venous blood) is estimated. Alternative methods consist of measurement of the systemic or renal uptake of $^{99m}$Tc-labelled macroaggregates of albumin (MAA), which are trapped in pulmonary capillaries, but pass through PAVMs. We first measured $C_{aO_2} - C_{vO_2}$ in 12 HHT patients before and after embolization of PAVMs. We obtained a mean value of 4.4 ml/100 ml, instead of the usual 5 ml/100 ml. Subsequently, we measured right-to-left shunt in 21 HHT patients using the 100% oxygen method and with two different methods involving $^{99m}$Tc. We used the kidney–lung method (K/L method), in which it is assumed that the right kidney receives 10% of the cardiac output, and we also used a method with two tracers (HSA/MAA method): (1) $^{99m}$Tc-labelled human serum albumin (HSA) (which passes through pulmonary capillaries) to measure the fraction of the cardiac output perfusing the kidneys, and (2) MAA to measure the shunt fraction. In 35 shunt measurements we evaluated this new technique and the K/L method, by comparing the results with those from the 100% oxygen method. There was poor agreement between the 100% oxygen method and the K/L method, with 95% limits of agreement for the shunt fraction of -15.2% to +15.2%. There was moderate agreement between the 100% oxygen method and the HSA/MAA method, with limits of agreement of -8.3% to +7.7%. We conclude that the different methods cannot replace each other, because the limits of agreement are too wide for clinical use.

Key words: arteriovenous malformations/diagnosis, hereditary haemorrhagic, technetium, telangiectasia.
Abbreviations: AVM, arteriovenous malformation; $C_{aO_2}$, oxygen content of arterial blood; $C_{vO_2}$, oxygen content of mixed venous blood; Hb, haemoglobin; HHT, hereditary haemorrhagic telangiectasia; HSA, human serum albumin; K/L method, kidney–lung method; MAA, macroaggregates of albumin; PAVM, pulmonary arteriovenous malformation; $P_{O_2}$, partial pressure of $O_2$; R–L shunt, right-to-left shunt; ROI, region of interest.
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INTRODUCTION

Pulmonary arteriovenous malformations (PAVMs) are unusual abnormalities of the pulmonary vascular tree, which are often associated with hereditary haemorrhagic telangiectasia (HHT) [1–3]. They lead to a right-to-left (R–L) shunt, due to a direct connection between the pulmonary artery and vein. These R–L shunts may cause hypoxaemia, dyspnoea, cyanosis and sometimes polycyaemia. In addition, PAVMs can allow emboli and bacteria which are normally trapped in the pulmonary capillaries to pass directly into the systemic circulation, resulting in a stroke or cerebral abscess [1,4]. These potentially serious complications justify transcatheater embolization of PAVMs, even in asymptomatic patients [5,6]. With this procedure, coils are placed in the feeding arteries of the PAVMs, close to the aneurysmal sacs of the PAVMs. This treatment usually does not compromise normal lung tissue.

The quantification of R–L shunts in patients with PAVMs is important both in diagnosis and in follow up after therapy [1,2,7,8]. Traditionally, this shunt is measured by the 100% oxygen breathing method, originally described by Berggren [9] and Saxton [10]. This method measures the R–L shunt, including the physiological shunt from bronchial, mediastinal, cardiac and Thebesian veins to the left atrium [11]. The method may be inconvenient for the patient, because it requires breathing of 100% oxygen for at least 20 min with a clip on the nose. In addition, sampling of arterial blood is required. In the equation used to calculate the shunt fraction (see the Methods section), the mixed venous oxygen content is usually estimated by subtracting a value of 5 ml/100 ml from the arterial oxygen content [10,11]. This assumption may be invalid in HHT patients, because of the presence of a left-to-right shunt, caused by multiple telangiectases or AVMs in other organs. The arteriovenous difference in oxygen content (\( C_{aO_2} - C_{VO_2} \), where \( C_{aO_2} \) is the oxygen content of arterial blood and \( C_{VO_2} \) is the oxygen content of mixed venous blood) has not been measured in a series of HHT patients.

An alternative method of quantification of R–L shunts involves measurement of the systemic uptake of \(^{99m}\text{Tc}\)-labelled albumin microspheres or macroaggregates of albumin (MAA), which are normally trapped in pulmonary capillaries, but pass through PAVMs [12]. This method measures the anatomical intrapulmonary shunt, which is the shunt of interest in patients with PAVMs. Chilvers et al. [13] and Whyte et al. [14] described a method in which they quantified R–L shunts by comparing the activity over the right kidney with the total dose administered or with the activity over the lungs. In this kidney–lung method (K/L method) it is assumed that the right kidney receives 10% of cardiac output. The fraction of cardiac output perfusing a target organ can also be determined by measuring the fraction of an intravenous injected bolus of a tracer small enough to pass the pulmonary capillaries. Strauss et al. [15] used unbound technetium to this end. We have used \(^{99m}\text{Tc}\)-labelled human serum albumin (HSA), which passes the pulmonary capillaries, to measure the fraction of cardiac output perfusing the kidney, and MAA to measure the shunt fraction, by comparing activity over the kidney with that over the lung (HSA/MAA method).

In the present study we first measured \( C_{aO_2} - C_{VO_2} \) in patients with HHT, before and after embolization, in order to obtain an accurate value for the arteriovenous difference in oxygen content in patients with HHT, for calculation of R–L shunts. Next we evaluated the HSA/MAA method as well as the K/L method, by comparing the results obtained with those from the 100% oxygen method.

METHODS

Patients

We measured \( C_{aO_2} - C_{VO_2} \) in 12 patients with HHT and PAVMs (four men and eight women). The mean age of the patients was 39.0 years (range 23–66 years). All patients had multiple telangiectases. One patient had some minimal AVMs in the liver, and another patient had a small cerebral AVM.

Subsequently we measured the R–L shunt in 21 other patients with HHT and PAVMs (10 men and 11 women). The mean age of the patients was 40.7 years (range 19–72 years). There was no evidence of co-existing intracardiac shunts. In 14 patients we repeated shunt measurements after embolization. The R–L shunt was measured with the 100% oxygen method, the K/L method and the HSA/MAA method.

All patients gave written consent to participate in the study, which was approved by the local medical ethics committee.

Measurement of \( C_{aO_2} - C_{VO_2} \)

In the first 12 patients we measured the R–L shunt with the subject in the supine position, before and directly after embolization, using the 100% oxygen method (see below). An arterial blood sample and a sample from the pulmonary artery were obtained after breathing pure oxygen for 30 min. The oxygen content (C) was calculated as follows:

\[
C \text{ (ml of O}_2/100 \text{ ml of blood) = 0.0225} \times P_{O_2} + 2.24 \\
\times [Hb] \times S_{aO_2}/100
\]

where \( P_{O_2} \) is partial pressure of \( O_2 \) (kPa), [Hb] is haemoglobin concentration (mmol/l) and \( S_{aO_2} \) is arterial oxygen saturation (%). The total blood oxygen content is composed of dissolved \( O_2 \) plus \( HbO_2 \). The solubility of oxygen in blood is 0.0225 ml·100 ml⁻¹·kPa⁻¹.
Figure 1  Quantification of R–L shunt with $^{99m}$Tc-MAA and $^{99m}$Tc-HSA: static images and time–activity curves

Left panels: static (summed) images in posterior view of a patient with an R–L shunt, during the first minute after injection of $^{99m}$Tc-MAA (upper panel) and during the first minute after injection of $^{99m}$Tc-HSA (lower panel). The images show overlap from the spleen to the left kidney. Right panel: time–activity curves generated from lungs (upper trace) and kidneys (lower case) of a patient with an R–L shunt.

The R–L shunt fraction was calculated with an estimated $C_{ao_2} - C_{vo_2}$ of 5 ml/100 ml (shunt$^{est}$), as well as with the measured value (shunt$^{meas}$).

100% oxygen method

Patients breathed 100% oxygen from a Douglas bag, via a closely fitting mouthpiece and a two-way valve, while wearing a noseclip. They were instructed to take a deep breath every 1 min. An arterial blood sample was obtained at functional residual capacity after the subject had been breathing oxygen for 30 min. The blood samples were taken with glass syringes, cooled on ice, and analysed immediately for oxygen and carbon dioxide tensions.

The R–L shunt was then calculated using the classical equation [16,17]:

$$Q_s/Q_t = (C_{co_2} - C_{ao_2})/(C_{co_2} - C_{vo_2})$$

in which $Q_s/Q_t$ is shunt as a fraction of cardiac output. $C_{co_2}$ is oxygen content at the end of the pulmonary capillary. $P_{co_2}$ is assumed to equal alveolar $P_{o_2}$ ($P_b - P_{aco_2} = P_{ah_o}$), where $P_b$ is barometric pressure (101.3 kPa) and $P_{ah_o}$ is saturated water vapour pressure in the alveoli, which is 6.3 kPa at a body temperature of 37 °C. $S_o_2$ at the end of the pulmonary capillary is assumed to be 100%.

HSA/MAA method

With the patient in the supine position, a bolus injection of 185 MBq of $^{99m}$Tc-MAA (Pulmocis*) was injected into an antecubital vein. The distribution of the MAA was measured, in posterior view, by dynamic acquisition.
The shunt fraction was then calculated as follows:

\[
\text{Shunt} \% = \frac{\text{MAA-activity}_{\text{kidneys}} \times \frac{1}{Q_k}}{\text{MAA-activity}_{\text{kidneys}} \times \frac{1}{Q_k} + \text{MAA-activity}_{\text{lungs}}}
\]

**K/L method**

For calculation of the R–L shunt, ROIs were drawn over the right kidney and both lungs, using the data from the first injection of \(^{99m}\text{Tc}-\text{MAA}. In cases of overlap from the lung to the kidney region, the ROI over the right kidney was not adjusted. For calculation of the R–L shunt according to the K/L method, it was assumed that the right kidney receives 10% of cardiac output \([13,14]\). The following equation was used for calculation of the shunt fraction:

\[
\text{Shunt} \% = \frac{\text{MAA-activity}_{\text{kidneys}} \times 10}{\text{MAA-activity}_{\text{kidneys}} \times 10 + \text{MAA-activity}_{\text{lungs}}}
\]

**Statistical analysis**

The differences between \(\text{shunt}^{\text{meas}}\) and \(\text{shunt}^{\text{est}}\) were evaluated using the paired \(t\) test. A 95% confidence interval was calculated for the mean value of the measured \(\text{CaO}_2 - \text{CVO}_2\), and we assessed whether the standard value of 5 ml/100 ml was included within this interval.

The three methods of quantification of R–L shunt were compared by: (1) ANOVA, using the methods and subjects as main factors, (2) calculation of the correlation coefficient, (3) the method suggested by Bland and
Altman [18], and (4) calculation of the intra-class coefficient, as suggested by Kramer and Feinstein [19]. The method of Bland and Altman plots the differences between two methods with twice the S.D. against their mean. The latter is done because of the absence of a 'gold standard'. The intra-class correlation coefficient calculates the conformity of two parameters and corrects the correlation for systemic bias. Its value can vary between −1 and +1; a value of > 0.75 is considered to be a minimum for concordance.

**RESULTS**

**Measurement of \( C_{aO_2} \) − \( C_{vO_2} \)**

Table 1 shows the results of the measurements of \( C_{aO_2} \) − \( C_{vO_2} \) and quantification of the R–L shunt with 100% oxygen. The mean value of \( C_{aO_2} \) − \( C_{vO_2} \) before embolization was 4.2 ml/100 ml; this rose to 4.5 ml/100 ml after embolization. This change was not significant (\( P < 0.28 \)). The mean (±95% confidence interval) value of \( C_{aO_2} \) − \( C_{vO_2} \) when combining data obtained before and after embolization was 4.4 (±0.3) ml/100 ml, i.e. significantly less than 5 ml/100 ml (\( P < 0.001 \)).

The mean value for shunt using combined data obtained before and after embolization was 7.6% (S.D. 6.0%), and that for shunt using was 8.6% (6.3%). This small error of 1.0% was significant (\( P = 0.001 \)) and represents approx. 10% of the shunt fraction. Therefore a \( C_{aO_2} \) − \( C_{vO_2} \) value of 4.4 vol.% was used in the second part of the study, instead of the usual value of 5 vol.%.

Pulmonary artery pressure did not change significantly after embolization (\( P = 0.27 \)).

**Quantification of the R-L shunt with \(^{99m}\text{Tc}\) and 100% oxygen**

Table 2 shows the shunt measurements obtained using the different methods. Table 3 shows the percentage of cardiac output received by the right kidney. The data showed a normal distribution.

The mean values (95% confidence intervals) of the shunt measurements were 10.1% (7.9–12.3%) for the 100% oxygen method, 10.4% (7.8–13.0%) for the

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<td>S.D.</td>
<td>7.8</td>
<td>8.4</td>
<td>13.3</td>
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Table 3 Percentage of cardiac output perfusing the right kidney, measured using 99mTc-HSA

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<th>Q (%)</th>
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<th>Q (%)</th>
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<tr>
<td>11</td>
<td>4.3</td>
<td>Mean (S.D.)</td>
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Figure 2 Bland–Altman plot of shunts measured by the K/L and 100% O₂ methods
The differences between the results are plotted against their mean.

Figure 3 Bland–Altman plot of shunts measured by the HSA/MAA and 100% O₂ methods
The differences between the results are plotted against their mean.

DISCUSSION

We measured a mean value for \( \text{CaO}_2 - \text{CvO}_2 \) of 4.4 ml/100 ml in supine HHT patients breathing 100% oxygen. The 'standard' value of 5 ml/100 ml is based on several studies, carried out 40–70 years ago, which revealed different data: from a minimum value of 4 ml/100 ml to a maximum of 6 ml/100 ml [9,10,20]. \( \text{CaO}_2 - \text{CvO}_2 \) depends on several factors, such as oxygen consumption, cardiac output (according to the Fick formula), left-to-right shunt, and Hb level and systemic arterial saturation, both of which influence cardiac output. The Hb level in our patients was in the normal range, as was arterial saturation, due to the breathing of pure oxygen. All of our patients had some left-to-right shunt because of the presence of telangiectasia, and of minor systemic parenchymatous AVMs in a few. A left-to-right shunt will increase the oxygen content of mixed venous blood, thereby reducing \( \text{CaO}_2 - \text{CvO}_2 \).

Patients with PAVMs usually have a high cardiac output [21], which will also result in a low value of \( \text{CaO}_2 - \text{CvO}_2 \). Cardiac output was not measured in the present study, and therefore its contribution to \( \text{CaO}_2 - \text{CvO}_2 \) is not known. The decrease in cardiac output caused by breathing pure oxygen is likely to be small in the patients studied, because in general they had no large R–L shunts. One might expect a decrease in cardiac output after embolization of PAVM and thus a rise in \( \text{CaO}_2 - \text{CvO}_2 \). However, \( \text{CaO}_2 - \text{CvO}_2 \) increased in only seven of our 12 patients directly after embolization.

On the basis of our measurements of \( \text{CaO}_2 - \text{CvO}_2 \) in supine HHT patients without large systemic AVMs and with normal haemodynamic features and Hb levels, we assumed a value for \( \text{CaO}_2 - \text{CvO}_2 \) of 4.4 ml/100 ml, instead of the usual 5 ml/100ml, in the calculation of R–L shunts when breathing 100% oxygen.
We found moderate agreement between the classical 100% oxygen method and the HSA/MAA method, but poor agreement between the 100% oxygen and the K/L methods. Although the correlation coefficients are rather high, both the Bland–Altman plots and the intra-class coefficients indicate only moderate conformity. Several factors can be held responsible for the lack of conformity. The methods rely on different approaches for shunt measurement. The 100% oxygen method is based on measuring the alveolar–arterial oxygen difference, which is converted into a shunt magnitude. The arteriovenous difference in oxygen content is not measured routinely in the 100% oxygen method. As mentioned above, we assumed a value of 4.4 ml/100 ml. A deviation of 1.0 ml/100 ml from this assumed value would result in a deviation from the calculated shunt fraction of between 1.5 and 3.5%. The two other methods are not influenced by the accuracy of the estimate of the arteriovenous oxygen content difference. Measurement of the actual individual arteriovenous difference would improve the accuracy of the 100% oxygen method, but is not feasible in daily practice. Also, the 100% oxygen shunt fraction will be influenced by the presence of multiple small PAVMs, in which oxygen uptake may still take place when alveolar \( P_{O_2} \) is high [22]. Any oxygen uptake through these malformations will lead to an underestimation of the actual shunt. The HSA/MAA and K/L methods are insensitive to this source of error, and will measure these small malformations to their full extent. This type of error in the 100% oxygen method will lead to a systemically lower shunt fraction compared with that measured using the HSA/MAA and K/L methods. On the other hand, the values with the 100% oxygen method should be higher than those with the HSA/MAA method, because the former also measures the physiological shunt, whereas the latter measures only the anatomical intrapulmonary shunt. Healthy people may have a physiological shunt of 1–3%, with a maximum of 4% during exercise [14]. Most patients still had an R–L shunt greater than physiological after embolization, due to the presence of residual small PAVMs that could not be embolized.

Unfortunately, both the HSA/MAA and K/L methods also harbour sources of error. Among these are the non-uniformity of the particle size of MAA and the labelling efficiency of the radiopharmaceutical. Both phenomena may lead to an overestimation of the intrapulmonary shunt due to non-trapping of small MAA particles and ‘leakage’ of the label (\(^{99m}\)Tc) from the lung. In addition, the accuracy is limited by background activity and the possibility of an overlap of the ROIs in the K/L method. In the HSA/MAA method the ROIs used are free from overlap; HSA is used for determination of the fraction of the cardiac output perfusing the ROIs. Because the patient’s position, the radioactive compound and the ROIs are identical for both \(^{99m}\)Tc-HSA and \(^{99m}\)Tc-MAA, no corrections for attenuation or background activity have to be made. In both methods it is assumed that attenuation over the lungs is equal to attenuation over the kidneys. Extrapolation of the peaks obtained from the ROIs after injection of HSA may also lead to a possible source of error, especially with small R–L shunts.

We found poor agreement between the K/L method and the 100% oxygen method, with limits of agreement for the R–L shunt of \(-15.2% \pm 15.2\%\). Overlap from the lung to the kidney leads to an overestimation of the shunt fraction. In addition to this, the assumption that the right kidney receives 10% of the cardiac output proved to be a potential source of error. In Table 3 we listed the percentage of the cardiac output received by the right kidney, measured with HSA. The values varied from 4.3 to 17.2% (mean 9.0%), and were sometimes influenced by overlap from the right lung. A lower percentage of the cardiac output to the kidneys than the assumed 10% will lead to an underestimation of the shunt fraction using the K/L method. These additional sources of error explain why we found wider limits of agreement relative to the HSA/MAA method. Chilvers et al. [13] and Whyte et al. [14] previously described the results of R–L shunt quantification by a similar K/L method. Differences between their method and ours are: (1) the use of microspheres instead of MAA, (2) the measurement of activity 5 min after injection, and (3) the breathing of 100% oxygen. Albumin microspheres are 7–25 \( \mu m \) in diameter, whereas MAA have a diameter of 10–80 \( \mu m \). Whyte et al. [14] found larger shunts and good agreement between their K/L method and the 100% oxygen method. However, their results essentially do not differ from ours: the limits of agreement between the 100% oxygen method and their K/L method were \( 0.63 \times (100\% O_2 \text{ shunt}) \pm 1.57 \times (100\% O_2 \text{ shunt}) \). Due to their method of calculation, the 95% limits of agreement were dependent on the shunt fraction measured. In practice, this means that there is a 95% probability that an R–L shunt of 20% measured by the 100% oxygen method would be in the range 12.6–31.4% when measured by their K/L method. On the basis of our study, an R–L shunt of 20% measured by the 100% oxygen method would be in the range 12.3–28.3% when measured by the HSA/MAA method, and 4.8–35.2% when measured by the K/L method. Whyte et al. [14] described slightly better results with the kidney-dose method, in which the activity over the kidney was related to the dose administered, correcting for background activity and attenuation. The limits of agreement between this method and the 100% oxygen method were still rather wide: \( 0.68 \times (100\% O_2 \text{ shunt}) \pm 1.45 \times (100\% O_2 \text{ shunt}) \).

Thus we conclude that the K/L method of measuring shunts is less accurate than the HSA/MAA method, due to additional sources of error. Our results show that the...
100% oxygen method and the HSA/MAA method match best, but the conformity is in our opinion too low to allow the methods to be used interchangeably: the shunt measured with HSA/MAA may be 8.3% higher or 7.7% lower than the shunt measured with 100% oxygen. The decision whether to use the 100% oxygen method or the HSA/MAA method depends on local facilities and experience. Because the sources of error in the different methods are not identical or correlated, the differences between the methods in an individual case will be random. Neither method can be used as a gold standard.

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