Non-invasive estimation of venous admixture: validation of a new formula

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Summary

We have developed a computer program that estimates venous admixture (intra-pulmonary shunt) from four measurements: haemoglobin concentration, end-tidal carbon dioxide tension ($P_{E'CO_2}$), fractional inspired oxygen concentration ($F_{I O_2}$) and pulse oximetry ($S_{PO_2}$). The formula was tested on patients in an intensive therapy unit by using it to estimate shunt while it was measured simultaneously by a standard, invasive method. A total of 101 measurements were made in 29 patients. After correcting the systematic errors in the assumed differences between $P_{E'CO_2}$ and arterial $PCO_2$, and between $S_{PO_2}$ and co-oximetrically measured $S_{aO_2}$, and correcting for a trend in the arteriovenous oxygen content difference ($C(a - v)O_2$) with shunt, the bias of the non-invasive minus invasive shunt differences was negligible, with no significant dependence on shunt. The limits of agreement were then $\pm 16\%$ shunt overall ($\pm 13\%$ within patients). When $S_{aO_2}$ was used instead of $S_{PO_2}$, the limits were $\pm 11\%$ ($\pm 8\%$ within patients). (Br. J. Anaesth. 1995; 74: 538-543)

Key words

Lung, shunting. Measurement techniques, lung shunting.

It is widely accepted that shunt fraction is the best single measure of the gas-exchange function of the lung, and that abnormally high values are common in the perioperative period and in the intensive therapy unit (ITU). Many of the factors which affect shunt are under the direct control of the anaesthetist.

Normally, however, shunt can be measured only by means of blood-gas analysis of paired samples of arterial blood and blood from the pulmonary artery. Such invasive monitoring is not generally justified. In 1973, Benatar, Hewlett and Nunn [1] showed how "virtual shunt" (the shunt that would exist if the arteriovenous oxygen content difference were 5 g dl$^{-1}$) could be estimated from measurements of inspired oxygen concentration ($F_{I O_2}$) and arterial oxygen tension ($P_{AO_2}$). Now, the ready availability of pulse oximeters, capnographs, oxygen analysers and small, powerful computers presents an opportunity to extend the Benatar technique and estimate shunt entirely from non-invasive methods.

We have developed a formula that estimates shunt fraction from measurement of end-tidal carbon dioxide partial pressure ($P_{E'CO_2}$), fractional concentration of oxygen in inspired gas ($F_{I O_2}$), oxygen saturation of arterial blood as estimated by pulse oximetry ($S_{PO_2}$), and haemoglobin concentration (Hb). It assumes normal values for the arterial to end-tidal carbon dioxide gradient ($P_{A CO_2} - P_{E'CO_2}$), arteriovenous oxygen content difference ($C(a - v)O_2$) and base excess. To test the formula we have made both invasive measurements and non-invasive estimates of shunt simultaneously in patients in the ITU.

Theory

Shunt fraction is calculated according to the conventional "shunt equation" [2, 3]:

$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{Cc_O^{'2} - Ca_O^{'2}}{Cc_O^{'2} - CVO_2}$$

(1)

where $\dot{Q}_S$ = shunt flow, $\dot{Q}_T$ = cardiac output, $Cc_O^{'2}$ = end-capillary oxygen content, $Ca_O^{'2}$ = arterial oxygen content and $CVO_2$ = mixed venous oxygen content. The result is usually expressed as a percentage.

Each of the three oxygen contents is calculated according to the formula:

$$Co_2 = (0.0136 \times \text{Hb} \times S_{O_2}) + (P_{O_2} \times 0.023)$$

(2)

where content is expressed in ml of gas (at STPD) per 100 ml of blood, Hb = haemoglobin concentration (g dl$^{-1}$) (assumed equal in arterial, venous and end-capillary blood), $S_{O_2}$ = relevant haemoglobin saturation ($\%$) and $P_{O_2}$ = relevant partial pressure of oxygen (kPa).

When this formula is used to calculate $Ca_O^{'2}$ and $CVO_2$, all quantities can be measured invasively. In the case of $Cc_O^{'2}$, the relevant $S_{O_2}$ and $P_{O_2}$ cannot be measured, even invasively. They are therefore taken to be the saturation ($S_{aO_2}$) at the "ideal" alveolar oxygen tension ($P_{AO_2}$), as derived from a version of the "ideal alveolar gas equation" [4]:

$$P_{AO_2} = F_{I O_2} \times (P_B - P_{H_2O}) - P_{ACO_2}$$

$$\times [F_{I O_2} + (1 - F_{I O_2})R]$$

(3)

where $F_{I O_2}$ = inspired oxygen fraction, ($P_B - P_{H_2O}$) = barometric pressure minus vapour pressure of
water at body temperature (assumed to be 95 kPa), 
$P_{ACO_2} =$ ideal alveolar carbon dioxide partial pressure 
which is taken to be equal to $P_{ACO_2}$ arterial tension, 
and $R =$ respiratory quotient (assumed to be 0.8).

$S_AO_2$ is then calculated from the following formula for the in vivo oxyhaemoglobin dissociation curve:

$$S_AO_2 = \frac{(n^4 + An^3 + Bn^2 + Cn) \times 100}{n^4 + An^3 + Dn^2 + En + F} \tag{4}$$

where $n = -P_{O_2}, 10^{0.48-P_{H^+} -1.40}$ and $A \to F =$ constants defined by Thomas [5]. This simplified form of Thomas's equation involves the assumptions that base excess is zero and body temperature is 37 °C.

Thus the unknown quantities are $F_{O_2}, Hb, P_{Aco_2}, S_{Aco_2}, P_{ACO_2}, S_{VO_2}, P_{ACO_2}$ and arterial pH. End-capillary pH is assumed to equal arterial pH. In the invasive method, all of these quantities are measured. In the non-invasive method, measurements of $F_{O_2}$ and Hb are used but the other quantities are estimated indirectly. $S_AO_2$ is estimated by pulse oximetry ($S_{PO_2}$), $P_{ACO_2}$ is then obtained by an iterative use of equation (4). Instead of estimating $P_{VO_2}$ and $S_{VO_2}$ for insertion in the venous version of equation (2), venous oxygen content is estimated directly from:

$$CvO_2 = CaO_2 - k_1 \tag{5}$$

where $k_1 =$ a constant, initially taken to be 5 ml dl$^{-1}$, as suggested by Nunn [3].

$P_{ACO_2}$ is estimated from:

$$P_{ACO_2} = P_{ECO_2} + k_2 \tag{6}$$

where $k_2 =$ another constant, initially taken to be 0.67 kPa. Finally, pH is estimated from the calculated $P_{ACO_2}$ using the Henderson–Hasselbach equation and assuming a bicarbonate concentration of 24 mmol litre$^{-1}$:

$$pH = 6.1 + \log[(24/0.229) \times P_{ACO_2}] \tag{7}$$

Patients and methods

The study was approved by the local Ethics Committee. Informed consent was obtained from the patient, or from a relative if the patient was incapacitated.

All patients in the ITU at the University Hospital of Wales, Cardiff, who had a pulmonary artery catheter in situ during the study period were eligible. Pairs of blood samples (arterial and mixed venous) were taken when clinically indicated, usually every 6–8 h. For each patient, the diagnosis and any chronic diseases were recorded. At each sampling event, $P_{ECO_2}, F_{O_2}$ and $S_{PO_2}$ were recorded and shunt fraction was calculated using the usual method (‘invasive shunt’) and by the new formula (‘non-invasive shunt’).

Precautions were taken to minimize errors in sampling and measurement. Blood samples were obtained after aspiration of at least 5 ml of deadspace fluid, representing three times the volume of the sampling apparatus deadspace. They were taken immediately to the on-site laboratory and promptly analysed using an ABL 520 blood-gas analyser (Radiometer, Copenhagen) running software version 1.02. Determinations of $P_{O_2}, P_{CO_2}$, pH, base excess, total Hb and fractional Hb saturation (co-oximetrically) were made in both arterial and mixed venous samples. The blood-gas measurements took account of the patient’s temperature measured from the pulmonary artery catheter.

$F_{O_2}$ was measured by the internal oxygen analysers (fuel cell 478841, Catalyst Research) of the Veolar ventilators used, (Hamilton Medical) which were calibrated daily and whenever they disagreed with the set oxygen fraction. $P_{ECO_2}$ and $S_{PO_2}$ were taken from Hewlett–Packard Component Monitoring Systems. These comprised a pulse oximeter (module M1020A) with a finger probe (M1190A), and an averaging time of 10 s, together with an in-line capnograph (module M1016A, transducer 14360A, adapter 14363A), all running revision C1 software. Several machines of the same model were used but both modules were always calibrated daily. To ensure an accurate estimate of end-tidal gas expansion was prolonged by disconnecting the ventilator for up to 10 s until a plateau was seen.

STATISTICAL ANALYSIS

Preliminary screening of the data was done by plotting histograms of the raw measurements.

The non-invasive estimates are designed to predict the “true” value of shunt as best estimated by the invasive measurements. Therefore, the interest is in the differences between the non-invasive estimates and the invasive measurements and these are well expressed by Bland and Altman’s [6] limits of agreement. However, the present circumstances differ from those considered by Bland and Altman in two respects. First, the errors in the invasive measurements are much less than those in the non-invasive estimates so that, in the context, the invasive measurements constitute something of a “gold standard”. Accordingly [7], we plotted the differences (non-invasive minus invasive) against the invasive measurements, not against the mean of the invasive and non-invasive. Second, Bland and Altman do not consider the possibility that the bias (the mean difference) might vary systematically with the “true” value. Accordingly [8], this possibility was tested by fitting a regression line to the differences. Regressions were performed on the raw data and on data sets which incorporated various corrections designed to eliminate the trend found with the raw data and also to reveal the effect of systematic and random errors in the three estimated input variables $(S_{PO_2}, P_{ACO_2}$ and $C(a–v)_O)$. This permitted the production of a plot which, in addition to showing the conventional, horizontal bias and limits of agreement lines, also showed closer, within-patient, limits of agreement. Details of the procedure are explained and justified in appendix 1.

The preliminary processing was done with version 1.2 of the statistical package Statview 512 +, running on a Macintosh LC computer under the System 7 operating system. The regressions were performed using GLIM 3.77 [9, 10] update 3, running on a DEC mainframe computer under the Ultrix operating system V4.2A (Rev. 47).
Results

A total of 101 sets of measurements were made on 29 patients. Of these, nine had septic shock and respiratory failure, eight had cardiogenic shock, four were post cardiorespiratory arrest and the remainder suffered from a variety of medical conditions.

Histograms of the raw measurements drew attention to three improbable values for \( P_{\text{O}_2} \), all of which belonged to the same patient. The four values obtained for this patient were 11.8, 17.1, 11.6 and 4.7 kPa. The first three values had the effect of making the calculated invasive shunt very high, despite high saturations on relatively low inspired oxygen tensions. Possible explanations were measurement errors, sampling errors or an undiagnosed left-to-right shunt. This patient was excluded from analysis.

It was discovered that, when the measured \( S_{\text{O}_2} \) (displayed by the oximeter only to the nearest whole percent) was 100%, the formula for the oxyhaemoglobin dissociation curve (equation (4)) gave impossibly large estimates for \( P_{\text{O}_2} \) up to 132 kPa. A value of 99.5% was substituted in the 13 readings of 100% that occurred, leading to \( P_{\text{O}_2} \) values of up to 30 kPa compared with a directly measured maximum of 23 kPa.

\( \text{Hb} \) concentrations measured in arterial and mixed venous samples did not always agree. The mean difference (\( \text{Hb}(\text{arterial}) - \text{Hb}(\text{venous}) \)) was 0.06 (SD 1.07) g dl\(^{-1}\). It was decided to use the higher of each pair of measurements, reasoning that sampling error is more likely to cause dilution than concentration of a sample.

Figure 1 shows the differences (raw non-invasive estimate minus invasive measurement) plotted against the invasive measurements, together with a regression line (see appendix 1). The slope of the regression line (\(-0.233 (\text{SE } 0.063)\)) was highly significant \((P < 0.001)\).

Table 1 shows that the measured mean differences between some variables differed systematically from the assumed, constant differences. When the mean measured differences were used in preference to the assumed differences, and when the trend in \( C(a-\nu)_{\text{O}_2} \) with shunt was allowed for (see appendix 1), the slope of the regression became small and non-significant. Therefore, these corrected results were displayed as a modified Bland and Altman [6] type

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Variable & Assumed difference & Observed difference & \multicolumn{2}{|c|}{SD} \\
\hline
\( S_{\text{O}_2} - S_{\text{O}_2} \) & 0 & 0.76 & 2.1 & 0.21 \\
\( P_{\text{CO}_2} - P_{\text{CO}_2} \) & 0.67 & 0.82 & 0.74 & 0.076 \\
\( C_{\text{O}_2} - C_{\text{O}_2} \) & 5 & 3.92 & 0.95 & 0.097 \\
\hline
\end{tabular}
\caption{Assumed constant differences used in the original calculation of non-invasive shunt and corresponding differences measured in the present sample of patients.}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Model & Bias & Limits of agreement \((\% \text{ shunt})\) & Overall & Within-patient \\
\hline
M1 & Sys. errors corrected & 0.7 & 15.8 & 12.9 \\
M2 & Measured \( S_{\text{O}_2} \) & 1.3 & 10.7 & 7.5 \\
M3 & Measured \( P_{\text{CO}_2} \) & 1.4 & 15.4 & 12.6 \\
M4 & Measured \( C(a-\nu)_{\text{O}_2} \) & 0.6 & 10.2 & 7.8 \\
M5 & All measured arterial & -0.3 & 10.9 & 7.6 \\
M6 & \( P_{\text{CO}_2} \) assumed to be 5.3 kPa & -0.4 & 16.0 & 13.3 \\
\hline
\end{tabular}
\caption{Bias and limits of agreement for the differences between the non-invasive estimates and the invasive measurements of shunt for various versions of the non-invasive estimates.}
\end{table}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{Difference in shunt (non-invasive estimate minus invasive measurement) vs invasive measurement, using raw non-invasive estimates, with fitted regression \( y = 0.95 - 0.233x \).}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{Difference in shunt (non-invasive estimate minus invasive measurement) vs invasive measurement, using estimates derived from values of \( S_{\text{O}_2} \), \( P_{\text{CO}_2} \), and \( C(a-\nu)_{\text{O}_2} \) which have been corrected for the systematic errors listed in table 1 (including the trend in \( C(a-\nu)_{\text{O}_2} \) with shunt, see appendix 1). The horizontal lines show the "bias" (mean difference, continuous line), and the overall (dashed lines) and within-patient (dotted lines) limits of agreement.}
\end{figure}
plot, with bias and limits of agreement, in figure 2. The within-patient limits of agreement (mean ± 2 × within-patient SD) represent the likely (95% probability) spread of differences in any one patient.

To determine the contribution of each estimated input variable to the random errors, each was replaced in turn by the corresponding measured variable and the bias and limits of agreement recalculated. Using oximetric SaO₂ (model M2 in table 2) instead of SpO₂ (M1) closed the limits of agreement from ±16% to ±11% overall (±13% to ±8% within patients); using measured PaCO₂ (M3) gave limits of ±15% overall (±13% within patients); using measured C(a–v)O₂ (M4) gave ±10% (8%). Finally, to simulate a situation where arterial sampling would be justified but not mixed venous, measured values were used for SaO₂, PaCO₂ and PaO₂ (M5). This gave limits of ±11% (8%).

Discussion

When the estimates of shunt from the raw data were corrected for systematic errors, by correcting the systematic errors in the three estimated input variables (SaO₂, PaCO₂, and C(a–v)O₂) (M1 in table 2), the bias was negligible and the limits of agreement were ±16% overall and ±13% within patients. This implies that, if a single estimate of shunt is made in one patient, there is a 5% chance that the estimate will be in error by more than ±16% shunt; or, if repeated estimates are made at intervals in the same patient, then 5% of them may be in error by more than ±13%, relative to any other error in the estimate which is systematic to that patient but random to the population.

There is always a hazard in using systematic errors found in one group of patients to correct estimates made in another group. It is perhaps particularly risky to use a trend correction in this way. However, additional analysis showed that the systematic errors in the estimates of PaCO₂ and SaO₂ accounted for only a small part of the systematic error in estimated shunt (0.1% and 1.8% shunt, respectively). Also, there is external evidence in support of the trend of C(a–v)O₂ found in the present group of patients. First, the difference of 5 ml dl⁻¹ quoted by Nunn [3] is relevant to healthy individuals; studies in ITU patients have quoted mean values of 3.5, 4.0 and 4.6 ml dl⁻¹ [11–13, respectively], which are consonant with our mean of 3.9% and trend from 5 ml dl⁻¹ at 0% shunt to 3 ml dl⁻¹ at 60% shunt. Second, a trend of approximately this type is to be expected theoretically (appendix 2). Therefore, if future estimates of shunt are corrected on the basis of the C(a–v)O₂ trend found in the present set of patients, it seems likely that there would be little systematic error left.

A further potential problem is that, when non-invasive estimates of shunt are required, contemporaneous measurements of Hb might not be available and the most recent measurement might need to be used as an estimate. However, equation (2) shows that, apart from a small contribution from dissolved oxygen (especially at the PaO₂ values common in the presence of shunt), oxygen content is proportional to Hb concentration. Therefore, it follows from equation (1) that errors in Hb concentration largely cancel and have very little effect on calculated shunt. Sample calculations indicate possible errors of less than 1% shunt.

This leaves the likely random errors: the limits of agreement showed that 5% of estimates are out by more than ±16% shunt overall or ±13% within patients, which would seem to make the method of limited value. However, it is helpful to review the sources of this random error. Table 2 shows that errors in PaCO₂ make a negligible contribution to the total random error in shunt (compare M1 and M3). Indeed, when PaCO₂ was assumed always to be normal (5.3 kPa) (instead of using the mean corrected values which ranged from 2.2 to 7.7 kPa), the maximum change in calculated shunt was 2% shunt and the limits of agreement widened to a negligible extent (compare M1 and M6 in table 2). Therefore, measurement of PaCO₂, or FeCO₂, is not important.

On the other hand, knowledge of either SaO₂ (M2) or C(a–v)O₂ (M4) leads to a substantial and roughly equal reduction in random error. Knowledge of all of the arterial variables (M5) adds nothing to knowledge of SaO₂, no doubt because of the small contribution of dissolved oxygen and the unimportance of PaCO₂. The only exception to this might be at very high SaO₂ (and hence at a small shunt) where a change of 1% in SpO₂ (the minimum change in the value displayed by the pulse oximeter) is associated with a large change in calculated PaO₂ and hence a larger than otherwise change in calculated C(a–v)O₂ (see equation (2)). However, reducing the 13 readings of 100% SpO₂ to 99% increased the calculated shunt by 3.8–5.9% shunt, and reducing the eight readings of 99% to 98% increased shunt by 0.9–3.8% shunt. Reducing readings of 98% or less increased shunt by less than 2.5%. Therefore, the integer nature of the display of SpO₂ is not an important source of random error in the estimation of shunt if very high saturations are avoided.

It is natural to wish to compare the present results with those of Benatar, Hewlett and Nunn [1] who estimated shunt from measurements of just FIO₂ and PaO₂. However, they made no direct measurement of actual shunt and they made many measurements in each of only four patients compared with our average of three to four measurements in each of 28 patients. Therefore, the only comparison of results that can be made is in terms of within-patient reproducibility. Their different within patient measurements were obtained largely by changing FIO₂ at 25-min intervals and therefore under essentially steady-state conditions (up to only 25% shunt); also, they were estimating only "virtual shunt" (which is not affected by differences between the actual C(a–v)O₂ and 5 g dl⁻¹ which they assumed). On the other hand, our measurements were made at 6- to 8-h intervals, sometimes over a wide range of shunt. Therefore, it is not surprising that their pooled within-patient SD of estimated shunt (which we calculated to be 3.2%) was only half our within-patient SD of 6.4% for the non-invasive method (M1 in table 2). Despite this difference in reproducibility, the present results do provide experimental confir-
mation of their conclusions concerning the importance of \( C(a-v)O_2 \) and \( SaO_2 \) and the relative unimportance of values of \( Hb \) and \( PaCO_2 \).

Mixed venous oxygen content is available only with a fully invasive procedure, but \( SaO_2 \) would be available in those patients in whom an occasional arterial sample would be justified, for example those undergoing major surgery or on a high dependency ward. In these circumstances, 95% of estimates would be within about ±11% shunt overall and ±8% within patients. We think that such information could be genuinely useful.

It should be remembered that the present patients were at the extreme of cardiopulmonary organ failure so that peripheral circulation was probably severely impaired and this may account for the large sd of 2.1% saturation of the \( SpO_2 - SaO_2 \) differences (table 1) compared 14 with the 1% typically reported in volunteer studies. Therefore, in less severely ill patients for whom the non-invasive method was designed, a better performance of the oximeter might be expected leading to results intermediate between those of M1 and M2 in table 2: 95% limits of agreement between ±16% and ±11% shunt overall and between ±13% and ±8% shunt within-patients.

The recent study by Petros, Doré and Nunn 15 showed that, if there is (constant) ventilation–perfusion mismatch in the lungs rather than just a frank shunt, the calculated value of shunt varies with \( FlO_2 \), below 60%. To that extent, the model we used is incomplete. However, \( FlO_2 \) enters the calculation of both non-invasive and invasive shunt in exactly the same manner (equation (3)) and therefore this would not be expected to affect the ability of the non-invasive estimates to match the invasive measurements. In our results, both the invasive and non-invasive values of shunt were strongly associated with \( FlO_2 \) but this was, at least principally, because the \( FlO_2 \) was deliberately set high in those patients for whom the non-invasive method was designed: the large shunt "caused" the high \( FlO_2 \), not the reverse.

We conclude that our method would be useful when arterial samples are justified, especially for within-patient changes, and also in patients where this is not justified but in whom a pulse oximeter would be more reliable than in the present study—at least for within-patient changes. However, the crucial test will be whether the results prove useful in clinical practice.

Acknowledgement

We are grateful to Hewlett-Packard for the loan of equipment.

### Table 3: Linear regressions of the difference (non-invasive minus invasive shunt) on invasively measured shunt, for three circumstances (95 degrees of freedom)

<table>
<thead>
<tr>
<th>Regression No.</th>
<th>Non-invasive estimates</th>
<th>Intercept estimate (SE)</th>
<th>Slope (% shunt) estimate (SE)</th>
<th>( P ) Intercept Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>Raw data</td>
<td>0.95 (2.09)</td>
<td>-0.233 (0.063)</td>
<td>ns</td>
</tr>
<tr>
<td>R2</td>
<td>Mean-corrected</td>
<td>6.48 (2.19)</td>
<td>-0.203 (0.066)</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>R3</td>
<td>Mean-and-trend corrected</td>
<td>1.99 (2.57)</td>
<td>-0.041 (0.077)</td>
<td>ns</td>
</tr>
</tbody>
</table>

### Appendix 1

**DETAILS OF REGRESSION AND LIMITS OF AGREEMENT ANALYSES**

When the raw estimated values of shunt were used, the slope of the regression showed a marked dependence of the non-invasive to invasive difference on the invasive shunt (fig. 1): there was a highly significant negative slope (R1 in table 3). If bias and limits of agreement are calculated without reference to such a trend, the limits are unnecessarily wide: it can be seen in figure 1 that a pair of horizontal lines that included 95% of the points would also include a substantial amount of systematic variation. Therefore, it is tempting to draw parallel lines at ± twice the residual sd each side of the regression line on the basis that these will exclude the systematic error but include approximately 95% of the points. However, these lines underestimate the width of the limits of agreement that would be obtained after the systematic trend had been eliminated by some correction procedure. The reason for this is not obvious but can be deduced by taking a pair of points that are widely separated in the \( Y \) direction but at the same \( X \) value: if the corresponding non-invasive estimates are calculated and corrected for the trend (basing each correction on the non-invasive estimate itself) it is found that the corrected non-invasive values are further apart than the raw values. Therefore, it is necessary first to correct for the systematic errors, or at least for the systematic trend, and then calculate bias and limits of agreement by using the differences of the corrected non-invasive estimates from the invasive measurements. This can be done in two ways.

One approach is simply to incorporate the regression equation in the calculation of non-invasive shunt; the other is to correct the systematic error in each of the three estimated input variables, \( SaO_2, PaCO_2 \) and \( C(a-v)O_2 \), before calculating shunt. Both methods are subject to the objection that systematic errors may be different in other circumstances (see discussion). The second method is preferable here because it reveals the separate effects of systematic and random errors (see below).

When the mean errors in the input variables were corrected by using the observed mean differences in table 1 instead of the assumed differences, the mean estimated difference did indeed become zero but this was achieved primarily by all of the non-invasive shunt estimates increasing equally (mean +6.5%, shunt, sd 0.6%). This is reflected in the regression (R2 in table 3) which showed an increased intercept with little change in slope. Theory showed that this resulted from neglecting the marked trend in \( C(a-v)O_2 \), with shunt (table 1). To correct for this trend requires an initial knowledge of shunt. Each mean-corrected estimate of shunt was used in a theoretical equation to correct itself for the trend given in table 1. This led to a regression (R3 in table 3) with non-significant intercept and slope. That is, after correcting all the systematic errors in the input variables, the systematic errors in the estimated values of shunt were not significant.

The contribution of the random error in each input variable to the total random error in non-invasive shunt was determined as follows. For each estimated input variable in turn (\( SaO_2, PaCO_2 \) and \( C(a-v)O_2 \)), the estimated values (corrected for the systematic error as above) were replaced by the corresponding invasively measured values and the regression repeated. None of the slopes was significant. Accordingly, in the main paper, the results for these circumstances are presented and compared in terms of bias (the mean difference) and limits of agreement (±2 sd of the differences). Within-patient limits of agreement were obtained by allowing a separate bias for each patient; these limits therefore estimate the range of random variation in the average patient around some unknown mean difference.
Appendix 2

THEORY OF DEPENDENCE OF $C(a - v)_{O_2}$ ON SHUNT

If, as shunt increased, the rate of oxygen uptake were maintained and cardiac output increased such that pulmonary perfusion remained unaltered, then a normal 5 ml dl$^{-1}$ difference would be maintained between mixed venous and end-capillary content, but this end-capillary content would be progressively “diluted” by mixed venous blood from the increasing shunt. At 50% shunt, cardiac output would be twice normal and $C(a - v)_{O_2}$ would be half normal (i.e. 2.5 ml dl$^{-1}$), and at 100% shunt (impossible except mathematically) cardiac output would be infinite and $C(a - v)_{O_2}$ would be zero. In fact, our regression of $C(a - v)_{O_2}$ on shunt indicates 3.3 ml dl$^{-1}$ at 50% shunt not 2.5%. This implies that pulmonary perfusion has decreased (and cardiac output has less than doubled), especially if oxygen uptake has decreased.

References