SOLUBILITY CHARACTERISTICS OF THE IDEAL AGENT FOR MEASUREMENT OF CARDIAC OUTPUT BY SOLUBLE GAS UPTAKE METHODS

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SUMMARY

Measurements of the rate of uptake of soluble gases such as nitrous oxide or acetylene has been used as the basis of a method of cardiac output estimation since 1912. Using theoretical models of single, multiple and rebreathing techniques of cardiac output measurement, we determined the effect of solubility in blood and lung tissue on the changes in the final expired concentration of the gas. Decreasing lung tissue solubility increased the sensitivity of all three models to cardiac output changes. When the lung tissue/blood partition coefficient was 1, the optimum blood/gas partition coefficients were 2.6 for the single-breath model, 4.1 for the three-breathe-model and 3.5 for the rebreathing model. A selection of gases, including volatile anaesthetic agents was studied using the same models. Under most conditions, enflurane approximated most closely to the requirements for an ideal agent for use in this technique of cardiac output measurement. (Br. J. Anaesth. 1993; 71: 398-402)

KEY WORDS

Heart: cardiac output. Measurement techniques: cardiac output.

The rate of uptake of soluble gases from the lungs may be used to quantify cardiac output. Many gases have been used for this purpose, including oxygen, carbon dioxide, acetylene and nitrous oxide. The techniques have been reviewed comprehensively by Sackner [1].

The use of non-physiological gases (that is, not oxygen, carbon dioxide or nitrogen) for this purpose has the particular advantage that the venous concentration may be assumed to be zero, provided all measurements are completed before recirculation occurs. In man, without significant cardiovascular disease, recirculation occurs after 14-18 s at rest and after 8 s during heavy exercise [2,3]. In general, the agents used are those which anaesthetists consider relatively insoluble, with blood/gas partition coefficients (Abl/g) less than 1, such as nitrous oxide [2, 4] (Abl/g = 0.47) and acetylene [5-7] (Abl/g = 0.74). Physiologists frequently describe such gases as soluble, in contrast to the "insoluble gases" such as helium and sulphahexafluoride.

Assuming uptake is perfusion-limited, the rate of uptake of any agent is proportional to the solubility in blood of that agent. Therefore, a more soluble agent is taken up initially at a greater rate than a less soluble gas, producing a larger reduction in alveolar concentration which should be easier to measure.

Studies with ether [4,8] (Abl/g = 13) and acetone [4] suggest they are "too soluble", particularly in the mucosa of the airway and other parts of the ventilatory tract not forming part of the gas exchange space. These gases diffuse into these tissues during inspiration, but only a small amount is removed by blood flow; most of the gas remains in the tissue and is released into the airway during expiration, contaminating the expiratory alveolar gas sample. This "extra-alveolar" uptake does not appear to be a problem with relatively insoluble agents such as nitrous oxide and acetylene [4]. Recent theoretical [9] and experimental [5] work also suggested there is more variability in results obtained using ether than when acetylene is used. Agents with solubilities between those of acetylene and ether have not been studied previously.

We hypothesized that modern volatile anaesthetic agents such as halothane (Abl/g = 2.4), enflurane (Abl/g = 1.9) and isoflurane (Abl/g = 1.5) might fall in the middle ground, with greater blood solubility producing a useful increase in concentration change, whilst not being so soluble as to contaminate end-tidal samples.

The aim of this study was to determine the conditions which produced the greatest change in expired concentration (FA) as a fraction of inspired concentration (Fi) for a given change in cardiac output. We also wanted to rank different soluble gases, and particularly volatile anaesthetics, in the same way, to determine which are the most sensitive to cardiac output changes. The second part of our hypothesis, which considers the effect of extra-alveolar solubility, required experimental work and is not part of the studies reported here.


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METHODS

To describe the relationship between cardiac output and expired concentration, we used three mathematical models representing different ventilatory manoeuvres: a single breath; three breaths, with the same inspired concentration for each breath; and rebreathing with the inspired concentration for each of seven breaths determined by the contents of the rebreathing bag.

The relationship between the rate of uptake and cardiac output (taking cardiac output (Q) to be equal to the effective pulmonary blood flow) is described by the Fick equation [10,11] which states that, for a substance Z:

\[
\text{rate of uptake of } Z = \dot{Q} \cdot (\text{arterial} - \text{venous content of } Z) \]

which may be written as:

\[
\text{rate of uptake of } Z = \dot{Q} \cdot \lambda_{bl/g} \cdot [F_a - F_v] \]

where \( \lambda_{bl/g} \) = the blood/gas partition coefficient; \( F_a \) and \( F_v \) = arterial and venous partial pressures, respectively, of \( Z \) (expressed as fractions of ambient atmospheric pressure). If uptake is not diffusion-limited, \( F_a = F_a^0 \), where \( F_a \) = fractional alveolar concentration.

During a breath-holding period and while \( F_v = 0 \), it can be shown [4,12] (using the abbreviations listed in the Appendix) that:

\[
F_a = F_a^0 \cdot \exp \left[ \frac{\lambda_{bl/g} \cdot \dot{Q} \cdot t}{V_a^{eff}} \right] \quad (1) \]

where \( t \) = time since the end of inspiration; \( V_a^{eff} \) = effective alveolar volume, assuming perfect instantaneous mixing into homogeneous alveoli and constant alveolar volume.

After the initial inspiration, \( F_a^0 \) is given by:

\[
F_a^0 = F_l \cdot (V_T - V_d) / V_a^{eff} \quad (2) \]

Combining these equations gives:

\[
F_a = F_l \cdot [(V_T - V_d) / V_a^{eff}] \cdot \exp \left[ \frac{-\lambda_{bl/g} \cdot \dot{Q} \cdot t}{V_a^{eff}} \right] \quad (3a) \]

or, dividing both sides by \( F_l \):

\[
F_a / F_l = [(V_T - V_d) / V_a^{eff}] \cdot \exp \left[ -\lambda_{bl/g} \cdot \dot{Q} \cdot t / V_a^{eff} \right] \quad (3) \]

Many gases dissolve readily in the lung tissue itself and reach equilibrium in less than 2 s [13]. Thus the product of the lung tissue/gas partition coefficient (\( \lambda_{lu/g} \)) and the lung volume (\( V_{lu} \)) represents an extra "space" that acts as if it were part of the alveolar gas space [4,14]. The lung tissue/gas partition coefficient is the product of the blood/gas and lung tissue/blood partition coefficients. Hence:

\[
V_a^{eff} = V_a^0 + \lambda_{bl/g} \cdot \lambda_{lu/b} \cdot V_{lu} \quad (4) \]

or

\[
V_a^{eff} = V_a^0 + \lambda_{bl/g} \cdot V_{lu} \]

represents the total "volume of distribution" of the particular agent. Using the values for tissue solubilities shown in table 1, if \( V_{lu} = 0.5 \) litre [4,14] then, for halothane, \( \lambda_{lu/g} \cdot V_{lu} = 2.4 \) litre, while for nitrous oxide \( \lambda_{lu/g} \cdot V_{lu} = 0.235 \) litre. If the end-inspiratory alveolar gas space is 3.5 litre (using \( V_a^0 = 2.5 \) litre and \( V_T = 1 \) litre), the total effective gas exchange space is 5.9 litre for halothane, but only 3.735 litre for nitrous oxide.

Equation (3) describes the single-breath model and is the basis for the three-breath and rebreathing models.

To allow for more than one breath, a simple model of ventilation [15] was used. In this model of ventilation, inspiration and expiration occur instantaneously and therefore the time-volume plot is a square wave. This model allows uptake over a series of ventilatory cycles to be considered as a sequence of "single breaths" using equation (3), but with different initial concentrations and lung volumes for each phase.

Concentrations in the lung were calculated at three times during each ventilatory cycle: at the end of inspiration (\( F_a' \)); at the end of the inspiratory hold period (\( F_a'' \) — the actual end-expired concentration); and at the end of expiratory hold (\( F_a''' \) — the concentration in the lungs at the start of the next breath). \( F_a'' \) and \( F_a''' \) were calculated by applying equation (1) using appropriate initial concentrations (\( F_a' \) and \( F_a'' \)), lung volumes (\( V_a^{eff} + V_l \) for the inspiratory hold period and \( V_a^{eff} \) for the expiratory hold period) and times (\( t_{in} \) and \( t_{ex} \)). End-inspiratory concentration (\( F_a' \)) was calculated as:

\[
F_a' = [F_a'' \cdot V_a^{eff} + F_a''' \cdot V_T + F_l \cdot (V_T-V_d)] / [V_a^{eff} + V_T] \quad (5) \]

where \( F_l \) and \( F_a' \) are expressed as fractions of the initial \( F_l \).

Equations (3) and (5) define the three-breath model, which can be extended to any number of breaths.

In the rebreathing model, the inspired concentration for each breath was the concentration in the rebreathing bag at the end of the previous expiration. This was calculated as:

\[
F_{bag} = [F_l \cdot (V_{bag} - V_T) + F_l \cdot V_T + F_a'' \cdot (V_T - V_d)] / V_{bag} \quad (6) \]

where \( F_l \) = \( V_{bag} \) from the previous breath.

In addition to the assumptions common to all models, the rebreathing model assumes no additional deadspace (equipment deadspace = 0), no uptake of the agent onto the bag, and that the total volume of the system remains constant; that is, uptake is minimal compared with the total volume of the lung-bag system.

| Table 1. Specific agents studied and partition coefficients used. Values are those used by Lowe and Ernst [16], except for helium [4] |
|---------------------------------|-----------------|-----------------|-----------------|
| **Agent**                       | **Partition coefficient** |                  |                  |
|                                 | Blood/gas       | Lung/blood      | Lung/gas        |
| Helium                          | 0.0086          | 1.07            | 0.0092          |
| Nitrous oxide                   | 0.47            | 1.0             | 0.47            |
| Acetylene                       | 0.75            | 1.03            | 0.77            |
| Isoflurane                      | 1.5             | 1.8             | 2.7             |
| Enflurane                       | 1.9             | 1.3             | 2.5             |
| Halothane                       | 2.4             | 2.0             | 4.8             |
| Methoxyflurane                  | 11              | 2.1             | 23.1            |
| Ether                            | 13              | 1.0             | 13              |
Standard conditions listed in the Appendix were used. The single-breath model was studied for 15 s, while the three-breath and rebreathing models were studied at three breaths (12.5 s) and seven breaths (13 s), respectively. These values were chosen to be less than the recirculation time of man at rest (14–18 s) [2]. Values of the partition coefficients used are listed in table I. Results are expressed as end procedure expired concentration divided by initial $F_i$ or $F_A/F_i$.

The three models described above calculate $F_A/F_i$ after completion of the test manoeuvre and assume perfect instantaneous mixing of gas, with no ventilation perfusion abnormalities. Similar models have been shown to produce valid results in patients without significant lung pathology [6,9].

We chose to look at the effects of a change in cardiac output from 1 litre min$^{-1}$ to 10 litre min$^{-1}$ and defined the difference in $F_A/F_i$ between these values as:

$$F_A/F_i(\Omega_{Q1-10}) = F_A/F_i(\Omega_{1 litre min^{-1}}) - F_A/F_i(\Omega_{10 litre min^{-1}})$$

$F_A/F_i(\Omega_{Q1-10})$ was calculated for a range of combinations of $\lambda_{bl}/g$ and $\lambda_{lu}/bl$ ($\lambda_{bl}/g$ (1–15), $\lambda_{lu}/bl$ (0–5)) using the single-breath, three-breath constant inspired concentration and rebreathing models. This was repeated for a selection of anaesthetic gases and vapours. For comparison, examples of very soluble (methoxyflurane) and very insoluble (helium) agents were included.

In addition, the difference in $F_A/F_i$ produced by a 25% increase in cardiac output was calculated for initial values of cardiac output between 1 and 10 litre min$^{-1}$.

**RESULTS**

Families of curves for different values of $\lambda_{lu}/bl$ using a single breath of 15 s duration (fig. 1), the three-breath model (fig. 2) and the rebreathing model (fig. 3) show that optimum combinations of $\lambda_{bl}/g$ and $\lambda_{lu}/bl$ existed for each model. The maximum value on each curve represents that blood solubility which gave the greatest change in expired concentration for a change in cardiac output from 1 litre min$^{-1}$ to 10 litre min$^{-1}$ at that $\lambda_{lu}/bl$. These values increased slightly as $\lambda_{lu}/bl$ decreased.

Table II shows the change in end procedure $F_A/F_i$ with a change in cardiac output from 1 litre min$^{-1}$ to 10 litre min$^{-1}$ for a variety of anaesthetic agents and helium. Enflurane was the most sensitive to changes in cardiac output in all models, although ether performed well in the three-breath model. The three-breath model produced the greatest changes in $F_A/F_i$ for the cardiac output change studied, but these were only marginally greater than those seen with the rebreathing model.

Figure 4 illustrates the effect of a 25% increase in cardiac output on the change in alveolar concentration and demonstrates that enflurane produced the greatest change at almost all values modelled. With the exception of the very soluble agents, ether and methoxyflurane, the curves are nearly linear over the range studied.
surprising because, given the same initial concentration, the only real difference between the two models is that the total mass of drug delivered to the alveolar gas space is greater with the three-breath model.

From table II it is apparent that there are considerable differences between agents with similar blood solubility, such as isoflurane and enflurane. We were initially surprised that enflurane, with a smaller partition coefficient, produced a greater change than that seen for halothane. The pattern of results may be explained by considering the physical process being modelled. For small values of \( \lambda lb/g \) (nitrous oxide) the rate of uptake is small and \( FA/Fh \) is close to 1 (equation (1)). If cardiac output doubles, the decrease is, at most, double, but \( FA/Fh \) is still close to 1. Conversely, if \( lb1/g \) is large (for example ether), uptake is rapid and almost completely resulting in a small value for \( FA/Fh \). In this case doubling cardiac output has little added effect, as \( FA/Fh \) (and \( FA/Fi \)) is already close to zero. Between these extremes lies an optimum value for \( lb1/g \) with which a change in cardiac output produces a usefully large change in \( FA/Fh \) and consequently in \( FA/Fi \).

Increasing \( \lambda u/bl \) increases \( VA/Fi \) and consequently decreases \( FA \). This places a limit on the amount by which \( FA \) can change. In addition, increasing \( \lambda u/bl \) also increases the time constant of the exponential decrease in \( FA \) (equation (1)), thereby slowing the decrease in \( FA \). The largest change in \( FA/Fi \) is seen with small values of \( \lambda u/bl \).

The interplay of these various effects was shown in figure 4, which illustrated the effect of a 25% increase in cardiac output. The gradient of the curves for the more soluble agents such as ether and methoxyflurane decrease as cardiac output increases.

The step change in cardiac output from 1 to 10 litre min\(^{-1}\) was chosen to look at the effects of solubilities over a useful range of cardiac outputs. Many applications of cardiac output measurement are at extreme values, either in patients with presumed small cardiac outputs, or in exercise physiology. Although ether, with a large \( lb1/g \) and a small \( \lambda u/bl \), produced the greatest differences in \( FA/Fi \) when the initial cardiac output was small, this advantage was lost when the initial cardiac output or the change in cardiac output was large. Figure 4 demonstrated that the changes seen with enflurane were approximately linear for any cardiac output change in the range 1–10 litre min\(^{-1}\), but this was not the case for ether.

To determine if the pattern of results would have been significantly different if another cardiac output change had been studied, the optimum \( lb1/g \) for \( \lambda u/bl = 1 \) and a 25% increase in cardiac output (from 5 litre min\(^{-1}\) to 6.25 litre min\(^{-1}\)) was calculated in the three-breath model. This value of 3.6 was only slightly less than the optimum value for a cardiac output change from 1 to 10 litre min\(^{-1}\) of 4.1. The difference in \( FA/Fi \) values for any agent with \( lb1/g = 3.6 \) compared with 4.1 was less than 4% for any of the 25% cardiac output changes studied and 4.4% for the change from 1 to 10 litre min\(^{-1}\). These results suggest that the general pattern of results is similar over a wide range of cardiac output changes. If an
agent was required for a specific application or group of patients (for example those with decreased cardiac output states), specific calculations to determine the ideal theoretical and actual agent may be appropriate.

It would appear from these studies that the ideal soluble agent for measurement of cardiac output would be one with a moderate blood/gas solubility and a very low lung tissue/blood solubility. Such an agent would be relatively water soluble and relatively poorly soluble in fat. It would still need to diffuse readily across the alveolar membrane, so that uptake remained perfusion- rather than diffusion-limited. Of agents readily available to the anaesthesist, enflurane comes closest to this ideal.

Other factors may need to be considered when choosing a suitable agent, including the ability to increase Fi (especially for nitrous oxide) and the accuracy of the measuring system. The actual inspired concentrations of anaesthetic agents able to be used depend on the speed of onset of side effects, including sedation, and possible direct effects on cardiac output.

Enflurane may be able to replace less soluble agents such as acetylene or nitrous oxide as the soluble agent in currently used methods of cardiac output estimation by soluble uptake. Use of enflurane in these methods may produce more accurate results, and be slightly less unpleasant for the subject than agents currently used. The possible role of the volatile anaesthetic agents deserves further experimental investigation.

APPENDIX

ABBREVIATIONS AND STANDARD VALUES USED.

(standard values shown in parentheses)

\( \lambda_{bl}/g \) Blood/gas partition coefficient
\( \lambda_{lu}/bl \) Lung tissue/blood partition coefficient
\( \lambda_{lu}/g \) Lung tissue/gas partition coefficient (\( = \lambda_{bl}/g \cdot \lambda_{lu}/bl \))
\( V_t \) Tidal volume (1 litre)
\( V_d \) Deadspace (0.15 litre)
\( V_{lu} \) Volume of lung tissue (0.5 litre)
\( V_A \) Alveolar gas volume (i.e. functional residual capacity - \( V_{lu} \)) (2.5 litre)
\( V_{A_{eff}} \) Alveolar gas volume at time 0 (\( V_A + V_t \))
\( V_{bag} \) Rebreathing bag volume (2 litre)
\( t_e \) Elapsed time since start of breath-hold (s)
\( t_s \) Inspiratory hold time (15 s for single breath; 2.5 s for three-breath model; 1 s for rebreathing)
\( t_{ext} \) Expiratory hold time (\( = t_{in} \))
\( P_{in} \) Inspired concentration
\( P_A \) Fractional concentration in alveoli after time \( t \)
\( P_{lu} \) Fractional concentration in blood at time 0
\( P_{lu}^e \) End-expired concentration
\( P_{lu}^e \) Fractional concentration in alveoli at end of inspiratory hold (start of expiratory hold)

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\( FAE \) Fractional concentration in alveoli at end of expiratory hold
\( FAT \) Fractional concentration in alveoli at end-inspiration (start of inspiratory hold)
\( Q \) Pulmonary blood flow (5 litre min\(^{-1} \))

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