EFFECT OF VENTILATION AND CARDIAC OUTPUT ON THE UPTAKE OF ANAESTHETIC AGENTS FROM DIFFERENT BREATHING SYSTEMS: A THEORETICAL STUDY

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SUMMARY
We have investigated the influences of ventilation and cardiac output on uptake of anaesthetic with different breathing systems, by analysis of simple equations and by computer simulation. Increases in cardiac output and ventilation increased uptake from those systems which provided a constant inspired concentration, but not from completely closed systems with the vaporizer out of the circle (VOC), or when using the technique described by Lowe and Ernst. When the vaporizer was inside the circle, uptake increased with ventilation but not with cardiac output. With servo control of end-tidal concentration, uptake increased with cardiac output but not with ventilation. When the fresh gas flow to VOC systems was increased from basal, independence of uptake from ventilation was well maintained until fresh gas flow approached alveolar ventilation, but the independence of uptake from cardiac output was lost much sooner.

KEY WORDS

When drugs are given by mouth, uptake from the gut is known only approximately. Improved control requires parenteral administration because uptake is then equal to the dose administered. Conventional inhalation anaesthesia, using a constant inspired concentration of anaesthetic agent, resembles oral administration in that uptake is unknown. The equivalent of the parenteral route is the completely closed system, in which the quantity of agent vaporized is the dose taken up by the patient (uptake). Although the anaesthetic effect of an inhalation agent is related to its alveolar partial pressure, examination of uptake enables us to understand the influence of physiological variables on anaesthetic alveolar partial pressure. In addition, the total body uptake of inhalation agents is important when considering metabolism and the effects of toxic metabolites.

The importance of ventilation and cardiac output in regulating uptake of anaesthetics from an open system is well understood. However, the influence of breathing system configuration on uptake is not well known. With the increased interest in low flow and closed system anaesthesia, it seems appropriate to examine this question. This paper considers the effects of changes in cardiac output and ventilation on uptake from different breathing systems. We shall consider systems which deliver a constant inspired concentration of anaesthetic, and contrast them with the completely closed circle system. States intermediate between these two extremes are found in clinical practice, and we shall consider these later in this discussion. The second gas effect produces only small variations in uptake, but it is simpler to exclude it from the discussion by considering a single anaesthetic agent in oxygen.

“Constant inspired” systems include Mapleson systems A to E [1] (when the fresh gas flow (FGF) is sufficient), systems using a non-rebreathing...
valve and, in circle systems, the arrangement H of Eger and Ethans [2] (with FGF greater than minute volume—vide infra).

By the term "completely closed system" (CCS) we imply a system in which no valve is open to the atmosphere, and FGF matches patient uptake. The CCS can be operated in a number of modes: (1) Vaporizer outside the circle system (VOC); (2) Vaporizer inside the circle system (VIC); (3) the Lowe technique [3]; (4) servo controlled systems [4, 5].

The first two are well known and have been examined in detail for halothane in the classic paper by Mapleson [6]. The Lowe technique involves injection of a fixed dose of anaesthetic (calculated according to body weight and desired alveolar concentration) directly into the system at set times, and is designed to achieve rapidly, and then maintain, that alveolar concentration. Servo controlled systems use measurement of end-tidal anaesthetic concentration for feedback control of anaesthetic injection into the system to reach and maintain a prescribed alveolar anaesthetic concentration.

We use three equations to clarify our discussion. The first is well known and based on the Fick principle:

\[ U_B = (P_a - P_v) \cdot Q \cdot \lambda_{B/G} \]  

(1)

where \( U_B \) = rate of uptake of vapour into blood (ml min\(^{-1}\)); \( P_a, P_v \) = partial pressures of anaesthetic in arterial blood and in mixed venous blood (expressed as a fraction of ambient pressure), respectively; \( Q \) = cardiac output (ml min\(^{-1}\)); \( \lambda_{B/G} \) = blood/gas partition coefficient.

Similarly, if we neglect the difference between inspired and expired volumes, we have:

\[ U_L = (P_i - P_A) \cdot V_A \]  

(2)

where \( U_L \) = rate of uptake of vapour into the lungs from the breathing system (ml min\(^{-1}\)); \( P_i, P_A \) = inspired and alveolar partial pressures of anaesthetic (expressed as a fraction of ambient pressure), respectively; \( V_A \) = alveolar ventilation (ml min\(^{-1}\)).

The difference between \( U_L \) and \( U_B \) is the rate of change of volume of anaesthetic vapour in the functional residual capacity (FRC) and dissolved in lung tissue, and so is proportional to the rate of change of \( P_A \). Except for the period of washin into the FRC after a change of anaesthetic concentration in the fresh gas flow, this difference is small relative to the values of \( U_L \) and \( U_B \) themselves, and we neglect it here. Thus we can solve (2) for \( P_A \) and use the resulting expression as an approximation for \( P_A \) in (1) [7]. Re-arranging, we obtain:

\[ \frac{P_i - P_v}{1 + \frac{1}{Q \cdot \lambda_{B/G} \cdot V_A}} \]  

(3)

It follows from (3) that rate of uptake increases with inspired concentration of anaesthetic. Under normal circumstances we have little knowledge of \( P_v \), even though it is of such importance in determining uptake. For the purposes of our discussion, we can say that any effect cardiac output and ventilation may have on uptake is greatest when \( (P_i - P_v) \) is maximal—that is, at the start of the anaesthetic or after the inspired concentration is increased.

Equation (3) gives us the effect of cardiac output, blood/gas partition coefficient and alveolar ventilation on uptake for given values of \( P_i \) and \( P_v \). Furthermore, we see that when the value of either \( V_A \) or \( Q \cdot \lambda_{B/G} \) is small, the effect produced by changes in the other is diminished. Consequently, uptake of an agent may be ventilation-limited or perfusion-limited. In particular, use of agents with a low blood/gas partition coefficient (e.g. nitrous oxide, desflurane or sevoflurane) ensures that uptake of the agent is perfusion-limited, and therefore little influenced by changes in ventilation.

Conclusions drawn from these equations are qualitative in nature because there is no simple method of estimating \( P_v \). We have used a computer program (Narkup—see Appendix) to simulate patient uptake from different breathing systems [8]. Data from this program have been used to produce the graphs which illustrate the points made in this paper by showing cumulative uptake of liquid anaesthetic.

We stress that we are discussing anaesthetic uptake, not the change in alveolar concentration with which most anaesthetists are more familiar. To emphasize the difference, consider induction of anaesthesia using an open system. Increased cardiac output slows the increase in alveolar concentration of an anaesthetic agent, but increases its uptake (vide infra). On the other hand, increased ventilation increases both the uptake and the rate of increase of alveolar concentration.
UPTAKE FROM DIFFERENT BREATHING SYSTEMS

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CONSTANT INSPIRED CONCENTRATION SYSTEMS

Equation (3) describes the effect of cardiac output on uptake when the inspired concentration is held constant—the rate of uptake increases with cardiac output (fig. 1A). Hypoventilation attenuates this response.

We also see from (3) that uptake increases with ventilation (fig. 2A), but that this effect is seen less well when cardiac output is depressed or solubility is low (because uptake is perfusion-limited).

COMPLETELY CLOSED SYSTEMS

Vaporizer outside the circle

The situation changes when $P_i$ is no longer held constant. Consider a VOC system with a fixed concentration of anaesthetic entering the system in the basal FGF. Effectively, the whole system of patient and CCS is receiving an infusion of anaesthetic at a constant rate. If, for any reason, rate of uptake by the patient decreases, the balance of the anaesthetic infusion increases the concentration within the breathing system. Equation (3) predicts that this has the effect of restoring uptake, at least to some extent. Similarly, if uptake increases, inspired concentration must decrease, thus slowing uptake. At first sight, it is remarkable that this effect of uptake on inspired concentration produces almost perfect compensation for those factors affecting uptake (figs 1B, 2B), but it is a simple consequence of the fact that the system is completely closed.

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**Fig. 1.** Cumulative uptake of isoflurane from different breathing systems at three fixed values of cardiac output. A: Constant inspired concentration of 1%. B: VOC (FGF 200 ml min$^{-1}$, vaporizer set to 5%). VIC and Lowe techniques are similar.) C: Servo controlled system with target end-tidal concentration 0.5%. All for 70-kg patient, minute volume 5500 ml min$^{-1}$, deadspace/tidal volume ratio 0.35. Data for all curves generated by Narkup—see Appendix.

**Fig. 2.** Cumulative uptake of isoflurane from different breathing systems at three minute volumes. A: Constant inspired concentration of 1%. B: VOC (FGF 200 ml min$^{-1}$, vaporizer set to 5%). Lowe technique and servo controlled systems are similar.) C: VIC (FGF 200 ml min$^{-1}$, vaporizer set to 0.3%). All for 70-kg patient, cardiac output fixed at 5000 ml min$^{-1}$ and a deadspace/tidal volume ratio of 0.35. Data for all curves generated by Narkup—see Appendix.
Consider the case when uptake is reduced, from any cause. Unless this reduction is catastrophic (apnoea or circulatory arrest), it follows from (3) that it is possible to overcome it by a sufficient increase in inspired concentration. Provided oxygen uptake is maintained and the system remains closed, the excess anaesthetic flowing into the system produces an increase in inspired concentration limited only by the saturation vapour pressure of the agent, so there is the potential for very large increases in inspired concentration of an agent such as halothane or isoflurane. (It has been accepted hitherto that the concentration of anaesthetic within a completely closed circle system with VOC does not increase to more than that in the fresh gas [9]. In practice, this is substantially true for agents such as halothane, but may not be true for new agents of lesser blood solubility. We expect the concentration of desflurane within the circle often to be greater than in the fresh gas.) Under the circumstances described (reduction of uptake from any cause) the inspired concentration increases until a new balance is attained, with the inspired concentration just sufficient to drive anaesthetic into blood at a rate equal to the infusion of agent into the system.

This implies that uptake from a CCS with VOC is independent of cardiac output and of ventilation.

**Vaporizer inside the circle**

When the vaporizer is in the circle, anaesthetic is vaporized approximately in proportion to minute volume. If ventilation is held constant, a VIC system is functionally identical to a VOC system, and so uptake is not affected by changes in cardiac output (fig. 1B). However, because vaporization is proportional to minute volume, an increase in ventilation increases the concentration of anaesthetic within the system. We conclude from equation (3) that, with the vaporizer inside the circle, uptake increases with ventilation (fig. 2C).

**The Lowe technique**

Although this technique actually involves the injection of liquid anaesthetic into the system, we may consider it as a special form of VOC for the purposes of our discussion (that the vaporizer would have to produce supersaturated vapour does not affect our arguments). The injected doses (analogous to vaporizer setting multiplied by volume of fresh gas since last dose) are predetermined and independent of ventilation and of cardiac output, so that the system is functionally equivalent to a VOC system. Thus, when Lowe’s technique is used, uptake of anaesthetic is not affected by changes in ventilation or cardiac output (figs. 1B, 2B).

**Servo controlled systems**

These systems (described above) maintain a constant alveolar concentration and cannot be simulated conveniently by a VOC system, but their functional characteristics are deduced easily from equation (1).

In this equation, ventilation does not appear explicitly. However, we use $P_A$ as an estimate of $P_a$, and $P_A$ may depend on ventilation. Servo controlled systems hold $P_A$ constant so that, in this case, equation (1) suggests that uptake is independent of ventilation (fig. 2B). Furthermore, we see that uptake is directly proportional to cardiac output and blood/gas partition coefficient. With this system, uptake is affected more by changes in cardiac output than is the case for the constant inspired systems (fig. 1C, A, respectively).

The changes shown in figures 1 and 2 are summarized in table I.

<table>
<thead>
<tr>
<th>System</th>
<th>Increase in Ventilation</th>
<th>Increase in Cardiac output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>VOC</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>VIC</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Lowe</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Servo</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>

**TRANSITIONAL STATES: OPENING THE CLOSED SYSTEM**

What happens to the functional characteristics of the circle system as FGF is increased from basal requirements to the minute volume or more? These conditions are more difficult to analyse than the two cases (constant inspired and CCS) described, in which one of the factors controlling uptake is fixed. We have therefore relied exclusively on our computer model of uptake and distribution (see Appendix). The breathing sys-
thin we consider is the H arrangement of the circle system [2], which is characterized ideally by absence of rebreathing of alveolar gas when FGF equals or exceeds the alveolar ventilation; that is, when the FGF equals alveolar ventilation, the soda-lime canister is unnecessary. This characteristic holds for both spontaneous and controlled ventilation. When FGF equals alveolar ventilation, some of the inspired gas must come from the circle reservoir. The circle configuration is such that some of this gas must be inspired into the alveoli, so the inspired isoflurane concentration does not equal that in the fresh gas at this rate of flow. We have assumed that the inspired gas comprises only fresh gas when FGF equals (or is greater than) the minute volume, and is otherwise a perfect mix of fresh and circle gas.

The results of these investigations are shown in figure 3. As FGF increases from basal, thus opening the system, the effect of cardiac output on uptake becomes gradually more important (fig. 3A). In contrast, ventilation has negligible effect on uptake until FGF exceeds 3000 ml min⁻¹ (fig. 3B). The reason for this difference is that the degree of “openness” of the system depends not only upon FGF, but also on minute volume. Because we have assumed that Pi is constant when the FGF is greater than or equal to the minute volume, we can quantify openness in the following simple way:

\[
\text{openness} = \frac{\text{minimum (FGF, minute volume)} - \text{basal flow}}{\text{minute volume} - \text{basal flow}} \times 100\%
\]

Thus a CCS is 0% open and, for a given minute volume, the percentage openness increases linearly with FGF, to a maximum value of 100% when FGF is sufficient to ensure a constant inspired concentration.

If the curves in figure 3 are redrawn using openness as the horizontal axis, the effects of both cardiac output (fig. 4A) and ventilation (fig. 4B) are seen to increase evenly as the system is opened.

Do these findings have any practical significance? It might be considered undesirable
that a system maintain uptake in the face of decreasing cardiac output, for this would imply that, if the patient’s circulation was impaired by any cause (e.g. blood loss, excessively deep anaesthesia), then alveolar concentration would increase and further embarrass cardiac output. This is contrary to clinical practice—the anaesthetist normally reduces the inspired concentration when these conditions occur. The only systems in which rate of uptake is reduced automatically by decreasing cardiac output are the constant inspired systems, and servo controlled systems (fig. 1A, C).

Reduced ventilation in a spontaneously breathing patient is a sign that anaesthesia is too deep in relation to surgical stimulation. The constant inspired and the VIC systems are self-regulatory in this respect (fig. 2A, C). This may be advantageous.

The findings presented in figure 3b suggest that, in a low flow circle system (e.g. FGF less than 3000 ml min⁻¹), an increase in ventilation does not increase uptake because the larger minute volume renders the system functionally less open. However, the data for figures 3 and 4 are derived from a computer simulation based on an idealized breathing system and an idealized patient. They await experimental verification.

APPENDIX

Our computer program Narkup models the H arrangement of the circle system [2]. It is assumed that the circle has an initial volume of 5000 ml, a maximum volume of 6000 ml (after which gas is expelled through the pop-off valve, with preferential loss of alveolar gas), that it contains 100% oxygen at the start of the anaesthetic, and that no isoflurane is lost into rubber and plastic components. The model assumes that inspired gas is composed of fresh gas, supplemented by gas from the circle—these are mixed perfectly before being inspired. Expired gas which is not vented from the system is assumed to mix perfectly with existing circle gas.

The patient is based on Eger’s four-compartment patient model [10], with the addition of a peripheral shunt. We use physiological data taken from those given by Davis and Mapleson [11]. Mathematical modelling is simplified by assuming “continuous alveolar ventilation”—it is assumed that inspired gas enters the alveoli continuously, and that, simultaneously, alveolar gas is being expired at a rate that maintains a constant FRC in the face of uptake. Gas within the alveoli is always a perfect mixture. Although a mechanical analogue of this would require separate inflow and outflow pipes to and from a mixing chamber, nonetheless we have adopted it because it is computationally so convenient.

Physico-chemical properties of isoflurane are given by Fischerova-Bergerova [12] and by Lowe and Ernst [3]. The values used in the program are shown in table II.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Volume (litres)</th>
<th>Blood flow (% of CO)</th>
<th>λ_T/IG</th>
<th>λ_T/B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>5.5</td>
<td>1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vessel rich group</td>
<td>5.4</td>
<td>61.8</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Muscle group</td>
<td>38.6</td>
<td>17.7</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Vessel poor group</td>
<td>6.2</td>
<td>0.2</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>16.5</td>
<td>5.3</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>0.5</td>
<td>1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shunt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left-to-right</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right-to-left</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The algorithm presented below is repeated every 10 s of model time. It starts with known values for various variables (e.g. alveolar partial pressure of isoflurane is zero initially) and calculates how those values change in the next 10 s. The new values are then used to project a further 10 s, and so on. Mathematically, this is a process of interdependent integrations and the best numerical solution would take this interdependence into account. The implementation of such an approach would be extremely time consuming, with no clinically significant improvement of accuracy, and would be inappropriate for a model with so many arbitrary assumptions. We have adopted a simpler approach, using a classical fourth-order Runge-Kutta technique to solve the equations for alveolar, arterial and tissue isoflurane partial pressures (which empirical testing has shown to be the most critical), but cruder integration techniques elsewhere.

In the following, $P_t, P_a$ and $P_0$ denote the inspired, alveolar and mixed venous isoflurane partial pressures, respectively. All partial pressures are understood to be expressed as fractions of the ambient pressure, all volumes are in ml and all flows are ml min⁻¹. The program automatically augments the fresh gas flow to allow for vaporized agent, but no temperature corrections are made.

**Step 1.** The minute volume, $V_t$, comprises the fresh gas flow supplemented, if necessary, by rebreathed gas from the circle. It is divided into deadspace ventilation, $V_d$ and the inspired alveolar ventilation $V_{A1}$ in the proportion 35:65. When a constant inspired concentration system is used, the inspired concentration is simply the concentration in the fresh gas. When using VOC, the inspired isoflurane concentration is calculated as follows:

$$P_t = \min(\frac{(V_t - FGF)}{P_{\text{FGF}}} + \max(\frac{(V_t - FGF)}{P_{\text{FGF}}}, 0), P_{\text{circle}})$$

where $P_{\text{FGF}}, P_{\text{circle}} =$ concentration of isoflurane in the fresh gas flow and in the reservoir of the circle system, respectively.
For VIC, the vaporizer is assumed to be on the inspiratory limb, and it is calibrated so that when set to 1 % it increases the halothane concentration of the gas passing over it by 1%. To accommodate other agents, we assume that the rate of liquid vaporization is unchanged between agents, but because 1 ml of liquid isoflurane produces less vapor than 1 ml of liquid halothane, there is a small reduction in the output concentration. Thus:

\[
P_1 = \frac{P_{\text{circle}} \cdot \text{maximum} \cdot (V - \text{FGF}, 0) + P_{\text{vap}} \cdot V \cdot \text{FiO}}{V}\]

where \(P_{\text{vap}}\) = vaporizer setting.

**Step 2.** The expired alveolar ventilation is calculated:

\[
V_{A,E} = V_{A,I} \cdot \text{factor} - (U_b + V_{O} \cdot (1 - RQ))
\]

\[
\text{factor} = 1 + P_{A_{HI}} \cdot \left( \frac{\text{minimum} \cdot (V \cdot \text{FGF})}{\text{V}} \right)
\]

where \(V_{A,E}, V_{A,I}\) = inspired and expired alveolar ventilations, respectively; “factor” increases the volume of the inspired gas to allow for the vaporization of water needed to humidify the non-rebreathed gas (assuming that fresh gas is dry, rebreathed gas is saturated, and \(P_{A_{HI}} = 0.06\)); \(U_b\) = flow of alveolar vapor into the blood (and so is negative during eduction). This starts at zero and is recalculated repeatedly in step 7 on every cycle through the algorithm; \(V_{O} \cdot (1 - RQ)\) = difference between oxygen consumption and carbon dioxide production. The program assumes a constant oxygen uptake of 214 ml min⁻¹ and a respiratory quotient of 0.82 in the examples used here.

Thus the model of ventilation is of constant flow of inspired gas into the FRC, instant mixing there, and constant efflux of gas from the FRC at a rate which maintains a constant FRC.

**Step 3.** The alveolar isoflurane partial pressure, \(P_A\), is calculated using:

\[
\frac{d}{dt} P_A = \frac{P_{A_{HI}} \cdot \text{factor} - (U_b + V_{O} \cdot (1 - RQ)) \cdot \left( \frac{\text{minimum} \cdot (V \cdot \text{FGF})}{\text{V}} \right) \cdot \gamma_{P_{\text{tit}}} \cdot P_{\text{tiss}}}{\text{tissue blood flow} \cdot \text{tissue volume}}
\]

where \(\gamma_{P_{\text{tit}}}\) = tissue/blood partition coefficient for isoflurane.

**Step 4.** New values for the volume and composition of circle gas are calculated. First, a volume of gas equal to one-sixth of the rebreathed flow (i.e. 10 seconds-worth) is subtracted from the circle volume \(V_{\text{circle}}\). If FGF is greater than minute volume, the excess is ignored. The reduced circle volume is denoted \(V_{\text{circle}}\). This does not imply inspiration: as stated above, flow in and out of the alveoli is assumed to be continuous and simultaneous. We are merely forming a new set of approximations every 10 s:

\[
V_{\text{circle}} = V_{\text{circle}} - \frac{\text{maximum} \cdot (V - \text{FGF}, 0)}{6}
\]

The deadspace gas and the expired alveolar gas are added to the circle, ensuring that the circle volume does not increase to more than 6 litre (alveolar gas is wasted preferentially). Carbon dioxide is then absorbed:

\[
V_{\text{circle}} = V_{\text{circle}} + V_{\text{D,recr}} + (1 - P_{C_{O_2}}) \cdot V_{\text{A,recr}}
\]

\[
V_{\text{D,recr}} = \min \left( \frac{V_{D}}{6}, 6000 - V_{\text{circle}} \right)
\]

\[
V_{\text{A,recr}} = \min \left( \frac{V_{A,E}}{6}, 6000 - (V_{\text{circle}} + V_{\text{D,recr}}) \right)
\]

The new partial pressure of isoflurane within the bulk of the breathing system can now be calculated:

\[
P_{\text{circle}} = P_{\text{circle}} \cdot V_{\text{circle}} + P_t \cdot V_{\text{D,recr}} + P_{D} \cdot V_{\text{A,recr}}
\]

where \(P_{\text{circle}}\) = last calculated (or assumed) value of partial pressure of isoflurane within the circle.

**Step 5.** The arterial partial pressure of isoflurane is calculated, using the current value of right-to-left shunt and assuming that the mixed venous partial pressure is constant for the 10-s period. The calculation is based on:

\[
\frac{d}{dt} P_A = \frac{(P_A - P_{\text{tiss}}) \cdot \dot{Q}_{\text{tiss}}}{\text{tissue blood flow} \cdot \text{tissue volume}}
\]

where \(P_{\text{tiss}} = \text{tissue blood flow} \cdot \text{tissue volume} \cdot \lambda_{r/b} = \text{tissue/blood partition coefficient for isoflurane.}

**Step 6.** Calculate rate of uptake from the lungs, \(U_b\), and total uptake from the lungs, of isoflurane (note that agent trapped in the FRC and lung tissue is not included in this definition of uptake):

\[
U_b = (P_A - P_{\text{vap}}) \cdot \gamma_{P_{\text{tit}}} \cdot \lambda_{h/g}
\]

where \(\gamma_{P_{\text{tit}}} = \text{average of last and current estimate of } P_A\).

The rate of uptake is assumed constant over the 10-s interval, so the amount of uptake is simply the product of the rate of uptake and the 10-s time interval. Cumulative uptake is obtained by summing these small amounts, and this is the result used in the figures. It can be compared to the sum of the anaesthetic content of the four tissue compartments, and of the blood. The differences between the two values—which is a reflection of the accuracy of the numerical work—is never of clinical significance.

**Step 8.** Calculate the mixed venous isoflurane partial pressure by taking the average for the tissue compartments, \(P_{\text{tiss}}\):

\[
\frac{d}{dt} P_{\text{tiss}} = \frac{(P_A - P_{\text{tiss}}) \cdot \dot{Q}_{\text{tiss}}}{\text{tissue blood flow} \cdot \text{tissue volume}}
\]

where \(\dot{Q}_{\text{tiss}} = \text{blood flow through the tissue compartment} \cdot \text{total cardiac output, respectively. The sum is taken over five tissue compartments—Eger's four, and a fifth representing the peripheral shunt. The result is stored internally for 20 model seconds to simulate delay in the circulation, and the value used as the "next } P_{\text{tiss}}" \text{ is the result calculated 20 model seconds ago.}
Step 9. Start again at step 1.

The results obtained match equation (3) closely if predicted values of PV are used, and are also in accord with clinical data obtained from the Northwick Park Hospital servo controlled anaesthetic machine [13], and with data given by Lowe and Ernst [3].

Narkup can perform similar calculations for halothane, enflurane, sevoflurane, desflurane, cyclopropane and xenon, all with or without nitrous oxide. The nitrous oxide calculations are made in parallel with those for the other agent, allowing demonstration of the second gas effect. The program can model depression of ventilation and cardiac output by volatile agents, according to data given by Eger [14]. The age and weight of the patient, and the relative size and perfusion of the tissue compartments can all be varied. Results are presented in graphical and numerical form, and some effort has been made to make the program user-friendly. We are prepared to distribute copies to readers who request them.

REFERENCES