The two-compartment recirculatory pharmacokinetic model—an introduction to recirculatory pharmacokinetic concepts

R. N. Upton

Department of Anaesthesia and Intensive Care, Royal Adelaide Hospital, University of Adelaide, North Terrace, Adelaide, SA 5005, Australia
E-mail: richard.upton@adelaide.edu.au

Background. Some limitations of traditional (‘mamillary’) compartmental pharmacokinetic models of anaesthetic related drugs arise from representing the blood as a central compartment. Recirculatory pharmacokinetic models overcome these limitations. It is proposed that the simplest recirculatory model has only two compartments, and that understanding the properties of this model is a useful introduction to recirculatory pharmacokinetic concepts.

Methods. The compartments of the model are the lungs and the remainder of the body. The traditional rate constants (e.g. \(k_{12}\) and \(k_{21}\)) are replaced by terms that include cardiac output. Drug infusion is into the lung compartment, and drug clearance is from the ‘body’ compartment. The ‘total’ drug concentrations can be thought of as the sum of the first-pass and recirculated drug concentrations at any time. Equations for both first-pass and total drug concentrations in arterial and mixed venous blood are presented. The effects of cardiac output and injection time on these concentrations were analysed.

Results. The first-pass arterial concentrations were shown to make a significant contribution to the total concentrations for high-clearance drugs and/or bolus drug administration. There was an inverse relationship between these first-pass concentrations and cardiac output, and a direct relationship with bolus injection rate. Thus, the total arterial concentrations are affected by these factors in these circumstances.

Conclusions. The two-compartment recirculatory model is the simplest tool available for elaborating recirculatory pharmacokinetic concepts. The recirculatory approach may provide a conceptual framework of drug disposition that better matches the clinical experience of anaesthetists.

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data sets required for their validation for non-volatile drugs, and the fact that such models are not readily fitted to clinical pharmacokinetic data (although this has been done for pethidine in a detailed physiological model8).

Recirculatory pharmacokinetic models were developed over 20 yr ago,9-11 but recently have emerged in anaesthesia as a middle ground between the two schools of pharmacokinetic modelling discussed above.12-14 They retain the relative simplicity of mamillary models, but incorporate descriptions of key physiological processes that have emerged as important determinants of intravenous anaesthetic disposition. These include the role that cardiac output, lung kinetics, and injection rate play in dictating initial drug concentrations after i.v. bolus administration. Recent papers have shown that these factors can be incorporated into models of anaesthetic disposition and are consistent with data collected using instrumented sheep.15 16 The hypothesis explored in this paper is that the contribution of cardiac output, lung kinetics, and injection rate can be explained by considering the arterial drug concentrations (Ca) to be the sum of two components—the first-pass arterial concentrations (Ca,f) and the recirculated concentrations (Ca,r):

\[ Ca = Ca,f + Ca,r \] (1)

The first-pass concentrations are affected by cardiac output, lung kinetics, and injection rate in a manner that has a direct analogy to indicator dilution methods used to measure cardiac output.17 For bolus and short infusion administration, they can constitute most of the ‘total’ arterial concentration (Ca), and thus the peak arterial concentration in many cases is also affected predominantly by cardiac output, lung kinetics, and injection rate.

It is proposed that knowledge of the concepts underlying recirculatory pharmacokinetics is best achieved by starting with the simplest recirculatory system—a two-compartment recirculatory model. The aim of this paper is to describe the structure and behaviour of this model while addressing the hypothesis outlined above. The equations of the model are provided for completeness—they are most useful if they are entered into a spreadsheet program so that the effect of cardiac output, lung kinetics, injection, rate and other factors on the time-course of drug concentrations (both total and first-pass) can be examined graphically. The author proposes that this provides an introduction to a theoretical framework for drug disposition that matches the clinical experience of anaesthetists better than that provided by mamillary models.

Methods

Model structure

This paper will consider both the two-compartment recirculatory model (Fig. 2A), and a modified form of the model that describes only the first-pass concentrations (Fig. 2B).

Recirculatory model

In comparison with a two-compartment mamillary model (Fig. 1), the two compartments of the recirculatory model (Fig. 2A) are assigned physiological identities—the lungs and ‘rest of the body’, respectively. Drug transport between the compartments (described by abstract rate constants in the mamillary model) are
Two-compartment recirculatory pharmacokinetic model

replaced with rates of drug transport in real blood vessels. If, for convenience, the drug is infused into the pulmonary artery, there are two defining sites in the vasculature in the two-compartment recirculatory system: (1) mixed venous concentrations \((C_v)\) upstream of the infusion and measured in blood returning from the body and (2) arterial concentrations \((C_a)\) representing blood emerging from the lungs and entering the rest of the body. The rate of circulation of the blood between the two compartments is given by the cardiac output \((Q_{CO})\). The apparent distribution volumes of the lung and body compartments are \(V_L\) and \(V_B\), respectively, and drug clearance from the body compartment is given by \(Q_{Cl}\). The apparent distribution volumes can be thought of as the amount of drug \((mg)\) in each compartment normalized for (i.e. divided by) the arterial blood concentration \((mg \text{ litre}^{-1} \text{ blood})\), which works out as litres of blood. This is the volume of blood that would contain the same amount of drug as the compartment if the two were in equilibrium (as at steady state). Similarly, drug clearance can be thought of as the rate of removal of the drug \((mg \text{ min}^{-1})\) from the body divided by the arterial blood concentration \((mg \text{ litre}^{-1} \text{ blood})\), that is litres of blood per min \((\text{litre} \text{ min}^{-1})\). This is the flow of blood at arterial concentration that, if it were completely cleared of drug, would account for the observed rate of removal.

The system of differential equations for the model (Fig. 2a) are derived by mass balance of the rates that drug enters and leaves the compartments:

\[
\begin{align*}
V_L \cdot \frac{dC_a}{dt} &= R_0 - Q_{CO} \cdot (C_a - C_v) \\
V_B \cdot \frac{dC_v}{dt} &= Q_{CO} \cdot (C_a - C_v) - Q_{Cl} \cdot C_a
\end{align*}
\]

(2a, b)

Several issues should be pointed out. First, this model differs from that shown in Figure 1 in that elimination is from the 'peripheral' rather than the central compartment. If this were not so, the equations for the recirculatory model could be obtained by substituting terms into the well-known equations for the standard two-compartment mamillary model.\(^{18}\) Secondly, the equations describe an infusion at a rate given by \(R_0'\) (e.g. mg min\(^{-1}\)). For bolus doses, this infusion can be treated more conveniently as dose \((D,\text{ e.g. mg})\) given over a time interval equal to the duration of the injection (hereafter called the 'injection time', \(t_D\)).

\[
R_0 = \frac{D}{t_D}
\]

(3)

Thus, bolus doses cannot be specified without also specifying the time over which the injection was made—the implications of this will be discussed later. Thirdly, clearance cannot exceed cardiac output—this is evident if clearance is thought of as a blood flow, as discussed previously.

First-pass model

The first-pass model differs from the recirculatory model in only one respect—mixed venous blood is not returned to the lungs (Fig. 2b). The first-pass arterial concentrations are therefore those resulting from drug molecules that have been infused into the pulmonary artery and have passed once through the lungs. The first-pass venous concentrations are those resulting from drug molecules that have been infused and have passed once through the lungs and once through the body. The first-pass concentrations occur \emph{in vivo}, but are of course difficult to measure.

The first-pass arterial and mixed venous concentrations are designated \(C_{af}\) and \(C_{vf},\) respectively. In contrast, \(C_a\) and \(C_v\) from equation (2) will be called the 'total' drug concentrations. These are the blood concentrations that can be measured directly via blood sampling from the appropriate blood vessels, and are the sum of the first-pass (molecules that have made one circuit) and recirculated concentrations (molecules that have made more than one circuit) at any given time (equation (1)).

The differential equations for the first-pass model are:

\[
\begin{align*}
V_L \cdot \frac{dC_{af}}{dt} &= R_0 - Q_{CO} \cdot C_{af} \\
V_B \cdot \frac{dC_{vf}}{dt} &= Q_{CO} \cdot (C_{af} - C_{vf}) - Q_{Cl} \cdot C_{af}
\end{align*}
\]

(4a, b)

Note that this differs from equation (2a,b) only in that there is no term for \(C_v\) in the right hand side of the upper equation. That is, mixed venous blood is not returned to the lungs.

Model equations

Steady state during a constant rate infusion

At steady state, the rate of change of the concentrations (e.g. \(dC_a/dt\) and \(dC_v/dt\)) is zero. If this substitution is made into equations (2) and (4), then algebraic manipulation can be used to find equations (5)–(10) in Table 1, for the first-pass and total concentrations at steady state. Dividing 5 by 8 shows that the ratio of the first-pass arterial concentrations over the total concentrations at steady state is:

\[
\frac{C_{af}}{C_a} = \frac{Q_{Cl}}{Q_{CO}}
\]

(11)

Complete equations—first-pass model

Solving equations (2) and (4) for the non-steady-state case is more difficult. The most common approach is to use Laplace transforms to convert the differential equations to polynomal equations, which can then be solved using matrix methods. This method was used here and has been well-
described for other pharmacokinetic models, and will not be repeated. Solving any two-compartment model resolves two hybrid rates constants (λ₁ and λ₂). When the time-course of the concentrations is plotted on a log-scale, these hybrid rate constants dictate the slopes of the two linear portions of the curve representing each exponential phase. For the first-pass model, these are:

\[ \lambda_{1,f} = \frac{\dot{Q}_\text{CO}}{V_L} \]
\[ \lambda_{2,f} = \frac{\dot{Q}_\text{CO}}{V_B} \]  
(12a, b)

These hybrid rate constants can be expressed in other ways. Their inverse (1/λ) gives the time constants (t) of each compartment. They can also be converted to half-lives (ln(2)/λ).

The complete equations for the first-pass model are given in Table 2. The interplay of the parameter values is illustrated most simply in the exponential equation describing the time-course of the first-pass arterial concentrations (Table 2, 13a) expressed for a bolus dose (see equation (3)) and with equation 12b substituted for \( \lambda_{1,f} \) (equation (13b)).

\[ C_{a,f} = \frac{D}{\dot{Q}_\text{CO} \cdot t_D} \cdot \left( 1 - e^{\frac{-\dot{Q}_\text{CO} \cdot t_D}{V_L}} \right) \]  
(13b)

Thus, the first-pass arterial concentrations approach a steady-state value that is a function only of dose, injection time and cardiac output (equation (5) in Table 1). However, the rate at which they approach steady state (the exponential term) depends on cardiac output and the distribution volume of the lungs.

**Complete equations—recirculatory model**

Adding recirculation to the model increases its complexity yet again. The exact hybrid rate constants for the recirculating system are:

\[ \lambda_{1,2} = \frac{\dot{Q}_\text{CO} \cdot (V_L + V_B)}{2 \cdot V_L \cdot V_B} \pm \dot{Q}_\text{CO} \cdot \sqrt{\frac{(V_L + V_B)^2}{V_L^2 \cdot V_B^2} - 4 \cdot \frac{\dot{Q}_\text{CO}}{\dot{Q}_\text{CO}^2}} \]  
(21a, b)

### Table 1

<table>
<thead>
<tr>
<th>Arterial concentration</th>
<th>Mixed venous concentration</th>
<th>( E_a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-pass</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \frac{R_0}{\dot{Q}_\text{CO}} ) (5)</td>
<td>( \frac{R_0}{\dot{Q}<em>\text{CO}} \cdot (1 - \frac{\dot{Q}</em>\text{CI}}{\dot{Q}_\text{CO}}) ) (6)</td>
<td>( \frac{\dot{Q}<em>\text{CI}}{\dot{Q}</em>\text{CO}} ) (7)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \frac{R_0}{\dot{Q}_\text{CI}} ) (8)</td>
<td>( \frac{R_0}{\dot{Q}<em>\text{CI}} \cdot (1 - \frac{\dot{Q}</em>\text{CI}}{\dot{Q}_\text{CO}}) ) (9)</td>
<td>( \frac{\dot{Q}<em>\text{CI}}{\dot{Q}</em>\text{CO}} ) (10)</td>
</tr>
</tbody>
</table>

### Table 2

The complete equations describing the models shown in Figure 2. The values of the hybrid rate constants \( \lambda_{1,f}, \lambda_{2,f}, \lambda_1, \) and \( \lambda_2 \) are calculated from equations (12) and (21) as given in the text. \( X_1 \) and \( X_2 \) are \( \lambda_1/\dot{Q}_\text{CO} \) and \( \lambda_2/\dot{Q}_\text{CO} \), respectively. The values of \( C_{a,f}(t_D), C_{v,f}(t_D), C_{a,f}(t_D) \), and \( C_{v,f}(t_D) \) are the respective last intra-infusion concentrations—that is, the values of equations (13), (15), (17), and (19) evaluated at time \( t=t_D \).

**During infusion**

<table>
<thead>
<tr>
<th>( C_{a,f} = \frac{R_0}{\dot{Q}<em>\text{CO}} \cdot (1 - e^{-\lambda</em>{1,f} \cdot t}) ) (13a)</th>
<th>( C_{a,f} = C_{a,f}(t_D) \cdot e^{-\lambda_{1,f} \cdot (t-t_D)} ) (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{v,f} = \frac{R_0}{\dot{Q}_\text{CO}} \cdot (1 - \lambda_1 \cdot e^{-\lambda_1 \cdot t} - B_1 \cdot e^{-\lambda_2 \cdot t}) ) (15)</td>
<td>( C_{v,f} = \frac{1}{\dot{Q}_\text{CO} \cdot (V_B - V_L) \cdot \left( A_1 \cdot e^{-\lambda_1 \cdot (t-t_D)} + B_1 \cdot e^{-\lambda_2 \cdot (t-t_D)} \right)} ) (16)</td>
</tr>
<tr>
<td>( C_a = \frac{R_0}{\dot{Q}_\text{CI}} \cdot (1 - A_1 \cdot e^{-\lambda_1 \cdot t} - B_1 \cdot e^{-\lambda_2 \cdot t}) ) (17)</td>
<td>( C_a = \frac{1}{V_L \cdot V_B \cdot (X_1 - X_2)} \cdot \left( A_2 \cdot e^{-\lambda_2 \cdot (t-t_D)} + B_2 \cdot e^{-\lambda_2 \cdot (t-t_D)} \right) ) (18)</td>
</tr>
<tr>
<td>( C_v = \frac{R_0}{\dot{Q}_\text{CI}} \cdot (1 - A_5 \cdot e^{-\lambda_1 \cdot t} - B_5 \cdot e^{-\lambda_2 \cdot t}) ) (19)</td>
<td>( C_v = \frac{1}{V_L \cdot V_B \cdot \dot{Q}_\text{CO} \cdot (X_1 - X_2)} \cdot \left( A_6 \cdot e^{-\lambda_2 \cdot (t-t_D)} + B_6 \cdot e^{-\lambda_2 \cdot (t-t_D)} \right) ) (20)</td>
</tr>
</tbody>
</table>

Where:

\[ A_1 = \frac{-V_L}{V_B - V_L} \]
\[ A_2 = -C_{a,f}(t_D) \cdot V_L \cdot (\dot{Q}_\text{CO} - \dot{Q}_\text{CI}) \]
\[ A_3 = X_2 \cdot (V_B \cdot X_1 - 1) \]
\[ A_4 = C_{v,f}(t_D) \cdot V_L \cdot (X_1 \cdot V_B - 1) - C_{v,f}(t_D) \cdot V_B \]
\[ A_5 = -\frac{X_1}{X_1 - X_2} \]
\[ A_6 = -C_{v,f}(t_D) \cdot \dot{Q}_\text{CO} - \dot{Q}_\text{CO} \cdot V_B \cdot (X_1 \cdot V_B - 1) + C_{v,f}(t_D) \cdot \dot{Q}_\text{CO} \cdot V_B \cdot (X_1 \cdot V_B - 1) \]

**Post-infusion**

<table>
<thead>
<tr>
<th>( C_{a,f} = \frac{R_0}{\dot{Q}<em>\text{CO}} \cdot (1 - e^{-\lambda</em>{1,f} \cdot (t-t_D)} ) (14)</th>
<th>( C_{a,f} = C_{a,f}(t_D) \cdot e^{-\lambda_{1,f} \cdot (t-t_D)} ) (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{v,f} = \frac{1}{\dot{Q}_\text{CO} \cdot (V_B - V_L) \cdot \left( A_1 \cdot e^{-\lambda_1 \cdot (t-t_D)} + B_1 \cdot e^{-\lambda_2 \cdot (t-t_D)} \right)} ) (16)</td>
<td>( C_{v,f} = \frac{1}{V_L \cdot V_B \cdot (X_1 - X_2)} \cdot \left( A_2 \cdot e^{-\lambda_2 \cdot (t-t_D)} + B_2 \cdot e^{-\lambda_2 \cdot (t-t_D)} \right) ) (18)</td>
</tr>
<tr>
<td>( C_a = \frac{R_0}{\dot{Q}_\text{CI}} \cdot (1 - A_1 \cdot e^{-\lambda_1 \cdot t} - B_1 \cdot e^{-\lambda_2 \cdot t}) ) (17)</td>
<td>( C_a = \frac{1}{V_L \cdot V_B \cdot (X_1 - X_2)} \cdot \left( A_2 \cdot e^{-\lambda_2 \cdot (t-t_D)} + B_2 \cdot e^{-\lambda_2 \cdot (t-t_D)} \right) ) (18)</td>
</tr>
<tr>
<td>( C_v = \frac{R_0}{\dot{Q}_\text{CI}} \cdot (1 - A_5 \cdot e^{-\lambda_1 \cdot t} - B_5 \cdot e^{-\lambda_2 \cdot t}) ) (19)</td>
<td>( C_v = \frac{1}{V_L \cdot V_B \cdot \dot{Q}_\text{CO} \cdot (X_1 - X_2)} \cdot \left( A_6 \cdot e^{-\lambda_2 \cdot (t-t_D)} + B_6 \cdot e^{-\lambda_2 \cdot (t-t_D)} \right) ) (20)</td>
</tr>
</tbody>
</table>

Where:

\[ B_1 = 1 - A_1 \]
\[ B_2 = C_{a,f}(t_D) \cdot (V_B - V_L) - A_2 \]
\[ B_3 = 1 - A_3 \]
\[ B_4 = C_{v,f}(t_D) \cdot V_L \cdot (X_1 - X_2) - A_4 \]
\[ B_5 = 1 - A_5 \]
\[ B_6 = C_{v,f}(t_D) \cdot V_B \cdot (X_1 - X_2) - A_6 \]
For most biologically plausible parameter values, these complex equations can be approximated (±10%) with:

\[ \lambda_1 \approx \frac{Q_{\text{CO}} (V_L + V_B)}{V_L V_B} \]

\[ \lambda_2 \approx \frac{Q_{\text{CL}}}{V_L + V_B} \]

(22a, b)

Thus, \( \lambda_1 \) is dependent mainly on cardiac output, while \( \lambda_2 \) is dependent mainly on clearance. The equations for the time-course of the total arterial and venous concentrations (17–20, Table 2) utilize these hybrid rate constants (21a,b). These are relatively complex, but with care can be entered into a spreadsheet program (the author can supply an example spreadsheet on request). Once in a spreadsheet, the time-courses of both the first-pass and total concentrations in arterial and mixed venous blood can be calculated and plotted for any values of dose, injection time, cardiac output, clearance, and distribution volumes in the lungs and body. By way of example, these calculations were done for a hypothetical high-clearance induction agent under a variety of circumstances: with different cardiac outputs, different injection times for a fixed bolus dose, and a rhythmically fluctuating cardiac output during and after an infusion.

**Fitting to data**

While the main purpose in describing this model (Fig. 2a) is to illustrate recirculatory concepts, as for the two-compartment mammary model (Fig. 1), the recirculatory model can be fitted to concentration time-courses that show two exponential phases. However, the recirculatory model will only return meaningful parameter estimates when it is known that the fastest exponential is associated with lung kinetics (i.e. there are many early blood samples) and that lung kinetics can be adequately represented by a single compartment. A previously published data set reporting the arterial thiopental concentrations in sheep (500 mg over 2 min) meets these criteria—both types of model were fitted to these data for comparison. The software used was ‘Scientist for Windows 2.01’ (Micromath, Salt Lake City, UT).

**Results**

**Examples**

**Steady state**

The default parameter values of the hypothetical high-clearance induction agent were: \( Q_{\text{CO}} = 5 \text{ litre min}^{-1} \), \( Q_{\text{CL}} = 2 \text{ litre min}^{-1} \), \( V_L = 2.5 \text{ litre} \), and \( V_B = 15 \text{ litre} \). The steady-state total arterial concentration for this drug infused at 20 mg min\(^{-1}\) was therefore 10 mg litre\(^{-1}\), as given by the classical formula \( R_d/Q_{\text{CL}} \) (equation (8)). The steady-state total mixed venous concentration (equation (9)) was lower—6 mg litre\(^{-1}\); the difference is because of clearance depleting drug in the venous blood returning from the body. For many hepatically cleared drugs, this is usually a result of the hepatic venous blood (which would be almost devoid of drug) mixing with non-depleted blood returning from other parts of the body. The whole body extraction ratio is the weighted average of this process once all the cardiac output has been mixed together, and is given by \( Q_{\text{CO}}/Q_{\text{CL}} \) (equation (10)); in this example 2/5=0.4. Thus, the two-compartment recirculatory model introduces the concept of heterogeneity in the blood concentrations of a drug depending on whether blood at a particular site has been enriched by an upstream infusion (arterial in the present model), or depleted by an upstream organ of drug clearance (venous in the present model).

The steady-state first-pass arterial concentration is given by equation (5) \( (R_d/Q_{\text{CO}}) \); in this example 20/5=4 mg litre\(^{-1}\). The ratio of \( C_{\text{a,p}}/C_{\text{a}} \) at steady state (equation (11)) is \( Q_{\text{CL}}/Q_{\text{CO}} \) or 2/5=0.4. As \( Q_{\text{CL}} \) must be less than or equal to \( Q_{\text{CO}} \), it is apparent that the first-pass concentration will always be less than or equal to the total concentration. In other words, the higher the clearance, the less the mixed venous concentration contributes to the total concentration.

**Non-steady state**

The first-pass hybrid rate constants for the hypothetical drug were 2.0 and 0.33 min\(^{-1}\) for the lung and body, respectively (at a cardiac output of 5 litre min\(^{-1}\)), equating to time constants of 0.5 and 3 min, and half-lives of 0.35 and 2.1 min, respectively. Note the hypothetical drug passes rapidly through the lungs—this is representative of both thiopental and propofol; respective half-lives of 0.30 and 0.52 min have been reported for these drugs in the lungs of sheep. Such rapid equilibration of a drug in the lungs also means that the first-pass arterial concentrations approach steady state very quickly during an infusion (equation (13a)), and that they are gone soon after the infusion ends.

The total hybrid rate constants for the hypothetical drug were 2.2 and 0.12 min\(^{-1}\) for the lung and body, respectively (at a cardiac output of 5 litre min\(^{-1}\)), equating to time constants (\( \tau \)) of 0.45 and 8.3 min, and half-lives of 0.31 and 5.8 min, respectively. Figure 3 shows the time-course of both the first-pass and total concentrations for the hypothetical drug for a dose rate of 20 mg min\(^{-1}\) for 5 min. This shows the first-pass arterial concentration rapidly approaching its steady-state value (4 mg litre\(^{-1}\)), while the peak total arterial concentration (approximately 6.5 mg litre\(^{-1}\)) was short of its steady-state value (10 mg litre\(^{-1}\)). Thus, the first-pass concentrations made a significant contribution to the total arterial concentrations during the short infusion. Note that the total venous concentrations also had a significant component because of the first-pass venous concentrations.

**Sensitivity analysis**

The effect of altering cardiac output for a short infusion is shown in Figure 4. Increasing cardiac output decreased the
peak total arterial concentration; this can be explained by the large contribution of the first-pass arterial concentrations to the total concentration during and immediately after the bolus, and the significant influence of cardiac output on these first-pass concentrations (equation (13a)). The lowest cardiac output was associated with delayed recirculation in that the mixed venous concentrations were lower and peaked later.

The effect of changing the injection time of a fixed dose is shown in Figure 5. Injection time had a profound effect on the peak arterial concentrations. Again, because of the relatively short injection time in all three cases there was little contribution from the venous return to the peak arterial concentration; in other words the first-pass kinetics explain the arterial concentrations in the first few minutes after the dose. By virtue of equations (3) and (5), the steady-state values of the first-pass arterial concentration differed greatly with injection time ($C_{a,f}(ss)$ in Fig. 5). However, as the injection time was decreased, there was less time available for the first-pass arterial concentrations to approach their steady-state value. The net effect was that decreasing the injection time caused higher peak first-pass and total arterial concentrations (Fig. 5). Note that for these parameter values, the difference between a 30 and 120 s injection was more profound than that between a 10 and 30 s injection.

The effect of acute variations in cardiac output (Fig. 6) clearly illustrates the contribution of the cardiac output dependent first-pass concentrations to the total concentrations, even during a longer infusion. The first-pass concentrations quickly settled at a value given by $R_0/Q_{CO}$ as shown by equation (5). However, as the cardiac output varied, so did the first-pass concentration, albeit with a degree of ‘damping’ dictated by the distribution volume in the lung. As the recirculated concentrations were more heavily damped by the distribution volumes of the lungs and body, these varied less with cardiac output. During the infusion, the total concentrations (the sum of first-pass and recirculated) therefore varied with cardiac output reflecting the contribution of the first-pass component. However, very soon after the infusion, the first-pass concentrations approached zero, leaving total concentrations much less affected by cardiac output and reflecting the contribution of the recirculated component.

**Fitting to data**

Both the mamillary and recirculatory models provided excellent fits of the data (Fig. 7). The parameters of both models were also estimated with good precision (Table 3). The estimated apparent volume of the lung (3.15 litres) was in broad agreement with the value measured by more direct means (2.49 litres) for a different data set in sheep.$^{21}$

**Discussion**

This paper shows that a minor modification of a two-compartment model can improve the representation of some of the fundamental physiological processes underlying drug disposition. It supports the hypothesis that, in some cases, there is merit in considering the drug concentration at any time to be the sum of first-pass and recirculated components. For example, after bolus administration the influence of cardiac output, lung kinetics, and injection time on the total drug concentration can be explained by the influence of these factors on the underlying first-pass concentrations. It is also evident that the simplest recirculatory model introduces the basic concepts important in recirculatory pharmacokinetics.

By incorporating recirculation into the two-compartment model, three biological principles are acknowledged. The qualitative behaviour of these principles are well understood by anaesthetists—their incorporation into a model defines their quantitative behaviour. The principles are: first, that the blood recirculates at a rate given by the cardiac output. An i.v. drug is therefore added to a compartment through which blood is flowing at a defined rate (the cardiac output) rather than directly into a ‘pool’ of blood (the central compartment). The study of the addition of a drug or indicator to a flow is well developed, and when applied to the measurement of blood flow is broadly called indicator dilution principles.$^{17}$ Second, the lung is in the unique position of receiving all of the cardiac output, and all i.v. (and p.o., i.m., or s.c.) administered drugs must therefore pass through the lungs before entering the systemic circulation. The kinetics of drugs in the lung can therefore play a large part in modifying the initial concentrations of a drug. Thirdly, once the lungs are specified, the heterogeneity of blood entering and leaving the lungs and the remainder of the body must be acknowledged.
First-pass concentrations are governed by indicator dilution principles

Indicator (or tracer) dilution principles are familiar to many anaesthetists. The simplest principle describes the constant rate of addition of an indicator to a flow in a non-recirculating system—this is the basis for some continuous cardiac output monitors. Knowing the rate of addition, the flow can be deduced from the concentration downstream of the infusion. In the two-compartment recirculatory model, the first-pass arterial concentrations at steady state are governed by this principle in reverse, in that the concentrations are affected by the flow (equation (5)). For example, for the hypothetical drug discussed previously, if the dose rate is 20 mg min⁻¹ and the cardiac output is 5 litre min⁻¹, in 1 min 20 mg has been added to 5 litres of blood, giving a steady-state first-pass arterial concentration of 4 mg litre⁻¹.

If the cardiac output is increased to 10 litre min⁻¹, in 1 min 20 mg must be added to 10 litres of blood, giving a concentration of 2 mg litre⁻¹. This behaviour means that the first-pass arterial concentrations respond acutely to changes in cardiac output. This is evident in Figure 6, which shows a parameter set for which the total arterial concentrations during an infusion varied in response to an oscillating cardiac output. The recirculatory model predicts that arterial concentrations have the potential to be affected by transient changes in cardiac output much more during an infusion than after it.

The analogy with indicator dilution principles can be extended to bolus administration. Bolus administration of an indicator is used in the classical dye or thermodilution methods to measure cardiac output. The resultant indicator dilution curve can be used to estimate cardiac output from dose over AUC, where AUC is the area under the indicator curve with the effects of recirculation removed. The equations describing the first-pass arterial concentrations (equations (13) and (14)) have a direct analogy to this principle, except that they are again applied ‘in reverse’. They produce a curve for which the AUC is a function of dose over cardiac output \(D/Q_{CO}\). It is interesting to note that by fitting the recirculatory model to the thiopental data, it was possible to estimate a plausible value for cardiac output (Table 3, 4.5 litre min⁻¹) solely from drug concentration data. This was possible as early blood samples were taken (necessary to define lung kinetics), and there was no loss of thiopental on passage through the lungs (confirmed experimentally).

Similar reasoning can be used for the effect of injection time on the first-pass arterial concentrations. Injecting the same dose over half the time will double the amount of drug added to each volume of blood per unit time, thereby doubling the steady state first-pass arterial concentrations. In practice, the steady-state concentration is rarely reached for short infusions (Fig. 5), but the underlying effect remains when lung distribution volume is relatively small.

Lung kinetics

The need to incorporate the lungs into a model is a natural consequence of incorporating recirculation. Their unique location in the circulation means they are the only organ that can influence the first-pass arterial concentrations after i.v. administration.
The study of the kinetics of drugs in the lungs is complicated by the diversity of terminology and experimental methods used.\textsuperscript{16} It is known from dual indicator studies that the arterial concentration `peak' emerging from the lungs after `impulse' i.v. injection has a complex shape governed partly by the distribution of intravascular transit times across the lungs.\textsuperscript{22} It is known from isolated perfused lung studies that drugs can sequester into the lungs, and that some drugs exhibit multi-exponential washout curves.\textsuperscript{23} However, in some cases simpler models of the lungs are sufficient to capture the essential properties of lung kinetics in vivo on clinically relevant time-scales.\textsuperscript{21,24,25} Thus, representing the lungs as a small single compartment in the present model was adequate for the case for thiopental (Fig. 7 and Table 3). However, it does not follow that because a pharmacokinetic data set shows a bi-exponential increase or decline in blood concentration that the most rapid half-life is a function of lung kinetics. Blood samples must be taken sufficiently early and at frequent intervals to define the initial uptake or elution by the lungs before recirculation has an appreciable effect. Clearly, more confidence can be placed in the appropriateness of a recirculatory model if experimental data on lung kinetics are available.

**Heterogeneity of blood concentrations**

The concept of blood concentrations being heterogeneous is absent in mamillary models. While the two-compartment recirculatory model resolves into two important blood concentrations (arterial and mixed venous), in practice the blood concentration at any point in the vasculature is a complex mix of the relative contribution of blood from different eliminating and non-eliminating tissues and the site of drug administration. Failure to account for this heterogeneity may explain some of the disparity in kinetic data for drugs in the past, where the precise origin of the blood used for pharmacokinetic analysis is not documented. Importantly, recirculatory models provide the opportunity to curve-fit mixed venous blood concentrations for kinetic analysis without error.

**Limitations**

The two-compartment recirculatory model is clearly an oversimplification of the in vivo situation, particularly with the representation of the remainder of the body as a single compartment. Indeed, the use of compartments in itself is a limitation.\textsuperscript{9,26} This would be most apparent for very short injection times (e.g. 1 s) that are significantly less than the transit time of blood through the lungs. In this case, a more sophisticated representation of the lungs is required that accounts for the distribution of intravascular transit times.\textsuperscript{22}

It is possible to add additional `body' compartments to a recirculatory model if necessary, but this requires assumptions (or measurements) about the distribution of cardiac output in the body. However, the use of a single compartment is adequate for illustrating the principles underlying recirculatory models. A dynamic component can be readily incorporated into a recirculatory model by adding a target organ (e.g. the brain) for which there is a defined target organ concentration–effect relationship. This has been done for thiopental and propofol,\textsuperscript{21} and provides the recirculatory model with a more physiological analogue to the commonly

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Fig 5 The effect of the injection time ($t_i$) of a fixed bolus dose ($D=100$ mg) of the hypothetical drug on the time-course of its first-pass and total concentrations in arterial and mixed venous blood. The injection time was 10, 30, or 120 s as indicated. The other parameter values were $Q_{CO}=5$ litre min$^{-1}$, $V_L=2.5$ litre, $V_B=15$ litre, and $Q_{CI}=2$ litre min$^{-1}$ and are representative of a high-clearance i.v. induction agent. The steady-state values of the first-pass arterial concentrations, $C_{a,f}(ss)$, are also stated (equation (5)). The ratio of $t_i/r$ indicates how close the first-pass arterial concentrations at the end of the injection are to their steady-state value. A value of 3 indicates approximately 95% equilibration.
used effect compartment model for the analysis of kinetic/dynamic data.

An important organ that is not adequately represented by the two-compartment recirculatory model is the kidneys. Their high relative perfusion and large percentage of the cardiac output means that drugs with small renal distribution volumes will rapidly pass through the kidneys and recirculate more rapidly than the theory dictated by the two-compartment representation.

Finally, note that clearance was treated as independent of cardiac output in this model, but this may not be the case for drugs that are highly extracted across the liver and therefore have flow-limited clearance. As liver blood flow is often a fixed fraction of cardiac output, the clearance of this group of drugs will also be cardiac output dependent. This may exacerbate any cardiac output dependency in kinetics over that predicted by the present model.

### Table 3

Models fitted to thiopental data. The best fit values of the parameters of a two-compartment recirculatory model (Fig. 2A) and a two-compartment mamillary model (Fig. 1) fitted (Fig. 7) to previously published data on the mean arterial blood concentrations of thiopental during and after a 2 min infusion of 500 mg in five sheep. The $R^2$ value of the fit is also given.

<table>
<thead>
<tr>
<th></th>
<th>Recirculatory</th>
<th>Mamillary</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R^2$</td>
<td>0.9897</td>
<td>0.9895</td>
</tr>
<tr>
<td>$V_L$ (litre)</td>
<td>3.07 (0.365)</td>
<td>3.15 (0.362)</td>
</tr>
<tr>
<td>$V_B$ (litre)</td>
<td>12.3 (2.35)</td>
<td>1.04 (0.255)</td>
</tr>
<tr>
<td>$V_{CO}$ (litre min$^{-1}$)</td>
<td>4.54 (0.529)</td>
<td>3.52 (0.100)</td>
</tr>
<tr>
<td>$Q_{Cl}$ (litre min$^{-1}$)</td>
<td>1.15 (0.168)</td>
<td>1.16 (0.174)</td>
</tr>
</tbody>
</table>

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Clinical implications

Despite its simplicity, the two-compartment recirculatory model provides a plausible explanation for a number of clinical phenomena. For example, it shows (Fig. 5) why slowing the rate of bolus injection of a fixed dose of a drug can dramatically alter outcome. Depending on lung volume, significantly lower peak arterial concentrations are achieved when a bolus is injected over 120 s rather than 10 s. Furthermore, the central role of cardiac output in the model (Fig. 4) may provide an explanation as to why the bolus dose of drugs required for low cardiac output (e.g. shock) patients is smaller than that for high cardiac output patients (e.g. sepsis, anxiety). Accounting for this cardiac output effect may improve the predictive power of clinical pharmacokinetic models across patient groups.

The two-compartment recirculatory model is the simplest model that incorporates basic recirculatory concepts. These concepts may be more consistent with the clinical experience of many anaesthetists than those provided by its traditional mamillary counterpart. It is hoped that a wider knowledge of these concepts will facilitate research on the level of complexity of recirculatory models necessary to describe and predict clinical pharmacokinetic data.

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