A model of the first pass passage of drugs from i.v. injection site to the heart—parameter estimates for lignocaine in the sheep

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Summary
A general model, based on indicator dilution principles, of the initial distribution and effects of drugs in a target organ after i.v. bolus administration is presented. The model was validated from previous studies of myocardial pharmacokinetics and pharmacodynamics of lignocaine in sheep. It is proposed that i.v. drug injection produces a concentration “peak” of drug in venous blood, which is attenuated by vascular mixing, and lung and heart kinetics, as the drug is transported from the injection site to the heart where it exerts its effects. The model predicted that the first passage of this peak through the heart was the principal component of myocardial concentrations of lignocaine for 10 min after injection before recirculation became important. Injection rate, cardiac output and myocardial blood flow were important determinants of the magnitude of the first pass peak. The model provides a physiological framework for analysing the initial distribution of drugs. (Br. J. Anaesth. 1996; 77: 764–772)

Key words

Drugs that have direct effects on the heart (such as i.v. anaesthetics, anti-arrhythmics, analgesics and sedatives) are often administered as an i.v. bolus in anaesthesia and critical care medicine. After this type of administration, the time courses of both therapeutic and adverse effects change rapidly in the first 10 min after injection. As a generalization, clinical practice has empirically evolved dose regimens that minimize adverse effects by matching the dose and rate of injection of a drug to the pathophysiological state of the patient, but the physiological basis of the dose regimens is often poorly understood. While studies of the pharmacokinetics of these drugs in systemic blood provide some insight, evidence is accumulating that the time course of many of the direct myocardial effects in the period immediately after bolus administration are related closely to the time course of their concentration in the heart.

It has been increasingly recognized that the conventional one-, two- or three-compartment interpretation of bolus kinetics (for example, see Gibaldi and Perrier and Wood) is not well suited to the description of the initial kinetics of drugs administered as i.v. boluses. Limitations include poor description of vascular mixing, poor description of lung kinetics and in the case of cardioactive drugs, poor description of the time course of myocardial drug concentrations, and their determinants, in the period immediately after a drug bolus.

The origin of many of these limitations may be traced to the assumption that drug is added instantly to an initial distribution volume with little or no anatomical basis. Although the concept of an initial distribution volume is widespread in the literature, in reality, a bolus dose of a drug is added to a stream of flowing blood, which mixes with other blood in the venous “tree”, passes through the lungs and enters the organs of the body, including the heart, where it exerts its effects. The aim of this article is to develop a physiologically realistic model of this process based on indicator dilution principles, and to examine the predicted determinants of initial myocardial drug concentrations and effects after bolus administration. The validity of each component of the model is examined by comparison with a detailed set of physiological data from previously published experiments on myocardial pharmacokinetics and pharmacodynamics of lignocaine using a chronically instrumented sheep preparation.

AN “INDICATOR DILUTION” INTERPRETATION OF BOLUS KINETICS
The conventional compartmental approach to bolus kinetics recognizes that there is an initial period of “intravascular mixing” of drug with blood after bolus injection, but this process is generally ignored. However, the mechanisms of this process are well understood and can be described by indicator dilution principles developed for the measurement of blood flow. For example, a classical method for measuring cardiac output is based on injection of indocyanine green (ICG) into the stream of venous blood flowing to the heart. A hypothetical “dye curve” in the blood downstream from the injection site (e.g. the aorta) is shown in figure 1. Note that the
ICG concentration is initially zero, that there is a short lag between injection and first detection of ICG in blood, that there is a peak concentration \( C_{\text{peak}} \), and that there is often a second peak because of recirculation of ICG. For flow measurements, various techniques are used to subtract the contribution of recirculation, leaving the first pass peak shown in figure 1, and cardiac output is determined from dose and the AUC of this peak. By rearranging the formula for cardiac output,\(^\text{12}\) it is apparent that \( C_{\text{peak}} \) is some function \( f \) of dose and cardiac output \( Q_T \).

\[
C_{\text{peak}} = f \left( \frac{\text{dose}}{Q_T} \right)
\]

In this article this indicator dilution analysis is expanded to examine the determinants of the shape of this peak for the first pass passage of a drug from the venous injection site to the heart. A central hypothesis is that although these indicator dilution principles are only applicable over a period of less than 30 s for an intravascular indicator such as ICG, they are applicable over a larger time scale for drugs that can leave the vascular space.

**Methods**

**DEVELOPMENT OF THE MODEL AND PARAMETER ESTIMATION**

On anatomical and theoretical grounds, the injected drug peak would be expected to pass through several sites in its passage to the target organ. These sites, together with the factors which could modify the shape of the peak at each site, are summarized in figure 2 and are examined in turn (with the sites referred to by a letter for direct comparison with fig. 2).

In common with all physiological models, this model is highly dependent on estimation of the large number of parameters comprising the model. For the purpose of illustration, these parameters were estimated for the local anaesthetic and anti-arrhythmic lignocaine, with the heart as the target organ, from previously reported studies of lignocaine using a conscious chronically instrumented sheep preparation.\(^\text{2,4,13-15}\) Lignocaine causes significant reductions in myocardial contractility by a direct action on the myocardium,\(^\text{16}\) probably by a direct action on Na–Ca exchange.\(^\text{17}\)

**A. Venous injection site**

**General form.** It was assumed that for an i.v. bolus, the dose is injected at a constant rate over a period \( T \). The dose rate (given the variable name Doserate) is therefore as follows, where dose = total mass of drug given and \( t = \) time after the start of the dose:

\[
\text{Doserate} = \frac{\text{dose}}{T} \quad \text{for } 0 \leq t \leq T
\]

It was assumed that drug injection gives a square wave drug concentration peak in blood \( (C_{\text{inj}}) \) immediately downstream of the injection site, whose shape depends on local blood flow \( (Q_{\text{inj site}}) \) and the dose rate:

\[
C_{\text{inj}} = \left( \frac{\text{Doserate}}{Q_{\text{inj site}}} \right) \quad \text{for } 0 \leq t \leq T
\]

This is a direct application of indicator dilution principles—the higher the flow, the lower \( C_{\text{inj}} \), and vice versa.\(^\text{12}\)

**Parameter estimates for lignocaine.** A dose of 100 mg over 1 s was assumed for comparison with previously published work,\(^\text{2,4} \) and the injection was assumed to be made into the caudal end of the inferior vena cava, with a flow of 1 litre min\(^{-1} \) (Upton RN, unpublished observations).

**B. Vascular mixing and dilution with cardiac output**

**General form.** After injection, this hypothetical square wave was assumed to travel from the injection
site to the pulmonary artery, with two factors influencing its shape in transit. The first is progressive dilution with other venous blood until, by the pulmonary artery, the peak has been diluted with the entire cardiac output ($Q_t$). Assuming it is still in the form of a square wave and ignoring the time taken to travel from the injection site to the pulmonary artery, this concentration ($C_{\text{unmixed}}$) is given by the following equation, analogous to equation (3):

$$C_{\text{unmixed}} = \frac{(\text{Dose rate} / QT)}{\text{for } 0 \leq t < T}$$

However, in reality, as shown in figure 1, the shape of this peak is not a square wave, but has been modified by factors such as dispersion during transit along the vessel\textsuperscript{18} and the dynamics of the mixing process. It was assumed that these two processes occur sequentially, and that the shape of the peak after dispersion was equivalent to the passage of the square wave peak created by the first process (eqn (4)) through a small well mixed compartment through which the entire cardiac output flowed. The final concentration in the pulmonary artery ($C_{\text{pa}}$) was therefore given by the following equation, where $V_{\text{mix}}$ is the volume of this hypothetical mixing compartment:

$$\frac{dC_{\text{pa}}}{dt} = \left( \frac{Q_t}{V_{\text{lung}}} \right) \times \left( C_{\text{unmixed}} - C_{\text{pa}} \right)$$

Parameter estimates for lignocaine. A baseline value for cardiac output ($Q_t$) of 5.6 litre min\textsuperscript{-1} was assumed for comparison with previously published work.\textsuperscript{2} The volume of the mixing compartment was estimated from studies of the time course of ICG concentrations in the pulmonary artery for various combinations of injection duration and cardiac output\textsuperscript{19} using hybrid physiological modelling (appendix).

C. Passage through the lungs

General form. The kinetics of the passage of the peak through the lungs was represented as a single flow-limited compartment through which cardiac output flowed. An extraction term ($E_{\text{lung}}$) was included to account for any metabolism or prolonged retention of drug in the lung. The resultant drug concentrations in arterial blood emerging from the lungs ($Ca$) were therefore given by the following equations, where $V_{\text{lung}}$ = apparent volume of the lung and $Ca'$ = a temporary variable:

$$\frac{dC_{\text{a}}}{dt} = \left( \frac{Q_t}{V_{\text{lung}}} \right) \times (C_{\text{pa}} - Ca')$$

$$Ca = Ca' \left( 1 - E_{\text{lung}} \right)$$

Parameter estimates for lignocaine. $V_{\text{lung}}$ and $E_{\text{lung}}$ were determined by hybrid physiological modelling (appendix) from studies using chronically instrumented sheep in which arterial blood was sampled rapidly together with measures of cardiac output.\textsuperscript{14} Arterial drug concentrations in the first minute after injection were assumed to be a result of the first pass passage of the drug, and pulmonary artery concentrations were determined by application of the vascular mixing algorithm (eqns (2–5)).

D. Distribution to organs

Emerging from the lungs in arterial blood, the peak is distributed to all organs of the body (except the lung and those supplied by portal systems) in line with the fraction of cardiac output they receive. As outlined previously, this model addresses only the relevant target organ, as the fate of the drug in other organs does not influence the first pass peak in this organ.

F. Target organ kinetics

General form. The kinetics of the passage of the peak through the target organ was represented as a two-compartment model with membrane limited transfer from the first (nominally capillary) to the second (nominally parenchymal) compartment, where the transfer between the compartments was described by a permeability term (PS) in keeping with standard capillary permeability nomenclature.\textsuperscript{20} If $Q_{\text{org}}$ is the blood flow of the target organ, and $V_{\text{cap}}$ and $V_{\text{par}}$ are the apparent volumes of the nominal capillary and parenchymal compartments ($C_{\text{cap}}$ and $C_{\text{par}}$, respectively), the equations describing this system were as follows:

$$\frac{dC_{\text{cap}}}{dt} = Q_{\text{org}} (Ca - C_{\text{cap}}) + PS (C_{\text{par}} - C_{\text{cap}})$$

$$\frac{dC_{\text{par}}}{dt} = PS (C_{\text{cap}} - C_{\text{par}})$$

(8 and 9)

The advantage of this model is that a single-compartment, flow-limited model is a subset of its solution if PS is greatly exceeds $Q_{\text{org}}$.

Parameter estimates for lignocaine. These were determined by hybrid physiological modelling (appendix) of studies with chronically instrumented sheep in which arterial (afferent for the heart) and coronary sinus (effluent) blood were sampled rapidly, in conjunction with measures of myocardial blood flow using an ultrasonic Doppler flow probe on the left mainstem coronary artery.\textsuperscript{2} Initial trials showed a single flow-limited compartment model was preferred statistically, but was modified by the addition of a small first-order loss from the compartment (rate constant = $k_{\text{org}}$), which further improved the fit. Equation 8 was therefore modified as follows:

$$\frac{dV_{\text{m}}}{dt} = \frac{Q_{\text{m}}}{C_{\text{m}}} (C_{\text{a}} - C_{\text{m}}) - k_{\text{rad}} \times C_{\text{m}}$$

(10)

where $V_{\text{m}}$ and $C_{\text{m}}$ = apparent volume of, and concentration in, the heart, respectively. Note that the heart concentrations of this equation are equivalent to those in the coronary sinus, that is there is venous equilibrium).

G. Target organ dynamics

General form. The relationship between the target organ drug concentration and a drug effect in that organ ($E_{\text{org}}$) was represented by a sigmoidal $E_{\text{max}}$ relationship,\textsuperscript{21} where $E_{\text{max}}$ = maximum drug effect and $E_{\text{EC}_{50}}$ = drug concentration at which 50% of $E_{\text{max}}$ was achieved, $n$ = “Hill factor” controlling the steepness of the sigmoidal curve and “baseline” is the predrug magnitude of the effect:

$$E_{\text{org}} = \left( \frac{(E_{\text{max}} \times C_{\text{org}}^{n})}{(C_{\text{EC}_{50}}^{n} + C_{\text{org}}^{n})} \right) + \text{baseline}$$

(11)

This equation can describe several concentration effect relationships, as it includes linear and $E_{\text{max}}$ models as approximate subsets of its solutions, and the organ concentration can be for either the capillary or parenchymal compartments.
Parameter estimates for lignocaine. These were determined using hybrid physiological modelling (appendix) of studies in which myocardial contractility and coronary sinus blood concentrations of lignocaine were determined after bolus injection of lignocaine in sheep.\textsuperscript{1,14} Contractility was determined from the maximum rate of rise of left ventricular pressure (LV (dP/dt)\text{max}), which was measured using a left ventricular micromanometer catheter, and was expressed as the percentage reduction from baseline values. Initial trials showed that the sigmoid E\text{max} model had redundant parameters for this data set, and it was replaced with a linear effect model modified for a drug which caused reductions in the effect from a baseline value:

\[
\text{Em} = \text{baseline}_{\text{eff}} - \text{slope}_{\text{eff}} \times Q_{\text{m}}
\]

where Em = percentage reduction in myocardial contractility.

\textbf{Equation solving}

The model, as implied by equations (2–7), (10) and (12) was implemented as a set of differential equations in the “Scientist” modelling package (Scientist for Windows, Version 2, Micromath, Salt Lake City, UT, USA), although any differential equation solver would be suitable. In general terms, the model could be used to predict the shape of the peak at each of the sites shown in figure 2, and the resultant time course of a drug effect. Equation (3) is optional, and can be included if venous injection site concentrations are of interest.

Predictions of the model. The model was used to predict the peak first pass concentrations of lignocaine, and the times of these peaks, in venous, pulmonary artery and arterial blood and the heart after an injection of 100 mg over 30 s.

To examine to what extent the first pass peak contributed to initial distribution in vivo, the predictions of the model were compared with the experimental data reported previously for lignocaine pharmacokinetics and pharmacodynamics in the heart.\textsuperscript{1,14} The former accounted only for the first pass passage of the drug peak, while the latter in vivo measurements by definition included the first pass peak and the contribution of recirculation.

The sensitivity of the model to changes in various parameters was also analysed. Of the parameters shown in figure 2, it was thought that injection rate, cardiac output and target organ blood flow were the parameters that were most likely to vary in a “clinical” setting. The effect of changing these was summarized concisely by their effect on the coronary sinus concentrations alone as the simple linear nature of the pharmacodynamic model (eqn (12)) implies that the effect follows the same time course as the coronary sinus concentrations, and the kinetic model for the heart (eqn (10)) implies that the heart concentrations were proportional to the coronary sinus concentrations. To examine the effect of blood flow, cardiac output was increased or decreased by 50\% (from 5.6 to 8.4 and 2.8 litre min\textsuperscript{–1}, respectively). In a separate set of simulations, myocardial blood flow was increased or decreased by 50\% (from 0.122 to 0.183 and 0.061 litre min\textsuperscript{–1}, respectively). In a final set of simulations, cardiac output and myocardial blood flow were increased together by 50\% and then decreased together by 50\%. To examine the effect of injection rate, simulations were performed with the duration of injection set at values of 1, 10, 30, 60, 120 or 240 s.

\section*{Results}

\textbf{PARAMETER ESTIMATES FOR LIGNOCaine}

The values of the parameters of the model are summarized in table 1; all estimated parameters were determined with a high degree of confidence. Although the vascular mixing component of the model was entirely empirical, there was good agreement between the model and the published data,\textsuperscript{19} as shown in figure 3. The parameters for lung kinetics gave a good description of the observed arterial concentrations emerging from the lung (fig. 4), but the fit was improved by removing a small (0.08 min) lag from the measured concentrations consistent with previous observations of injection site to lung transit time.\textsuperscript{19} The membrane-limited model of the target organ collapsed to a single-compartment, flow-limited model on fitting. This latter model was able to describe coronary sinus concentrations within the confidence limits of the measured data; a better fit was obtained by adding a small first-order loss from the compartment (fig. 5). This may have a physiological basis, as loss of lignocaine from the surface of the heart into fluid (and presumably tissues) surrounding the heart has been documented.\textsuperscript{22} The linear pharmacodynamic model gave an adequate description of the relationship between the measured coronary sinus concentration and effect data (fig. 6).

\begin{table}
\centering
\caption{Parameters of the model for lignocaine in the heart}
\begin{tabular}{llll}
\hline
Parameter & Description & Value used (SD) & Source \\
\hline
\text{Dose} & Total dose & 100 mg & Assumed \\
\text{T} & Duration of injection & 1 s & Assumed \\
\text{Qinj} & Local blood flow at the injection site & 1 litre min\textsuperscript{–1} & Assumed \\
\text{Qf} & Cardiac output & 5.6 litre min\textsuperscript{–1} & Measured directly \\
\text{Vmix} & Volume of the hypothetical venous mixing compartment & 0.255 litre & Hybrid modelling \\
\text{Vlung} & Apparent volume of the lung & 1.06 (0.021) litre & Hybrid modelling \\
\text{Elung} & Apparent first pass extraction by the lung & 0.32 (0.03) & Hybrid modelling \\
\text{Qm} & Blood flow through heart & 0.122 (0.021) litre min\textsuperscript{–1} & Measured directly \\
\text{Vm} & Apparent volume of the heart & 0.450 (0.03) litre & Hybrid modelling \\
\text{kout} & First order loss rate constant from the heart & 0.062 (0.04) litre min\textsuperscript{–1} & Hybrid modelling \\
\text{Slope}_{\text{eff}} & Slope of linear pharmacodynamic model & 11.08 (0.56) & Hybrid modelling \\
\text{Baseline}_{\text{eff}} & Baseline of linear pharmacodynamic model & 3.16 (1.17) & Hybrid modelling \\
\hline
\end{tabular}
\end{table}
PREDICTIONS OF THE MODEL

The major prediction of this model was that bolus drug injection produces a large concentration peak in venous blood which is progressively attenuated by various kinetic processes in transit to the target organ (table 2). It was also shown that the predicted first pass peak contributed a large component to the experimentally determined coronary sinus lignocaine concentrations (and therefore myocardial effect) in the first 10 min after the dose (fig. 7). Of the parameters examined, changes in cardiac output alone produced the largest changes in peak coronary sinus concentrations (fig. 8), with the highest cardiac output associated with the lowest concentration. Conversely, changes in myocardial blood flow alone also produced large changes in peak coronary sinus concentrations (fig. 8), but with the highest flow associated with the highest concentration. When cardiac output and myocardial blood flow were increased or decreased simultaneously, the opposing factors were cancelled such that there was a less dramatic change in coronary sinus concentrations (fig. 8). However, the lower flow state was associated with a longer duration of action and a slight delay in the time of the maximum concentration. Altering injection rate from 1 to 240 s produced large changes in coronary sinus concentrations (fig. 9), but for injection rates in the range 1–30 s, the changes were only minor.

The units of the vertical axis are arbitrary.
It was shown that initial drug kinetics after an i.v. bolus injection were consistent with the concept of the formation of a concentration “peak” of drug in the flow of venous blood, which is attenuated by vascular mixing, and lung and target organ kinetics as the drug is transported from the injection site to the target organ. The first passage of the peak through the heart was the principal component of the myocardial concentrations of lignocaine for 10 min after injection. Injection rate, cardiac output and myocardial blood flow were important determinants of the first pass peak. While there are deficiencies in the model, it is clear that it provides a useful framework for studying initial distribution processes and their physiological determinants.

OTHER APPROACHES TO INITIAL DRUG DISTRIBUTION

The limitations in the interpretation of the initial distribution volume and half-life terms of conventional compartmental models have been raised by previous workers. Chiou showed the initial volume of distribution depended on the time that the first blood sample was obtained (i.e. the time allowed for “initial mixing”), and that there was considerable variation in the literature of the reported initial volume for the same drug. Indeed, the initial volume was related linearly to the time of the first blood sample. The role of the lung in first pass kinetics was also considered by this author. There have been three general approaches to addressing these limitations, which will be discussed in turn. First, some workers have developed revised compartment models. Niazi advanced the concept of volume of distribution as a variable that changes with time. However, the fundamental compartmental description of a drug added to a volume rather than a flow remains. By rapid sampling of arterial blood from 1 min after injection of thiopentone and an intravascular marker, Henthorn, Avram and Krejcie were able to show that thiopentone and the marker had a common central volume in humans.
Subsequent work in dogs with continuous sampling showed that this common volume was the first pass peak emerging from the lungs, and led to the construction of a physiological model of the process.\textsuperscript{9,25} The vascular mixing component of this model is essentially the same as that proposed in the current model. They differ in that their model incorporates a two-compartment model of the remainder of the body, and was validated against arterial concentrations rather than target organ drug concentrations and effects. The model of early alfentanil disposition proposed by Wada and Ward\textsuperscript{32} also shares similar features with the present model, and was validated by hybrid modeling of literature data.

Second, to avoid a compartmental description of the initial distribution process, stochastic recirculatory models of the process have been proposed.\textsuperscript{27–30} This approach greatly improves the ability of these methods to describe early blood drug concentrations compared with compartmental models and includes the role of cardiac output in initial distribution. Some disadvantages include lack of a physiological description for the “transport function”, validation against limited data sets, and neglecting the significant effect of cardiac output on the whole body transport function.

Third, there have been occasional theoretical and experimental reports of an indicator dilution approach to initial drug distribution in which the drug is considered to be added to a flow rather than as a volume. The most significant theoretical contribution is that of Crawford.\textsuperscript{31} It was proposed that rapid i.v. injection of a drug resulted in a “slug” of drug in blood which travelled for two or three circulations of the heart. The most significant theoretical contribution is that of Crawford.\textsuperscript{31} It was proposed that rapid i.v. injection of a drug resulted in a “slug” of drug in blood which travelled for two or three circulations of the blood before being dispersed. In his analysis, Crawford essentially analyzed the fate of the slug at each of the sites shown in figure 2, although many of his calculations were by necessity crude. Experimental studies reflecting indicator dilution principles include that of Crankshaw, Rosler and Ware,\textsuperscript{32} who studied the relationship between peak arterial concentrations of thiopentone and duration of bolus injection.

ASSUMPTIONS AND LIMITATIONS OF THE MODEL

The present model is essentially a refinement of the approach of Crawford,\textsuperscript{31} with the important addition of a detailed set of experimental data with which to validate the model. As the construction of any model requires making simple assumptions, these assumptions are examined. The most significant of these concerns the nature of the vascular mixing process (i.e. the relationship between drug injection and peak entering the lungs). Although the nature of this process has been described previously,\textsuperscript{33} this type of analysis is relatively complex.\textsuperscript{18} The approach used in the present model was essentially empirical and ignored intravascular transit time from the inferior vena cava to the pulmonary artery, which in the sheep was 4–9 s.\textsuperscript{19} Fortunately, despite this, the predicted results closely matched those observed for a variety of injection rates and cardiac outputs. Note that the volume of the vascular mixing compartment is independent of the physicochemical properties of a drug, and that the injection site blood flow \((Q_{inj})\) is not a determinant of the final concentration in the pulmonary artery.

The assumption of single-compartment, flow-limited kinetics in the lungs is also a simplification, as the lung probably behaves in a similar manner to a chromatographic column.\textsuperscript{34} Again, any lag introduced by the passage of the peak from injection site to the lung was ignored in the final model (although accounted for in the curve-fitting process). The contribution of intravascular transit time of blood through the lung is likely to be small. The concept of an apparent first pass “retention” by the lung, whether a result of metabolism or an apparent extraction caused by “deep” distribution, is well supported by the literature,\textsuperscript{19} particularly for basic drugs where the retention can be greater than 90%.

While more sophisticated models, such as dispersion models,\textsuperscript{35} may be a more physiological description of myocardial drug kinetics, it seems likely that the essentially flow-limited nature of myocardial uptake of lignocaine\textsuperscript{36} is retained in the present model.

The assumption that the target organ drug concentration is the sole determinant of the magnitude of target organ drug effects should also be made with caution, as this relationship does not hold if there is “tight” homeostatic control over the process affected by the drug (e.g. arterial pressure) or acute tolerance caused by receptor down regulation. For the lignocaine data, there is some suggestion of homeostatic control of myocardial contractility affecting the myocardial concentration–effect relationship as evidenced by the slight discrepancy between the model and data after 8 min in figure 6.

In general terms however, comparison of the model with these data (figs 3–6) suggests that addressing these assumptions would help “fine tune” the model, but that the assumptions are not sufficient to compromise the relevance of its quantitative and qualitative predictions.

IMPLICATIONS OF THE MODEL

While i.v. bolus administration of lignocaine is not common clinically, this drug was chosen because of the extensive published data set suitable for validating the model. However, it was felt that the general principles applicable to this drug and the heart would apply to any relatively lipophilic drug that acted in a well-perfused target organ.

CONTRIBUTION OF FIRST PASS DISTRIBUTION

Recirculation is often thought of as a rapid phenomenon, which is probably based on a knowledge of the behaviour of intravascular indicators. This study showed that recirculation of drugs takes considerably longer, and that the first passage through the heart can account for a large component of the myocardial concentrations and effects of lignocaine for the first 10 min after injection (the remainder is a result of recirculated drug entering the heart). This is consistent with the report of van Rossum and colleagues\textsuperscript{37} that the mean transit time of many drugs in

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the body is of the order of 10 min. Note that the heart, which has a high relative perfusion, is often thought of as an organ in which recirculation occurs rapidly. It seems likely that the dominance of the first pass peak in initial organ concentrations is not a function of a failure of drug to recirculate, but rather indicates that the recirculated concentrations are much less than the first pass concentrations in this period.

SENSITIVITY ANALYSIS
While it has been noted previously that some pharmacokinetic parameters are related to cardiac output,38 our work reinforces the fact that cardiac output is fundamental to the kinetics of bolus administration.27,29 Indeed, it is more appropriate to consider bolus injection of a drug as an “indicator dilution” experiment “in reverse” rather than the traditional addition of a drug to a hypothetical volume. The concepts of the latter approach are difficult to reconcile with the actual physiological events. The role of myocardial blood flow was also highlighted by the model. This information provides greater insight into the effects of pathophysiological changes in blood flow distribution on dose requirements.

The model also provides insight into the effect of injection rate on initial drug concentrations and effects. An interesting feature of figure 9 is that the damping action of the lung and vascular mixing result in little difference in the time course of initial heart concentrations for injection rates between 1 and 60 s. If applicable to other drugs, this may indicate why in clinical practice the rate of bolus drug injection preferred by different clinicians is variable within this range. The model can also be used to test the relative merits of injection rate profiles other than a “square wave”. We are currently pursuing this in our laboratory.

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Appendix
HYBRID PHYSIOLOGICAL MODELLING FOR PARAMETER ESTIMATION
This refers to the process whereby the parts of the system of interest are represented as a structural model, while the remainder is represented as empirical functions.20,30 The complete model is validated by independently validating each of its component submodels in turn. Each submodel is treated as a hybrid of the complete model for which only its inputs and outputs are of interest. For example, for modelling myocardial kinetics the submodel was based on a modified single flow-limited compartment. The input functions were arterial concentrations and myocardial blood flow. These were fitted to empirical equations (a sum of exponentials for the blood concentrations and a fifth-order polynomial for the blood flow data). The structure and origin of the input function is irrelevant provided it provides an excellent fit for the input data. The output (coronary sinus concentrations) of the structural submodel was then curve-fitted to optimize its parameters by a least squares method based on the maximization of the “model selection criteria (MSC)”, which is essentially the Akaike information criterion scaled to normalize for data sets (Y) of different magnitudes (Micromath Scientific Software, Salt Lake City, UT, USA):

\[
MSC=\ln\left(\frac{\sum\hat{w}_i(Y_{\text{obs}} - Y_{\text{pre}})^2}{\sum\hat{w}_i(Y_{\text{obs}} - Y_{\text{cal}})^2}\right) - \frac{2p}{n}
\]

where \(\hat{w}_i\) = a weighing term and \(p\) = number of parameters.

The input and output functions of each of the hybrid submodels discussed in the text are summarized in table 1a.

![Table 1a](image)

<table>
<thead>
<tr>
<th>Submodel</th>
<th>Input function(s)</th>
<th>Output function</th>
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<tbody>
<tr>
<td><strong>Vascular mixing</strong></td>
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<td>(eqns (2–5))</td>
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<td><strong>Lung kinetics</strong></td>
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<td>(eqns (2–7))</td>
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<td>Dose rate</td>
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<td>Myocardial kinetics</td>
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<td>(eqn (10))</td>
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<td>Myocardial dynamics</td>
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<td>Coronary sinus concentrations</td>
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<tr>
<td>(eqn (12))</td>
<td></td>
<td>Reductions in myocardial contractility</td>
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15. Huang YF, Upton RN, Rutten A, Mather LE. The myocar-


