GASEOUS HOMEOSTASIS AND THE CIRCLE SYSTEM

Description of a Model

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Models have been used widely in the study of the uptake, distribution and elimination of inhaled anaesthetic agents, the majority of those described being based on the description by Kety (1950, 1951) of the principles which govern the exchange of an inhaled inert gas at the lungs and tissues. In these models body tissues have usually been considered as consisting of a limited number of discrete compartments, each of which receives a fixed proportion of the cardiac output, and with anaesthetic agents assumed to have unique tissue-gas partition coefficients for each compartment. The well-known mathematical model of anaesthetic uptake (Eger, 1963) was used to predict events that could occur during the administration of an anaesthetic before in vivo substantiation of such events had been carried out (Eger, 1974). Models have been described for execution upon analogue (Mapleson, 1963; Severinghaus, 1963; Zwart, Smith and Beneken, 1972), digital (Mapleson, 1973; Cowles, Borgstedt and Gillies, 1973) and hybrid (Fukui and Smith, 1981a, b) computers. Such models have been used successfully as the basis of systems designed to automate the administration of an anaesthetic (Kye and Lowe, 1969; Tatnall, Morris and West, 1981; Chilcoat, Lunn and Mapleson, 1984). In a large number of the models that have been described, anaesthetic uptake has been calculated by assuming that either the inspired or the alveolar anaesthetic concentration of an agent remains constant, and that the uptake of that agent by each tissue compartment follows a simple exponential time course. Total uptake is then calculated as the sum of a number of exponential expressions.

Models of anaesthetic uptake such as those described above can be considered as being physiological in nature. They define a number of body compartments of known anatomical identity and relate uptake to known physiological facts. In this way they differ from the majority of models used for pharmacokinetic studies of non-inhaled drugs. These latter models are commonly empirical in nature, consisting of compartments which have no true anatomical identity. The validity of a physiological model will be influenced by the veracity with which it defines anatomical and physiological entities. Mapleson (1973) has pointed out the considerable differences between the manner in which various published models of anaesthetic uptake treat the magnitude and

SUMMARY

A model has been constructed of a subject breathing from a circle system. The subject model is based on the circulation-time model of anaesthetic uptake described by Mapleson. This is a multi-compartmental model of body tissues in which gas exchange in each compartment is calculated at each heart beat. The lung compartment of Mapleson’s model has been modified to allow for an unlimited number of gases to be present in the inspired gas mixture. The circle system model assumes total absorption of all expired carbon dioxide and full mixing of all gases within the system. The volume of gas in the system and its composition is calculated for each respiratory cycle. The subject model can be considered as being either attached to a non-rebreathing system, when inspired gas composition is under the control of the operator, or attached to the circle system, when the operator has control of fresh gas flow and composition. The model has been realized as a computer program written in Pascal.
distribution of blood volume, and has discussed the improbable results that could arise with some of the patterns of blood volume distribution that have been suggested. He has described a series of "circulation-time" models of anaesthetic uptake, in which a realistic pattern of blood volume distribution is used, and in which account is taken of both the overall circulation time and the variations in circulation time between different tissue compartments. Anaesthetic uptake by tissue compartments in these models is based upon the law of conservation of matter, rather than any assumed time course.

Mapleson (1960) described a series of equations to predict anaesthetic concentration within a circle system. In his analysis he assumed an acute steady state of gas exchange. These equations were used by Eger and Guardagni (1964) to predict the fresh gas halothane concentrations necessary to provide a constant alveolar halothane concentration when this gas was administered via a circle system. Holmes and Spears (1977) used a computer model to predict nitrous oxide and oxygen concentrations within a circle system supplied with these gases at flows of between 0.5 and 7 litre min\(^{-1}\). These authors assumed nitrous oxide uptake to proceed at a rate inversely proportional to the square root of elapsed time, regardless of the inspired nitrous oxide concentration. Lowe (1972, 1979) proposed a model of the closed circle system in which the uptake of all anaesthetic agents was related to the square root of elapsed time. In this model the alveolar concentrations of the anaesthetic were held constant, and the computations applied to the circle system model were limited to calculation of the amount of anaesthetic agent needed to replace that taken up by the subject. A more elaborate model of the closed system, but with similar limitations, was described by Goldberg and his colleagues (1978).

The present paper describes a model of a subject breathing from a circle system. The subject model is based upon Model P of the circulation-time models described by Mapleson (1973). In this model the tension and amount of each gas under consideration is calculated in the various tissue compartments at each heart beat. In the circle system model, gas composition and volume is calculated at each breath on the basis of the amount present at the start of the breath, the amount added in fresh gas, and the amount removed or added by uptake by the subject model. The present paper is confined to a description of the function of these two models. Validation of their function is the subject of the following paper (Conway, 1986).

### DESCRIPTION OF MODELS

#### Subject model

The subject model, apart from the lung compartment, is identical to the model P of gas exchange described by Mapleson (1973, 1978). This is a multi-compartmental model (lung, viscera, brain, lean tissue, fat, peripheral shunt) in which each compartment is associated with a blood pool of defined volume. Arterial and venous blood are assumed to exist in two well-mixed pools. At each heart beat a stroke volume of blood enters the arterial pool from the lung compartment, displacing an equal volume of mixed blood from the arterial pool to the tissues. At the same time a stroke volume of blood from the tissues enters the venous pool and displaces an equal volume of mixed venous blood into the lung compartment. Transit time in the circulation is, thus, dependent upon the volumes of the arterial and venous pools, heart rate and stroke volume. Variations in transit times between the tissue compartments are simulated by weighting the volumes of the blood pools associated with the compartments. It is assumed that in each compartment at the end of each heart beat a tension equilibrium exists for each agent under consideration between the tissue and its associated blood pool and blood (and in the case of the lung, gas) entering the pool during that heart beat. For each gas, knowledge of the amount present in the tissue at the start of each heart beat, the amount entering during the heart beat and the blood and tissue solubility of that gas allows calculation of the tension of that gas in the compartment and, thus, in blood draining the compartment at the end of the heart beat. The calculations used utilize the law of conservation of matter, and assume that all gases being considered obey Henry's Law.

The lung compartment of Mapleson's model has been modified so as to allow consideration of an unlimited number of gases being present, with calculation of the influence of gas uptake upon gas concentration for all components of the alveolar gas mixture. The compartment is assumed to consist of an alveolar space and a series deadspace. All gas within the alveolar space is assumed to be uniformly mixed. Deadspace gas, however, is assumed to undergo no longitudinal mixing, so
that gases at the mouth and alveolar ends of the deadspace may differ in composition. The alveolar space is assumed to adopt one of two prefixed values—an expiratory volume equal to functional residual capacity (FRC) minus deadspace volume, and an inspiratory volume equal to the expiratory alveolar volume plus the chosen tidal volume. Expressions have been derived to determine with each heart beat the alveolar tension of each gas present, and the amount of each gas taken up by solution in blood perfusing the lung, lung tissue and its associated blood pool. In order to maintain constancy of alveolar volume and pressure, the alveolar gas contents are incremented (or decremented) by an amount equal to the sum of this uptake by solution for all gases present. When overall gas uptake is positive in sign, the increment is taken from the alveolar end of the deadspace, and is replaced at the mouth end of the deadspace by an equal volume of gas from the breathing system. The composition of the bolus of gas added to the alveolar space will depend upon events within preceding cardiac cycles. During periods of overall gas elimination, when the summed uptake by solution will be negative in sign, it is assumed that a bolus of alveolar gas is displaced into the alveolar end of the deadspace, displacing an equal volume of gas from the mouth end of the deadspace into the breathing system. Therefore, during periods of overall gas uptake, expiratory ventilatory volume will be constant, equal to the prechosen tidal volume, and less than the inspiratory ventilatory volume, whilst during periods of overall gas elimination, inspiratory ventilatory volume will be equal to the chosen tidal volume and expiratory ventilatory volume will exceed this value. Both inspiration and expiration are assumed to occur instantaneously, inspiration always occurring at the start of a cardiac cycle and expiration occurring in the interval between two cardiac cycles. For convenience of use, heart rate in the model has been set at four times the respiratory rate. Inspiration is assumed to occur at the start of the first heart beat in each respiratory cycle, and expiration to occur between the second and third beats.

The expressions derived to determine alveolar concentration and uptake at the lungs of each component of the alveolar mixture are detailed in the Appendix. A tension equilibrium for all gases under consideration is assumed to exist in the lung compartment at the end of each heart beat. The law of conservation of matter is used to define, in each heart beat, a series of simultaneous equations from which can be derived the total gas uptake by solution (in blood perfusing the lung, lung tissue and the related blood pool). The same equations are then used to determine, for each gas being considered, the alveolar tension and the uptake by solution of that gas.

At the start of each study the subject model can be considered either to be free of nitrogen or to be in nitrogen equilibrium with the subject breathing atmospheric air. In the latter case alveolar, mixed venous and tissue nitrogen tensions and body nitrogen content are determined by the model before the start of the first breath. The subject model can be considered as being attached to the circle system model or attached to a non-rebreathing system. It can also be used with an assumed constant tension of one or more gases in the alveolar space. Under these last conditions the model calculates the fresh gas composition needed to maintain such constancy of alveolar gas composition.

Circle system model
All gas within the circle system is considered to be uniformly mixed, and all carbon dioxide entering the system is assumed to be totally absorbed. The operator determines the initial volume of the system and the composition of gas initially present in the system, and sets the minimum and maximum values of circle system volume. When the maximum volume is exceeded, gas is assumed to be vented from the system, and this vented gas is of the same composition as the mixture present within the circle system. When the volume in the circle system decreases to equal the minimum volume, it is assumed that the reservoir bag has collapsed, and the operator is given the opportunity either to inject an aliquot of oxygen to the circle system or to increase fresh gas flow to the system. Volatile agents can be added to the circle system by means of vaporizers (which are assumed to be fully efficient) placed within the fresh gas stream. It is also possible to inject volatile agents directly to the system. All injected liquid is assumed to vaporize instantaneously, and the vapour to mix uniformly with the contents of the circle system. In calculating gas composition within the circle system following injection of liquid anaesthetic, it is assumed that the vapours of all injected agents behave as ideal gases.

During each respiratory cycle the volume and composition of gas within the circle system is
calculated on the basis of the volume and composition of gas present at the start of that respiratory cycle, the volume and the composition of fresh gas added during the cycle, and the amount of each gas removed from (or added to) the system as a result of the uptake of gas by the subject model. Uptake of individual gases here relates to the difference in the amounts of that gas present in inspired and expired gas, and is equal to the previously defined uptake by solution for each component plus any gas added to, or removed from, the gas phase of the lung compartment. The total amount of gas added to or removed from the circle system as a result of uptake by the subject model is equal to the summed uptake by solution of all gases under consideration, with the exception of carbon dioxide. The equations used to determine the changes in volume of the circle system and the composition of gas within the system are detailed in the Appendix.

All calculations of gas exchange in the tissue compartments of the subject model are carried out at BTPS. Gas uptake has been calculated at BTPD. Fresh gas is assumed to be at ATPD at 20 °C and, for convenience, calculations of circle system volume and composition have been carried out at ATPD. Data for quantifying the subject model have been taken from Mapleson (1973) and Davis and Mapleson (1981). Partition coefficients for the various agents have been taken from Stewart and colleagues (1973), Wade and Stevens (1981) and Eger (1981). In the version of the subject model described here, \( \dot{V}_O_2 \) and \( \dot{V}_C_0_2 \) are considered as being constant. Alveolar carbon dioxide concentration \( (F_{A CO_2}) \) is determined by the ratio between \( \dot{V}_C_0_2 \) and expired alveolar ventilatory volume, whilst alveolar oxygen is considered as the "balance" gas. Constancy of \( \dot{V}_O_2 \) in the model relates to the amount of oxygen removed from the alveolar space in pulmonary blood, and does not necessitate a constant oxygen exchange as measured at the mouth of the subject model. Whilst the general principles which govern gas exchange in the lung compartment are the same for all gases, metabolic gases are carried in blood in a different way from non-metabolic gases and have a different fate in tissues. Because body oxygen stores are of small magnitude and reside mainly in the FRC, the manner in which oxygen is considered in the subject model has a negligible influence on the validity of the manner in which other gases are treated. Body carbon dioxide stores are large, reside mainly in the tissues, and have an
appreciable time constant of change. Any perturbation of $F_A_{CO_2}$ will influence these stores and have an effect on the respiratory exchange ratio. The constraints used in the model ensure that, unless body variables are changed by the operator, perturbations of $F_A_{CO_2}$ will occur only during periods of overall gas elimination, when expired alveolar ventilation is increased. The consequent decrease in $F_A_{CO_2}$ will be associated with a transient increase in respiratory exchange ratio. A version of the subject model is being developed in order to study gaseous homeostasis during the use of breathing systems other than the circle system. This version of the model incorporates a more physiologically correct method of treating metabolic gas exchange.

In the model, inspiration and expiration are considered to be instantaneous events. In practice, respiratory flow occurs throughout much of the respiratory cycle. Gas exchange, be it positive or negative in sign, will commonly influence both inspiratory and expiratory alveolar ventilatory volumes. It is possible to conceive of circumstances, such as a state of constant volume ventilation of the subject model, in which gas uptake would result in changes in alveolar volume or pressure rather than a change in ventilatory volume. Under these conditions there would be an augmentation of the "concentration" and "second gas" effects as compared with those calculated here.

The lung compartment of the subject model is assumed to have ideal ventilation–perfusion relationships. The model could easily be modified so that the lung compartment consisted of several subcompartments, each receiving different proportions of cardiac output and alveolar ventilation. The model also assumes constant values of cardiac output and alveolar ventilation (unless these variables are changed by the operator). Non-linear models of anaesthetic uptake have been described in which, for instance, cardiac output is regulated in inverse proportion to the anaesthetic concentration in the vessel-rich tissue compartments (Munson, Eger and Bowers, 1973). Fukui and Smith (1981a, b) have described a model for execution on a hybrid computer which incorporates complex mechanisms to control both ventilation and the circulation. It has not been thought necessary to include such elaborations in the version of the model described here.

The two major assumptions made about the circle system model are that all gas within the system is uniformly mixed and that vented gas has the same composition as this mixture formed in the circle system. As fresh and expired gases invariably enter the circle system at different points, it is obvious that total mixing of all gases throughout the system cannot occur. Eger and Ethans (1968) have shown important influences of the geometry of a circle system upon its performance—infuences which imply a lack of mixing of fresh and expired gases within the system. Similarly, Schoonbee and Conway (1981) have demonstrated that variations in the respiratory pattern influence gas mixing in a circle system. However, these considerations apply at high fresh gas flows. Sporadic observations in this laboratory have shown that, when circle systems are used with flows of less than 1 litre min$^{-1}$, gas composition at the mouth tends to remain constant during the inspiratory phase of the respiratory cycle, and that gas vented from the system also has a constant composition within each breath which is close to that of inspired gas. These observations, together with the fact that, in practice, gas is usually vented from a circle system at a position somewhat remote from the subject, have led to the adoption of the assumption regarding the composition of vented gas.

The assumption of a fixed maximum volume of the circle system presupposes that the valve through which gas escapes from the system opens at a preset pressure and, thereafter, imposes a resistance to gas flow such that pressure in the system does not change until the valve closes. In practice, as the pressure across such valves commonly varies with the flow through them, the circle system will have a variable maximum volume.

All calculations concerning the circle system have been carried out at ATPD. Gas initially present in the circle system and fresh gas supplied during use will be at ATPD. Because of the addition of moist warm expired gas to the system and the generation of both heat and water vapour during carbon dioxide absorption, the state of gas within the system will be between ATPD and BTPS. The exact conditions will be influenced by the magnitudes of fresh and ventilatory gas flows. Accuracy of the various calculations is not influenced by this assumption of a state of ATPD. It would be reflected in the overall true measured values of circle system volume as compared with the calculated values.

The subject model described here may be considered as being unnecessarily elaborate. Under non-rebreathing conditions the perfor-
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Performance of the model is only slightly influenced by assuming that heart rate is equal to respiratory frequency, and thereby reducing both the number of cycles of computation per minute and the complexity of computation. The magnitude and influence of the concentration and second gas effects are similarly little influenced by making the simplifying assumption that expiratory ventilatory volume remains constant and that inspiratory ventilatory volume is either incremented or decremented in relation to uptake by solution. There are conceptual difficulties in adopting this latter assumption when heart rate is not equal to respiratory frequency. Whilst simplification of the model affects its performance little under non-rebreathing conditions, the small differences in uptake that this simplification causes have a more marked effect when the circle system is being used at low fresh gas flows, as the "errors" are both summed and compounded. The computation of gas exchange in the lung compartment of the subject model takes into account concentration and second gas effects of all components of the alveolar gas mixture. The second gas effect, for instance, of halothane uptake upon the uptake of concomitantly administered nitrous oxide is very small and under non-rebreathing conditions is of no consequence. When the circle system is used such a second gas effect will be magnified as it will influence inspired as well as alveolar gas composition (Conway, 1984).

APPENDIX

The nomenclature used here for the subject and circle system models is based upon that adopted by Mapleson (1973) and Chilcoat, Lunn and Mapleson (1984). The equations used are as follows:

\[ \Sigma Wc = \Sigma \left( \frac{K_1 \cdot (Vc \cdot Fc + Vc \cdot FC - Wc)}{K_1 - \Sigma Wc} \right) \]  

\[ Wc = K_1 \cdot (\Sigma Wc) \]

\[ PA' = (\Sigma Wc) \cdot (Qc + Wc + K) \]

\[ PA' = (\Sigma Wc) \cdot (Qc + Wc + K) \]

\[ P = \frac{P(c + Wc - \Sigma Wc)}{VC} \]

\[ FC' = (Vc \cdot FC + Vc \cdot FC - Wc - Vc \cdot FC) \]

\[ P = \frac{P(c + Wc - \Sigma Wc)}{VC} \]

\[ PA' = (\Sigma Wc) \cdot (Qc + Wc + K) \]

\[ PA' = (\Sigma Wc) \cdot (Qc + Wc + K) \]

\[ Vc' = Vc + Vc - \Sigma Wc - VCO \]

\[ P = \frac{P(c + Wc - \Sigma Wc)}{VC} \]

\[ PA' = (\Sigma Wc) \cdot (Qc + Wc + K) \]

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\[ Vc' = Vc + Vc - \Sigma Wc - VCO \]

An, alveolar; \( \tau \), tidal; \( \Delta \), deadspace; \( F \), fresh; \( L \), lung tissue; \( I \), inspired; \( I \), mixed inspired; \( c \), circle system; \( s \), stroke volume.

The term \( VA \) represents the alveolar volume at the start of each cycle of computation. \( VT \) is the volume of gas added to the alveolar volume at the start of each cycle of computation. With four heart beats per respiratory cycle, \( VT \) is equal to the predetermined tidal volume for the first cycle of computation in each respiratory cycle, and zero in the remaining three cycles of computation. \( VA \) is equal to the predetermined functional residual capacity minus deadspace volume for the first, third and fourth cycles of computation, and exceeds this volume by the prechosen tidal volume during the second cycle of computation. The symbol \( Pw \) refers to partial pressure in the aliquot of deadspace gas added to the alveolar space to replace gas uptake by solution (where this is positive in sign). The prime suffix (') represents a new value of a variable calculated in one cycle of computation, whilst the double prime (""") represents the value of a variable at the end of the previous breath.

In the alveolar space at each heart beat \( \Sigma Wc \) is initially assumed to be positive in sign and is calculated from (1). If equation (1) has a negative solution \( \Sigma Wc \) is recalculated from (1a). If only one gas is being considered, and thus \( \Sigma Wc = Wc \), equation (1a) can be solved as a quadratic. With \( n \) gases present, the model uses an iterative technique to derive the value of \( \Sigma Wc \) which satisfies the \( n \) versions of (1a). Given \( \Sigma Wc \), \( PA' \) is then calculated from either (2) or (2a), and individual value of \( Wc \) from (3). The sequence of calculations in the blood and tissue compartments is identical to that used by Mapleson (1973).

In the circle system model at the end of each breath \( Vc' \) and \( FC' \) are calculated from (4) and (5). The values of \( \Sigma Wc \) and \( PA' \) used in these equations relate to uptake by solution occurring during that breath, derived by summing the calculated values for the relevant number of heart beats. If, following the derivation of individual values of \( FC' \), \( Vc' \) exceeds the predetermined maximum volume of the system \( (V_{max}) \), then a volume of gas \( (Vc' - V_{max}) \) is considered to be vented from the circle system so as to reduce the volume to equal \( V_{max} \).

Not described above are the series of equations used at each heart beat to calculate deadspace gas composition, nor the various correction factors needed to convert between STPD, ATPD, BTPD, BTPS.
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