A Nonlinear Model for the Uptake and Distribution of Halothane in Man

Michael N. Ashman, M.D.,* William B. Blesser, M.E.E.,† Robert M. Epstein, M.D.‡

An analog computer simulation of the uptake and distribution of halothane in man which incorporates the effect of halothane on cardiac output is presented. The computed partial pressures in each tissue compartment in response to a constant inspired partial pressure of 1.0 per cent atm are given. A theoretical derivation of the inspired partial pressure necessary to achieve simultaneously a constant anesthetic depth is also included. Based on this information, a program for the induction of halothane anesthesia in man utilizing a nonrebreathing anesthesia circuit is developed. With a maximum inspired partial pressure of 4.0 per cent atm, this program achieves a partial pressure of 0.75 per cent atm in the well perfused tissues in six minutes without overshoot, and will maintain this partial pressure indefinitely. Comparing the nonlinear model with a linear model having fixed cardiac output, the authors have shown that the difference between these two models is significant for the first five minutes; however, the effect of the nonlinearity is to elevate the partial pressures in the well-perfused tissues and the lung by 6 per cent after one hour of anesthesia with an inspired partial pressure of 1.0 per cent atm. (Key words: Nonlinear model; Halothane; Analog; Computer; Cardiac output.)

In recent years there has been a steady increase in the information available regarding uptake and distribution of anesthetic agents in man. A number of mathematical models and electrical analogs based on linear system equations have been proposed.§–⁷ Linearity implies that the system under study (in this case, the physiologic processes of respiration and circulation responsible for gas uptake and distribution) remains unaltered in the presence of the anesthetic drug. The solutions to these linear equations correspond remarkably well with the observed uptake of inert gases. However, anesthetic gases are not pharmacologically inactive. Effects of these gases on the control of respiration and circulation or on blood and tissue solubilities will affect the rates at which gas is transported into the various organs. The uptake process thus becomes dependent on that uptake which has already occurred, and the system becomes nonlinear.

Nonlinearities traditionally have been ignored in descriptions of anesthetic uptake and distribution, for at least three reasons. They introduce mathematical complexity which can be formidable. The nature of many nonlinearities is well recognized, but dose-related quantitation needed for mathematical modeling is not available. Finally, the simpler models may provide adequate verisimilitude for clinical understanding.

§ An equation is linear if the variables are related to each other by constants of proportionality. A nonlinear equation would include mathematical expressions such as products of variables, variables with exponents other than one, trigonometric functions, etc. The nonlinearity which occurs in the uptake problem we have considered is the first of these.
All the same, there is reason for pursuing a nonlinear analysis. Evidence of the relative importance of nonlinearities can be obtained only by working out the models which incorporate them. Some anesthetic effects may be large, as under adverse conditions of hemorrhagic shock or poor cardiac reserve, and thus may alter anesthetic uptake rates significantly. A nonlinear model would allow these situations to be studied in greater detail.

Landois\(^4\) seems to have been the first to attempt a description of some nonlinear effects, in a simplified model of the physiologic system with venous return eliminated. He explored the effects on anesthetic equilibration of hypothetical respiratory stimulation occurring with the onset of anesthesia. A large change in uptake was predicted under the assumption of large effects of anesthesia on respiratory drive uncompensated by secondary $P_{\text{CO}_2}$ effects or mechanical ventilation. Since no specific anesthetic agent was studied, the results were entirely arbitrary.

A similar treatment of a cardiovascular nonlinearity does not seem to have been attempted. Recently, quantitative data describing the effect of halothane on cardiac output have been made available.\(^6\) It has been shown\(^10\)–\(^14\) that changes in cardiac output can affect the uptake of virtually all anesthetic gases, including halothane. A first step in obtaining a more exact mathematical description of the uptake and distribution of halothane, therefore, could be to include this cardiovascular nonlinearity in the system equations. This paper presents such a model and describes its response to a constant inspired partial pressure. We then use the model to develop a program for the induction of halothane anesthesia in man.

**Methods**

With the exception of nonlinearity, this mathematical model is similar to those described by Severinghaus\(^5\) and Munson.\(^2\) The physiologic circuit diagram is seen in figure 1. Alveolar ventilation is assumed to be continuous via a nonbreathing anesthesia circuit. The tissues of the body are divided into five compartments according to circulatory and solubility criteria: highly perfused lean tissue such as the viscera and endocrine glands (VE), with the brain taken as a separate compartment because of its importance to anesthesiologists; poorly perfused lean tissue such as muscle and skin (MS); poorly perfused tissue with high lipid content, such as fat (F); and connective tissue with practically no perfusion, such as bone and cartilage (BC). The perfusion of each compartment is assumed to be evenly distributed without shunting or diffusion barriers. All concentrations are expressed as partial pressures of anesthetic agent in percentages of one atmosphere. Based on these assumptions, it is possible to derive a set of differential equations describing the rate of change of compartmental partial pressures as

---

*Fig. 1. Physiologic circuit diagram. The physiologic system is divided into two parts. On the left, ventilation is represented by the continuous flow of gas through the lung. On the right, the circulation is divided into five compartments: viscera and endocrine glands (VE); brain; muscle and skin (MS); fat; and bone and cartilage (BC).*
a function of inflow minus outflow of anesthetic agent. (This derivation is explained in the appendix.)

The numerical values used to solve these equations were similar to those given by Eger,\textsuperscript{15} Munson,\textsuperscript{2} and Severinghaus\textsuperscript{6} for a typical 70-kg man; these values are listed in table 1. Cardiac output prior to anesthesia was assumed to be 6 l/min. A six-liter blood volume was divided into one liter of arterial blood and five liters of venous blood. Each tissue compartment was assumed to be in equilibrium with a fraction of the venous blood proportional to the fraction of cardiac output perfusing the tissue.\textsuperscript{4,6} For example, since 63.6 per cent of the cardiac output is delivered to the vissera (see table 1), the volume of venous blood in equilibrium with this compartment would be

\[
V_{\text{VEN}} = (0.636)(5.0) = 3.18 \text{ liters}
\]

Although not strictly valid, this approximation is useful in the absence of sufficient data for a more exact model. The Ostwald solubility coefficients (\(\lambda\)) for the compartments were
computed from data given by Eger\textsuperscript{15} and Larson\textsuperscript{16}. Alveolar ventilation was assumed to be constant at 4.0 l/min.

Quantitative information about the effect of halothane on cardiac output published by Eger\textsuperscript{9} in tabular form is shown graphically in figure 2. This relationship of cardiac output to alveolar partial pressure may be approximated most simply by a straight line determined by the method of least squares. The equation is

\[ \dot{Q} = \dot{Q}_0 (1.0 - 0.25 P_A) \]  

(1)

where \( \dot{Q}_0 \) is the control cardiac output measured awake. Since Eger's measurements were made during steady-state conditions, alveolar partial pressure was probably equal to the partial pressure in the well-perfused tissues of the body, that is, the viscera, endocrine glands, and brain. Therefore, for inclusion in our nonlinear model, alveolar partial pressure (\( P_A \)) was replaced by the partial pressure in the viscera and endocrine glands (\( P_{VE} \)) to give

\[ \dot{Q} = \dot{Q}_0 (1.0 - 0.25 P_{VE}) \]  

(2)

This equation, which defines a relationship between one of the components of compartmental time constants (time constant = volume/flow) and halothane partial pressure, makes the system nonlinear.

The equations representing the uptake and distribution of halothane were programmed on five EAI TR-20 analog computers according to the circuit diagram seen in figure 3. The five patch boards are drawn separately but were connected as indicated by the variables in the labeled boxes. Thus, they become equivalent to one large analog computer. The potentiometers, represented by numbered circles in the diagram, are set according to the values listed in table 2.

This model can be made linear (that is, cardiac output maintained constant at 6.0 l/min) by disconnecting the input to potentiometer number 9. This procedure has the effect of removing the influence of halothane on cardiac output, thus converting Equation 2 to: \( \dot{Q} = \dot{Q}_0 \). By this means, we could rapidly compare the outputs of the linear and nonlinear models when driven by the same input (for example, a constant inspired partial pressure of 1.0 per cent atm).

Response of the Model to Constant Inspired Partial Pressure

The uptake and distribution of halothane are shown graphically in figure 4 as predicted by the nonlinear model (continuous lines) for a constant inspired partial pressure of 1.0 per cent atm. These curves represent the rise in partial pressure in each compartment as a function of time and are similar to those published by Eger,\textsuperscript{16} Munson,\textsuperscript{14,15} and Severinghaus\textsuperscript{5} for the linear model. The difference between the two models can be seen by comparing the dashed lines (representing the linear model) with the continuous lines (representing...
the nonlinear model). As a result of the non-linearity, cardiac output falls from an initial value of 6.0 l/min to about 5.1 l/min after an hour. Therefore, the uptake and distribution of halothane are the same in both models initially but deviate as cardiac output falls, so that the partial pressures in the alveoli and the viscera are about 6 per cent higher in the nonlinear model after the inhalation of a constant inspired partial pressure of 1.0 per cent atm for an hour. In contrast, at the end of an hour, partial pressures in the poorly perfused compartments (MS, BC, and F) were slightly higher in the linear model. With the scale used in figure 4, these curves would partially overlap; therefore, they were omitted.

A Program for the Induction of Halothane Anesthesia

Eger\textsuperscript{11, 17} has presented programs for the induction of anesthesia and maintenance of a constant alveolar concentration for halothane and other inhalation anesthetic agents. We have gone one step further and designed a program to achieve a constant partial pressure in the well perfused tissues of the body. A similar
Table 2. Potentiometer Settings for the Model

<table>
<thead>
<tr>
<th>Potentiometer Number</th>
<th>Potentiometer Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.540</td>
</tr>
<tr>
<td>2</td>
<td>0.150</td>
</tr>
<tr>
<td>3</td>
<td>0.181</td>
</tr>
<tr>
<td>4</td>
<td>0.114</td>
</tr>
<tr>
<td>5</td>
<td>0.636</td>
</tr>
<tr>
<td>6</td>
<td>0.650</td>
</tr>
<tr>
<td>7</td>
<td>0.374</td>
</tr>
<tr>
<td>8</td>
<td>0.600</td>
</tr>
<tr>
<td>9</td>
<td>0.150</td>
</tr>
<tr>
<td>10</td>
<td>0.419</td>
</tr>
<tr>
<td>11</td>
<td>0.156</td>
</tr>
<tr>
<td>12</td>
<td>0.119</td>
</tr>
<tr>
<td>13</td>
<td>0.208</td>
</tr>
<tr>
<td>14</td>
<td>0.020</td>
</tr>
<tr>
<td>15</td>
<td>0.167</td>
</tr>
</tbody>
</table>

Program for methoxyflurane (but only in a linear model) has been described by Mapleson.15

The design of our program is constrained by the limitations of the vaporizers available for the accurate quantitative administration of halothane in oxygen. Maximum inspired partial pressures, therefore, were limited to 4.0 per cent atm so that either Fluotec Mark II or Copper Kettle vaporizers might be employed to test the program. With this sole restriction, we developed a program describing the inspiratory waveform (partial pressure vs. time) necessary: a) to achieve a partial pressure of 0.75 per cent atm in the brain in the shortest possible time; b) to avoid toxicity (that is, excessive depth at any time); c) to maintain this level constant indefinitely. A partial pressure of 0.75 per cent atm was chosen as representative of the minimum anesthetic concentration (MAC) of halothane.16

Visceral partial pressure, not alveolar partial pressure, was chosen as an end-point, for alveolar partial pressure always exceeds the partial pressure in the tissues during the induction of inhalation anesthesia. Therefore, a program designed to achieve a constant alveolar concentration would not induce anesthesia as rapidly as one that achieves a constant visceral concentration. Since it is apparent from figure 4 that the partial pressure in the brain follows the partial pressure in the viscera rather closely, we decided to derive a formula to achieve a constant partial pressure in the viscera in order to preclude the possibility of a small overshoot in the heart during induction.7

For a nonlinear system, it would be difficult to derive an induction program to attain a specified level of anesthesia. The mathematics would be unwieldy, and a practical solution might be impossible to achieve. To obviate this difficulty, the system was first linearized by fixing cardiac output at 4.875 l/min, the value when PVE = 0.75 per cent atm (see Equation 2). Standard linear techniques could be applied to this linearized system.

The heart is included in the visceral compartment (VE), which can be seen in figure 4 to saturate more rapidly than the brain, but the difference would be quite small. The time constants (TC) for these compartments are as follows:

\[
\begin{align*}
TC(\text{Br}) &= V_{\text{Br}}/Q_{\text{Br}} = 4.6 \\
TC(\text{II}) &= V_{\text{II}}/Q_{\text{II}} = 4.3 \\
TC(\text{VE}) &= V_{\text{VE}}/Q_{\text{VE}} = 3.1
\end{align*}
\]

Fig. 4. Comparison of linear and nonlinear model responses to a constant inspired partial pressure of 1.0 per cent atm. Partial pressures in the nonlinear model are represented by continuous lines; partial pressures in the linear model, by dashed lines. The dotted line represents the fall in cardiac output as a function of PVE in the nonlinear model. Cardiac output in the linear model would, of course, remain unchanged at 6 l/min.
then be used to determine the excitation required to produce the desired output. (The analytic development is included in the Appendix.) The result of such an analysis is an expression for the inspired partial pressure required to achieve in the viscer a constant partial pressure of 0.75 per cent atm. This equation consists of: a) two terms (a doublet and an impulse)** which are a measure of the amount of anesthetic needed to prime the system (in this case, the lung and the viscers); b) a term equal to the inspired partial pressure at equilibrium (0.75 per cent atm); c) a series of exponentially declining terms which represent the over-pressure needed to saturate those compartments (brain, MS, BC, and F) which fill at a slower rate. Since it is physically impossible to give anesthesia to patients with doublets and impulses of partial pressure, these analytic priming functions were replaced by a more practical pulse function of 4.0 per cent atm. The duration of this pulse was determined by a trial-and-error procedure, as indicated in figure 5.

The 4.0 per cent atm pulse was applied to the nonlinear system simulation for as long as was necessary to bring $P_{VE}$ up to 0.75 per cent atm. At this point (determined to be 4.44 minutes) the 4.0 per cent atm pulse was discontinued and anesthesia was given according to the remainder of the terms in the above-mentioned equation. In effect, therefore, we synthesized the following formula for the induction and maintenance of halothane anesthesia in man (based on a nonlinear model of uptake and distribution):

$$P_{IN} = 4.0 \quad (t < 4.44)$$

$$= 0.750 + 0.064 e^{-0.120(t-4.44)}$$
$$+ 0.367 e^{-0.00586(t-4.44)}$$
$$+ 0.031 e^{-0.06250(t-4.44)}$$
$$+ 0.113 e^{-0.00125(t-4.44)} \quad (t \geq 4.44)$$

In order to generate this input function, another TR-20 analog computer was employed in addition to the five used to model the system equations. The analog computer circuit diagram for this programmed input is given in figure 6. The potentiometers were set according to the values listed in table 3. The initial conditions on all integrators were held as components of the 4.0 per cent atm pulse until $t = 4.44$, at which point exponential decay began. The response of the nonlinear system to this excitation appears in figure 7. $P_{VE}$ attained a value of 0.75 within six minutes and remained constant at this level for the duration of the experiment.

**Impulses and doublets imply the delivery of impractically high concentrations for impractically short times.
TABLE 3. Potentiometer Settings for the Input

<table>
<thead>
<tr>
<th>Potentiometer Number</th>
<th>Potentiometer Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.3670</td>
</tr>
<tr>
<td>2</td>
<td>0.7605</td>
</tr>
<tr>
<td>3</td>
<td>0.1130</td>
</tr>
<tr>
<td>4</td>
<td>0.1600</td>
</tr>
<tr>
<td>5</td>
<td>0.3020</td>
</tr>
<tr>
<td>6</td>
<td>0.7500</td>
</tr>
<tr>
<td>7</td>
<td>0.0640</td>
</tr>
<tr>
<td>8</td>
<td>0.1500</td>
</tr>
<tr>
<td>9</td>
<td>0.0310</td>
</tr>
<tr>
<td>10</td>
<td>0.0330</td>
</tr>
<tr>
<td>11</td>
<td>0.1000</td>
</tr>
<tr>
<td>12</td>
<td>0.2675</td>
</tr>
</tbody>
</table>

Discussion

All of the physiologic quantities represented in the equations describing the uptake and distribution of anesthetic agents are variables subject to anesthetic actions and with many interdependencies, some yet to be discovered. In order to incorporate any knowledge about the effects of anesthesia into a mathematical model, it is necessary to determine a quantitative relationship among the variables involved. In the past, these variables have been treated as constants, and the model of uptake as static. The pharmacologic effects of anesthetic agents on the system into which they are being absorbed have been deliberately ignored. The availability of computing machinery, either analog or digital, has now made it feasible to accept the mathematical complexities introduced by a more realistic model. A previous effort to do this for the dependence of solubility coefficients on the chemical concentration of anesthetics has been reported.

This investigation was undertaken in order to determine how a cardiovascular nonlinearity in the system equations would affect the uptake and distribution of halothane in man. The nonlinearity in this study was due to a uniformly distributed reduction of cardiac output as anesthetic partial pressure in the viscera increased. For a constant inspired partial pressure of 1.0 per cent atm, the difference between the linear and nonlinear models is insignificant for the first five minutes but progressively increases during the first hour to a maximum of 6 per cent. Unless greater anesthetic depths are employed, it would be difficult to prove by experiment that this nonlinear model provides a more accurate approximation of the true uptake and distribution of halothane in man than the traditional one. Since higher concentrations of halothane would further depress cardiac output, the effect of this nonlinearity would be amplified as a function of the inspired partial pressure.

Munson showed in a static model that changes in cardiac output accompanied by changes in distribution of blood flow markedly increased the effect on uptake. Unfortunately, available quantitative data on dose-related effects of anesthetic agents on distribution of blood flow are insufficient to apply to a more refined nonlinear model. There is, however, no

![Response of the nonlinear model to programmed input (P1) based on nonlinear system equations. P1 attained a value of 0.75 within six minutes and remained constant at this level for the duration of the experiment.](image-url)
doubt that such effects do occur under halothane anesthesia.9, 22, 23

In the absence of quantitative information sufficient to program on a computer, it is of interest to deduce predictions of a qualitative sort. The evidence suggests that vasodilatation occurs in the brain22 and the skin23 during halothane anesthesia, so that these tissues, primarily well perfused and of relatively low halothane solubility, receive an increased proportion of the reduced cardiac output. Changes in splanchnic and renal blood flow seem to be approximately proportional to the reduction of cardiac output.22, 23 By exclusion, the decrease in cardiac output can be expected to include a more-than-proportional decrease in the blood flow to adipose tissue. This effect on flow to a tissue of very great halothane solubility would significantly reduce the rate of absorption of anesthetic by fat. As a result, the well perfused tissues would receive a larger share of the total halothane absorbed. The excess partial pressure of anesthetic in the viscera and the brain produced by the application of a constant partial pressure of 1.0 per cent atm to this more complex nonlinear model might thus be even larger than the 6 per cent we have computed.

It is known that certain nonlinearities involving ventilation, such as the concentration effect24 and the second-gas effect25, 26 alter the rates of uptake and distribution of inhalation anesthetics. Other sources of nonlinearities in the system, such as variation in the total ventilation secondary to the pharmacological effects of anesthetics on respiratory control mechanisms, would likewise affect uptake,8 particularly during the early phases when fast compartments are filling rapidly and the entry of gas into the lung becomes the rate-limiting step. The simultaneous treatment of multiple nonlinearities is even more formidable than in the present instance where only cardiac output was varied. Nevertheless, the construction of more realistic models will depend on including respiratory as well as more detailed circulatory effects of anesthesia in the mathematical description of the system.

References

1. Cowles AL, Borgstedt HH, Gillies AJ: An electric analog for the uptake, distribution and excretion of inhalation anesthetics, Data Ac-


APPENDIX

The uptake and distribution of halothane may be described by a combination of six first-order differential equations and two linear algebraic equations. (See table 1 for an explanation of the symbols.) The lung compartment, with two entrance and two exit ports (a pair for ventilation and a pair for circulation), is represented by the following equation:

$$dP_v/dt = [\hat{V}_a/(\hat{V}_{FC} + \lambda_v \hat{V}_L + \lambda_a \hat{V}_{AN})][P_i - P_a] - [\alpha_v/(\hat{V}_{FC} + \lambda_v \hat{V}_L + \lambda_a \hat{V}_{AN})][P_a - P_v]$$

(1)

Each tissue compartment is represented by an equation of the following type:

$$dP_{vT}/dt = [\hat{V}_{TE}/(\hat{V}_{V} + \lambda_v \hat{V}_{TE} + \lambda_v \hat{V}_{AN})][P_a - P_{vT}]$$

(2)

Another equation is needed to relate the partial pressure in the mixed venous blood to the partial pressures in the various tissue compartments according to the fraction of cardiac output perfusing each tissue. This relationship may be expressed as

$$F_v = (\hat{V}_{TE} P_{vT} + \hat{V}_{AN} P_{AN} + \hat{V}_{VE} P_{VE} + \hat{V}_{PE} P_{PE})/\hat{V}_{TE}$$

(3)

The last equation relates cardiac output to the partial pressure in the viscera and makes the system nonlinear.

$$\hat{Q} = Q_0(1.0 - 0.25 P_{VE})$$

(4)

Using the methods of the Laplace transformation (a technique for manipulating and solving differential equations), we developed an induction program from a linearized version of the nonlinear system equations. A transfer function was derived analytically (that is, mathematically without a computer) to relate partial pressure in the viscera (P_{VE}) to the inspired partial pressure (P_i). This transfer function was used to find a time-dependent expression for the inspired partial pressure, P_i(t), that would produce a constant partial pressure in the viscera. Since the analytic function so derived could not be realized in clinical practice, the expression was modified to permit a more realistic induction program.

In order to derive the desired transfer function, it is necessary to constrain the system equations to a linear set. This is done by removing the dependency of cardiac output on halothane concentration. Therefore, Equation 4 is eliminated by fixing cardiac output at 4.875 l/min. This value for cardiac output was obtained by substituting the desired halothane partial pressure (0.75 per cent atm) into Equation 4. Thus,

$$\hat{Q} = Q_0(1.0 - 0.25 P_{VE}) = 6.0[1.0 - 0.25(0.75)] = 4.875$$

Inserting this value for \hat{Q} into the nonlinear system equations yields a set of six first-order differential equations with constant coefficients. After taking the Laplace transform of each equation, we solve for P_{VE}(s)/P_i(s) to obtain the following system transfer function:

* Due to round-off errors, high precision is necessary at this stage in order to assure three-figure accuracy for P_{i}(s).
NONLINEAR MODEL FOR HALOTHANE UPTAKE IN MAN

\[ T_{\text{xe}}(s) = \frac{P_{\text{ve}}(s)}{P_{\text{xe}}(s)} = \frac{(s^4 + 0.16355s^3 + 2.106502 \cdot 10^{-3} s^2 + 7.216142 \cdot 10^{-4} s + 2.002223 \cdot 10^{-9})}{(s^4 + 21.400600 s^3 + 0.560591 s^2 + 3.0151307 s^1 + 3.665295 \cdot 10^{-2} s^1 + 8.432361 \cdot 10^{-4} s + 2.002223 \cdot 10^{-9})} \]

We seek an expression for \( P_t \) that will give rise to a step function for \( P_{\text{ve}} \). Therefore, let

\[ P_{\text{ve}}(t) = 0.75 u(t) \]

where \( u(t) \) is the unit step function. The unit step, \( u(t) \), is defined:

\[ u(t) = \begin{cases} 0 & (t < 0) \\ 1.0 & (t \geq 0) \end{cases} \]

Taking the Laplace transform of Equation 6, we obtain

\[ P_{\text{ve}}(s) = \frac{0.75}{s} \]

We solve for \( P_t \) as follows:

\[ P_t(s) = \frac{P_{\text{ve}}(s)}{T_{\text{xe}}(s)} \]

We substitute Equation 5 and Equation 6 into Equation 9 and separate by the method of partial fractions to obtain

\[ P_t(s) = 5.649 s + 15.125 + 0.750 s + 0.064 (s + 0.150) + 0.367 (s + 0.007695) + 0.061 (s + 0.00550) + 0.113 (s + 0.006302) \]

Inverse Laplace transformation yields the following expression for an inspiratory waveform which, if applied to a linear model having a cardiac output fixed at 4.875 l/min, would instantaneously achieve and maintain a partial pressure in the viscera of 0.75 per cent \( \text{atm} \):

\[ P_t(t) = 5.649 \delta(t) + 15.125 \delta(t) + 0.750 u(t) + 0.064 e^{-0.124t} + 0.367 e^{-0.007695t} + 0.061 e^{-0.00550t} + 0.113 e^{-0.006302t} \]

where \( \delta(t) \) is the unit impulse and \( \delta(t) \) is the unit doublet. The unit impulse is the derivative of the unit step, and the unit doublet is the derivative of the unit impulse.\(^{23}\) If the transient terms (the doublet and the impulse) are excluded, this equation may be applied to the nonlinear model after the induction pulse produces a value of 0.75 for \( P_{\text{ve}} \).

Anesthesia

ANALGESIA FOR CARDIOVERSION Conscious analgesia (stage 1, plane 3) produced by the inhalation of methoxyflurane was used in 20 consecutive patients who underwent 22 elective direct-current countershock procedures for supraventricular arrhythmias. After the drug had been administered in concentrations adequate to produce signs of perseveration, loss of memory, delayed response to verbal commands, and inability to focus the eyes, the direct-current countershock was delivered. Although the patients responded to verbal commands just prior to the procedure, postoperative interviews revealed complete amnesia. No significant changes in heart rate, blood pressure, or ventilation were noted. Following the procedure, emergence to an alert, oriented state occurred within two to five minutes. The technique provided both analgesia and amnesia—but without general anesthesia. (Reier, C. E., and Hamelberg, W.: Conscious Analgesia and Amnesia for Cardioversion, J.A.M.A. 210: 2052 (Dec.) 1969.)

HYPERTHERMIA The development of hyperthermia during general anesthesia is unpredictable. Continuous temperature monitoring is the safest means of early diagnosis. The primary cause is unknown but is probably a drug-induced disturbance of the thermal regulating centers. Pathologic findings are the same as those in heat stroke. It has been suggested that a subclinical genetic disorder of the neuromuscular system might be a cause. (Thomford, N. R., and others: Sudden Hyperpyresia during General Anesthesia, Surgery 66: 850 (Nov.) 1969.)