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Effects of Anesthetic-depressed Ventilation and Cardiac Output on Anesthetic Uptake:

A Computer Nonlinear Simulation

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A nonlinear mathematical model of anesthetic uptake and distribution has been used to account for changes in ventilation and perfusion induced by progressive increase in anesthetic depth. The results show greater differences in anesthetic uptake than have been predicted from models that have not considered the effects of anesthetics on these physiologic variables. During spontaneous ventilation with halothane or isoflurane, the higher the inspired concentration, the slower the rate of alveolar anesthetic increase. Progressively increasing ventilatory depression, and eventually apnea, limit delivery of anesthetic to the lung and prevent alveolar concentration from rising above 3 per cent, regardless of the inspired concentration. During controlled ventilation with halothane, alveolar concentration increases as cardiac output diminishes. As cardiac arrest occurs, the alveolar curves become unstable and rapidly rise to the inspired concentration. The use of such nonlinear models may allow prediction of limits to which anesthetic drugs and techniques can be used safely. (Key words: Halothane; Isoflurane; Diethyl ether; Nonlinear computer model; Anesthetic uptake and distribution; Ventilation; Cardiac output.)

NUMEROUS MATHEMATICAL and electrical analog models have been developed to predict the uptake and distribution of anesthetic agents in man.[1-3] Although model systems have become increasingly complex, most still share a common failing—that of linearity. Linear models assume that physiologic variables such as ventilation, cardiac output, and the distribution of blood flow to various tissues remain constant from the induction of anesthesia, that is, are unaffected by progressive increase in anesthetic depth. Although the facts contradict this assumption, until recently the lack of quantitative knowledge of the cardiorespiratory changes induced by anesthetics has precluded prediction of the impact of such changes on uptake and distribution. However, sufficient *in-vivo* data are now available to make simulation possible.

Recently, Ashman, Blesser, and Epstein[4] developed a nonlinear model which accounts for the circulatory effects of halothane on its own uptake. Using *in-vivo* data,[5] they showed that the reduction in cardiac output induced by a 1 per cent inspired halothane concentration produced a 6 per cent increase in alveolar halothane concentration 60 minutes after induction. The smallness of this change resulted from their selection of a light level of anesthesia, one which only minimally reduced cardiac output and uptake. However, there are no reports of the effects of anesthetic-induced ventilatory depression on anesthetic uptake. We have developed a nonlinear mathematical model of anesthetic uptake that accounts for changes in both ventilation and perfusion induced by varying the anesthetic concentration. The results show greater differences in anesthetic uptake than have been predicted by models which do not consider the effects of anesthetics on these physiologic variables.

Methods

The mathematical model used is similar to that described previously.[6] The list of symbols used is presented in table 1. A constant in-

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TABLE 1. Symbols Used in the Description of the Mathematical Model

P_I	= inspired anesthetic partial pressure (fraction atm)
P_A	= alveolar anesthetic partial pressure (fraction atm)
Pa	= arterial anesthetic partial pressure (fraction atm)
P_J	= Jth compartment anesthetic partial pressure (fraction atm)
$P\bar{v}$	= mixed venous anesthetic partial pressure (fraction atm)
$\dot{V}_I$	= inspired alveolar ventilation (l/min)
$\dot{V}_A$	= expired alveolar ventilation (l/min)
$\dot{w}$	= anesthetic uptake (l/min)
V_{LG}	= volume lung gas (2.7 liters)
V_L	= volume of lung tissue and blood (1.5 liters)
V_J	= volume of Jth compartment (liters)
$\dot{Q}$	= cardiac output (6 l/min)
$\dot{Q}_J$	= blood flow to Jth compartment (l/min)
λ_{BG}	= blood-gas partition coefficient
λ_{JB}	= Jth tissue-blood partition coefficient
N	= number of compartments

spired anesthetic partial pressure is maintained. Functional residual capacity of the lung is taken to be 2.7 liters. The volume of blood within the lung is taken to be 1 liter. The remaining blood volume is divided in proportion to the distribution of the cardiac output to various tissues. Total cardiac output is taken to be 6 liters per minute. The body is divided into five compartments and grouped according to blood flow per unit of tissue and/or by solvent characteristics of tissues. The first compartment is the brain. The second is the vessel-rich group (VRG), which includes the heart, hepatoportal system, kidneys, and endocrine glands. The third is the muscle group (MG). The fourth is the fat group (FG), and the fifth is the vessel-poor group (VPG), which includes relatively avascular structures, such as bone.

A brief derivation of the equations, based on the model of Mapleson[1,7] and including the concentration effect,[8] follows, as well as a discussion of the assumptions underlying the model design. Anesthetic partial pressure in parenchymal lung tissue and pulmonary capillary blood is assumed to equal alveolar anesthetic partial pressure.

$$P_A = Pa \tag{1}$$

Since the respiratory quotient is assumed to be unity, the volume of inspired alveolar gas must equal the alveolar gas expired ($\dot{V}_A$), or appear as anesthetic uptake. The presence of water vapor and deadspace ventilation are ignored.

$$\dot{V}_I = \dot{V}_A + \dot{w} \tag{2}$$

Accumulation of anesthetic agent in alveoli is given by

$$V_{LG}\frac{dP_A}{dt} = P_I\dot{V}_I - P_A\dot{V}_A - \dot{w} \tag{3}$$

and in the lung as

$$\lambda_{BG}V_L\frac{dPa}{dt} = \dot{w} - \lambda_{BG}\dot{Q}(Pa - P\bar{v}) \tag{4}$$

Equations 3 and 4 express material balance for the alveolar and arterial compartment, and can be written in terms of partial pressures expressed as fractions of an atmosphere.

During constant expired ventilation, the equations may be expressed in terms of $\dot{V}_A$. Combining equations 1 through 4 eliminates $\dot{V}_I$, P_A, and $\dot{w}$, yielding:

$$[V_{LG} + (1 - P_I)\lambda_{BG}V_L] \times \frac{dPa}{dt} = \dot{V}_A(P_I - Pa) - (1 - P_I)\lambda_{BG}\dot{Q}(Pa - P\bar{v}) \tag{5}$$

where the mixed venous partial pressure is

$$P\bar{v} = \sum_{J=1}^{N} (\dot{Q}_J/\dot{Q})P_J \tag{6}$$

Finally, the accumulation of anesthetic in each compartment is given by

$$\lambda_{BJ}V_J\frac{dP_J}{dt} = \dot{Q}_J(Pa - P_J) \tag{7}$$

Equations 5–7 form the system that must be solved. Any number of compartments may be used. Mathematical calculations were performed with a Burroughs 5500 digital computer. Anesthetic partial pressures were printed on a Cal-Comp plotter.§ The differential equations were integrated in time by a step-by-step technique known as a "predictor–

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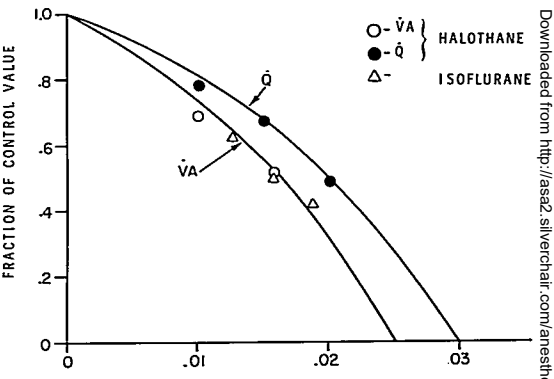

FIG. 1. Effects of halothane and isoflurane on alveolar ventilation ($\dot{V}_A$)[12] and halothane on cardiac output ($\dot{Q}$)[15] at constant arterial carbon dioxide partial pressure. Variables are plotted as fractions of control values and are expressed as functions of anesthetic partial pressures. Regression equations (see text) were extrapolated to the horizontal axis.

corrector method." The time steps were adjusted automatically to maintain a set degree of accuracy. In general, all quantities except Pa and P_J values were considered constants. Nonlinear effects of ventilation and circulation were simulated by making V_A and Q functions of the brain and heart compartment partial pressures (P_J), respectively. The values for V_A and Q were recalculated before each small time step from the P_J values at that time.

Halothane, isoflurane (Forane¶; 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether) and diethyl ether were selected for study. The solubility characteristics of these drugs in human blood and tissues have been described.[3,9,10] The known effects of these agents on ventilation[11–13] and cardiac output[14–17] were expressed as empiric functions of the anesthetic partial pressures within the brain (fast compartment) and heart, respectively. Brain volume and blood flow were adjusted so that cerebral blood flow equaled 80 ml/100 g/min. This approximates the value of the fast compartment cerebral blood flow measured by Ingvar *et al.*[18] in awake subjects. Blood flow to the VRG (heart) equals 70 ml/100 g/min, a value which agrees with the results of others.[19]

A common function was used to describe these relationships. Alveolar ventilation for halothane and that for isoflurane were calculated as follows:

$$\dot{V}_A = 4 \cdot f(100\ P_B, 100\ P_{B_0}) \quad (8)$$

where P_B equals brain anesthetic partial pressure and P_{B_0} equals 0.025 of atmospheric pressure, the partial pressure at which ventilation is zero. Cardiac output for halothane, at a constant arterial carbon dioxide partial pressure (V_A equals 4, as during controlled ventilation) was calculated as follows:

$$\dot{Q} = 6 \cdot f(100\ P_{VRG}, 100\ P_{VRG_0}) \quad (9)$$

where P_{VRG} equals the VRG halothane partial pressure and P_{VRG_0} equals 0.03 of atmospheric, the partial pressure where cardiac output is zero. In order to fit the experimental data, the modifying function is

$$f(P,P_0) = 1 - (9\ P + P^3)/(9\ P_0 + P_0^3) \quad (10)$$

These equations are shown graphically in figure 1. During spontaneous ventilation with halothane, cardiac output was maintained constant at 6 l/min. Cardiac output with isoflurane increased linearly from 6 l/min at induction to 7.8 l/min where the VRG partial pressure reached 0.0125 atm. Cardiac output

¶ Trademark, Ohio Medical Products, Division of Airco, Inc.

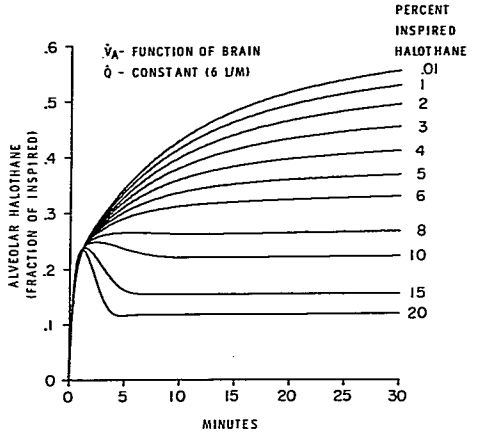

FIG. 2. Rates of increase of alveolar halothane concentration (partial pressure) plotted as fractions of inspired concentrations for a wide range of halothane concentrations. Ventilation is maintained as a function of the cerebral partial pressure of halothane (see text). The 0.01 value in this and subsequent figures represents a trace concentration of anesthetic that produces no ventilatory or circulatory depression.

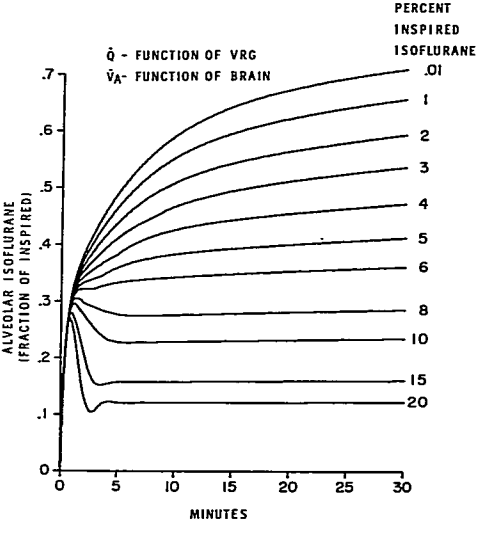

FIG. 3. Rates of increase of alveolar isoflurane concentration plotted as fractions of inspired concentrations for a wide range of isoflurane concentrations. Both ventilation and cardiac output are maintained as functions of cerebral and VRG (heart) partial pressures of isoflurane, respectively (see text).

was then maintained constant at this value. Ventilation with ether was maintained at 4 l/min until the brain partial pressure reached 0.059 atm. Then ventilation was decreased linearly and became zero at a brain partial pressure of 0.06 atm.

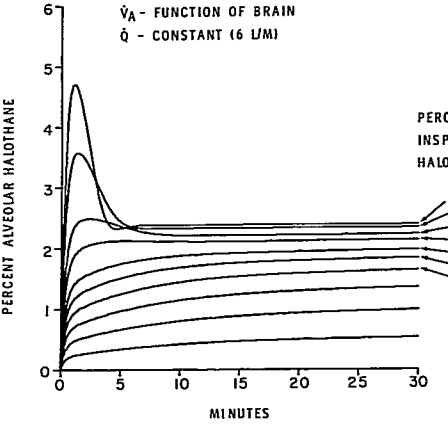

FIG. 4. Rates of increase of *absolute* alveolar halothane concentration from figure 2. Curves were obtained by multiplying the fraction of the inspired concentration at any time by the inspired value (fig. 2). Although the absolute alveolar concentrations are greater at higher inspired concentrations, ventilatory depression limits the absolute alveolar concentration attainable to about 3 per cent, regardless of the inspired concentration. The initial alveolar overshoot with the higher inspired concentrations occurs before the cerebral halothane partial pressure develops sufficiently to limit ventilation.

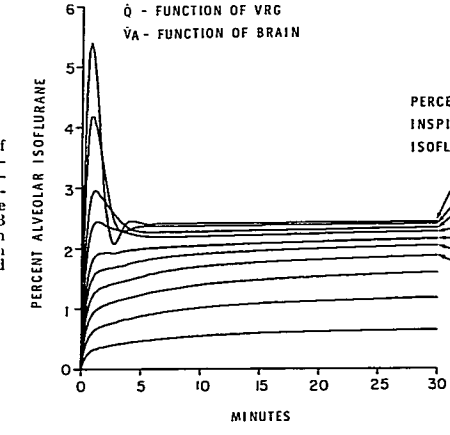

FIG. 5. Rates of increase of the *absolute* isoflurane concentration from figure 3. As with halothane (fig. 4), ventilatory depression limits the absolute isoflurane concentration attainable to about 3 per cent. Note the oscillation in alveolar concentration as ventilation changes from normal to apneic and back again.

Results and Discussion

VENTILATION VARIABLE

During spontaneous ventilation and constant cardiac output of 6 l/min (7.8 l/min at more than 1.25 per cent isoflurane) the higher the inspired halothane or isoflurane concentration, the slower the rate of alveolar anesthetic increase (figs. 2 and 3). Progressively increasing ventilatory depression at higher inspired anesthetic concentrations eventually reduced the rate of increase of alveolar concentration. This effect, found between 3 and 20 per cent inspired concentration, produces a family of curves resembling the tines of a fork. The slower *rate* of increase does not mean that the

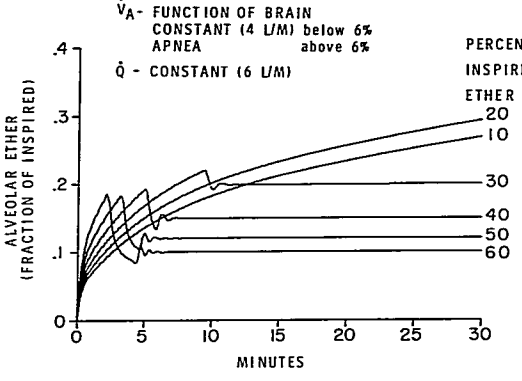

FIG. 6. Rates of increase of alveolar ether concentration (partial pressure) for inspired concentrations ranging from 10 to 60 per cent. In contrast to halothane and isoflurane (figs. 2 and 3), ventilation is maintained normal until the apneic threshold is reached (see text). This permits an overshoot in the cerebral partial pressure of ether, with a more evident oscillatory pattern in alveolar concentration as ventilation fluctuates from normal to apnea and back again. Note the effect of concentration on increasing the rates of rise in the initial portions of the alveolar curves.

absolute increase is less at the high inspired concentrations. The *absolute* alveolar concentrations are greater at higher inspired concentrations (figs. 4 and 5). However, the absolute alveolar concentration attained with either halothane or isoflurane does not rise above 3 per cent, regardless of the inspired concentration, because ventilatory depression, and eventually apnea, limit delivery of the higher inspired concentrations to the lung.

The curves given in figures 4 and 5 also may be used to estimate the depression of respiration imposed by various inspired concentrations. For example, figure 1 suggests that alveolar ventilation is halved at an alveolar concentration of approximately 1.6 per cent of

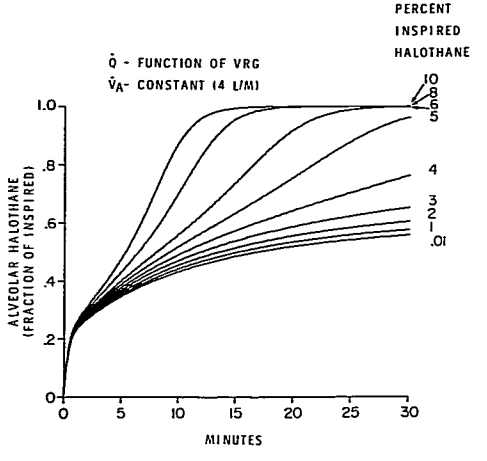

FIG. 7. Rates of increase of alveolar halothane concentration (partial pressure) plotted as fractions of inspired concentrations over a range of 0.01 to 10 per cent. Cardiac output is maintained as a function of heart (VRG) partial pressure of halothane. During constant ventilation halothane uptake decreases as cardiac output falls.

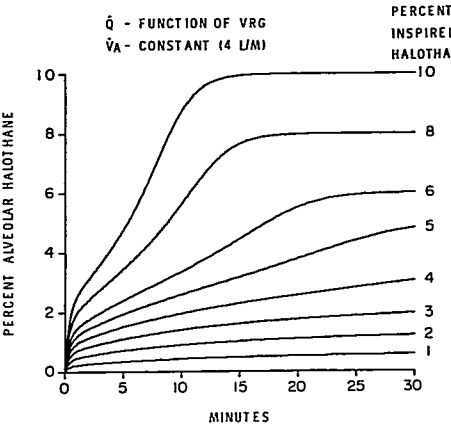

FIG. 8. Rates of increase of the *absolute* alveolar halothane concentration from figure 7. In contrast to the effect of ventilation, which limits the rate of alveolar anesthetic increase (figs. 4 and 5), depression of cardiac output increases these differences. The alveolar curves become unstable at higher inspired concentrations (between 5 and 15 minutes) as cardiac arrest occurs.

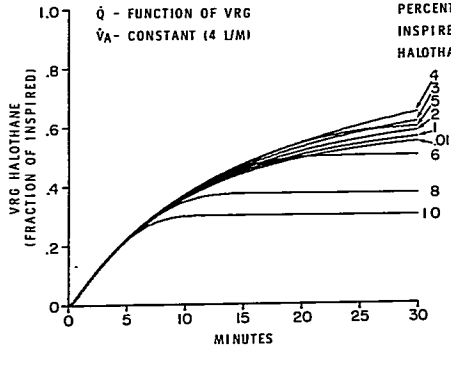

FIG. 9. Rates of increase of the heart (VRG) halothane concentration (partial pressure) expressed as fractional values of a wide range of inspired halothane concentrations. This graph corresponds to figure 7, showing that with less than 4 per cent the circulation is sufficiently maintained so that the VRG can appreciate the alveolar halothane partial pressure. At 30 minutes, circulatory depression induced by inspired concentrations of more than 4 per cent limits the relative delivery of halothane to the VRG.

either halothane or isoflurane. Inspired halothane concentrations of 4 per cent or more, or isoflurane concentrations of 3 per cent or more, cause the alveolar concentration of these agents to exceed 1.6 per cent within 10 minutes. The depression of ventilation to half-normal would shortly follow, as the brain anesthetic partial pressure approached the alveolar partial pressure.

One exception occurs on induction, where at higher inspired concentrations the alveolar anesthetic partial pressure is not immediately perceived by the brain. This permits alveolar and eventually brain anesthetic partial pressures to exceed these pressures, thus producing apnea. This is particularly evident with ether, since ventilation is not depressed until the apneic concentration is reached.[12] Alveolar ether concentrations produced by 10 to 60 per cent inspired concentrations are shown in figure 6. Note the effect of concentration and the oscillation of the alveolar concentration as

ventilation changes from normal to apnea and back again. The initial increase in brain partial pressure of ether above 6 per cent atm produces a sudden decrease in ventilation. Following anesthetic redistribution (cardiac output constant at 6 l/min), brain partial pressure falls and ventilation increases. These oscillations continue, but are progressively damped over several minutes. Alveolar and brain ether partial pressures subsequently come to the limit set by the apneic threshold.

Cardiac Output Variable

During controlled ventilation, the alveolar halothane concentration increases as cardiac output diminishes, and cardiac output diminishes as halothane concentration increases. Figure 7 shows the resultant acceleration of the relative rates of increase of the alveolar concentration toward progressively higher inspired concentrations. The alveolar curves for 0.01 and 1.0 per cent inspired halothane differ by roughly 5 per cent at 30 minutes—a finding nearly identical to that described by Ashman *et al.*[4] for these concentrations. This small difference expands as the inspired concentration is further increased. The maximum spread is attained with inspired concentrations of 8 to 10 per cent, where cardiovascular collapse—with consequent equality of the alveolar and inspired concentrations—occurs within the first few minutes of induction. The resultant elimination of uptake permits ventilation to increase the alveolar concentration at a rate dictated solely by the washin characteristics of this system. Collapse at a later time also is evident with the 6 and 5 per cent curves (fig. 7), and even a 4 per cent inspired concentration will force the alveolar level above the crucial 3 per cent within an hour (fig. 8).

Recall that these curves are based on the presumption that ventilation is normal (Pa_{CO_2} equals 40 torr) and that under these conditions collapse occurs as the alveolar concentration approaches 3 per cent. More vigorous ventilation might alter our conclusions regarding the safe upper inspired concentrations in two ways. First, the increased intrathoracic pressure and lower Pa_{CO_2} would lower the threshold for collapse while, second, the augmented respiration would accelerate the rate of increase of alveolar concentration toward the concentration inspired. A decrease in ventilation might have an opposite effect and permit the use of still higher inspired concentrations without producing cardiac arrest.

The corresponding *absolute* alveolar halothane concentrations are shown in figure 8. As opposed to the effect of ventilatory depression, which limits the spread of the absolute anesthetic rates of increase, depression of cardiac output increases these differences. The alveolar curves become unstable and rapidly rise toward the inspired concentration as cardiac arrest occurs. At the lower inspired halothane concentrations the relative rates of VRG halothane partial pressure increase are similar to the corresponding alveolar curves (fig. 7). Thus, at 30 minutes, the most rapid rate of VRG increase is at 4 per cent inspired concentration (fig. 9). Below this concentration the circulation is sufficiently maintained so that the alveolar partial pressure can be appreciated by the VRG. Although the alveolar rate of increase is more rapid at the higher inspired concentrations, the relative delivery of halothane to the VRG above 4 per cent inspired concentration is limited by anesthetic-induced circulatory depression.

As mentioned previously,[6] the design of the mathematical model is based on many assumptions. Although we have included nonlinear functions of ventilation, circulation, and the concentration effect, the present model does not account for anesthetic-induced changes in the distribution of cardiac output. Our previous work[20] illustrates the importance of the effects of alterations in regional blood flows on anesthetic uptake. Failure to account for such changes may result in oversimplification of the dynamic kinetic process, but data necessary for such an approach are not yet available. However, these predictions of anesthetic uptake and distribution explain the ventilatory and circulation interaction observed in a number of clinical circumstances. For example, when anesthetic-induced apnea occurs during spontaneous ventilation, circulatory redistribution of anesthetic results in a progressive decrease in the depth of anesthesia, with eventual resumption of ventilation. This mechanism may contribute to the safety of certain anesthetic techniques, such as open-drop ether and systems which incorporate in-circle vaporizers.

Interference with this feedback system by the imposition of controlled ventilation results in further increased anesthetic depth and circulatory depression. This relationship may also result from the development of hypothermia or the administration of cardiac depressant drugs such as thiopental. Conversely, any increase in cardiac output resulting from surgical stimulation may decrease the level of anesthesia. In our calculations, cardiac output during spontaneous ventilation was maintained normal with halothane anesthesia (figs. 2 and 4). However, this circulatory response probably represents some adjustments to moderate hypercapnia, so our results may not accurately represent what occurs during induction of halothane anesthesia when a greater degree of circulatory depression may be present. Our findings show that anesthetics markedly influence their own uptake through their effects on ventilation and circulation. The use of such nonlinear models may allow prediction of limits to which anesthetic drugs and techniques can be used safely.

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