

Interactions among Ventilation, the Circulation, and the Uptake and Distribution of Halothane—Use of a Hybrid Computer Multiple Model:

II. Spontaneous vs. Controlled Ventilation, and the Effects of CO₂

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The authors have described a basic hybrid computer multiple model of the circulation, ventilation, and uptake and distribution of halothane in a companion paper. A multiple model consists of two or more submodels, each of which is complete in itself and could operate independently. In a multiple model, however, each submodel interacts with the others. The present paper describes the addition of a CO₂-control loop (submodel), through which the partial pressure of CO₂ modulates ventilation, as well as myocardial "contractility," arterial pressure, cardiac output, and regional vascular resistances. The concentration of halothane modifies these CO₂-induced modulations. The CO₂- and halothane-induced changes in ventilation and circulation in turn modify the uptake and distribution of halothane. Thus, a complex set of interrelationships among the submodels and compartments exists. (Key words: Anesthetics, volatile: halothane. Equipment: computers. Pharmacokinetics: distribution; models; uptake. Ventilation: artificial; spontaneous.)

A COMPANION PAPER describes a multiple model that simulates the interaction between the circulatory effects and the uptake and distribution of halothane during controlled ventilation.¹ Anesthesia with halothane, however, is often induced and maintained during spontaneous ventilation. To make the basic model more realistic, we have added a CO₂-control loop (submodel) to observe the interactions among CO₂, ventilation, circulation, and the uptake and distribution of halothane.

Materials and Methods

The model is a hybrid computer multiple model, that is, a large model consisting of several independent

but integrated submodels, or loops. Our basic model¹ had three submodels (fig. 1, left and upper right sections): 1) a 15-compartment beat-to-beat cardiovascular model describing blood pressure–flow relations, 2) a two-compartment breath-by-breath model describing air pressure–flow relations in the airways, and 3) an 18-compartment model of halothane mass transport, characterizing the uptake and distribution of that agent. Assumptions for the basic model have been outlined.¹ The CO₂-control loop added to the basic model simulates the transport of CO₂ by a 15-compartment mass-transport model. Assumptions made for CO₂ transport are 1) a compartment represents a perfect mixing chamber, 2) CO₂ is produced in seven compartments, and 3) the effects of CO₂ and halothane on ventilation, myocardial "contractility," and the baroreceptor–heart rate loop are linear. The value for CO₂ production for each compartment is available in archives.‡

The partial pressure of CO₂ modulates ventilation as well as myocardial contractility, the baroreceptor–heart rate control loop, and regional vascular resistances. Increasing concentrations of halothane attenuate these CO₂-induced responses. A detailed mathematical explanation is available in archives.‡

The model was programmed on the hybrid computer facility of the University of Wisconsin. As with the basic model,¹ the time-scale factor was 0.1, that is, the model operated ten times faster than real time.

Results

Figures 2–6 illustrate some of the outputs from the model. Figure 2 compares the effects of spontaneous ventilation and controlled ventilation on the normal-

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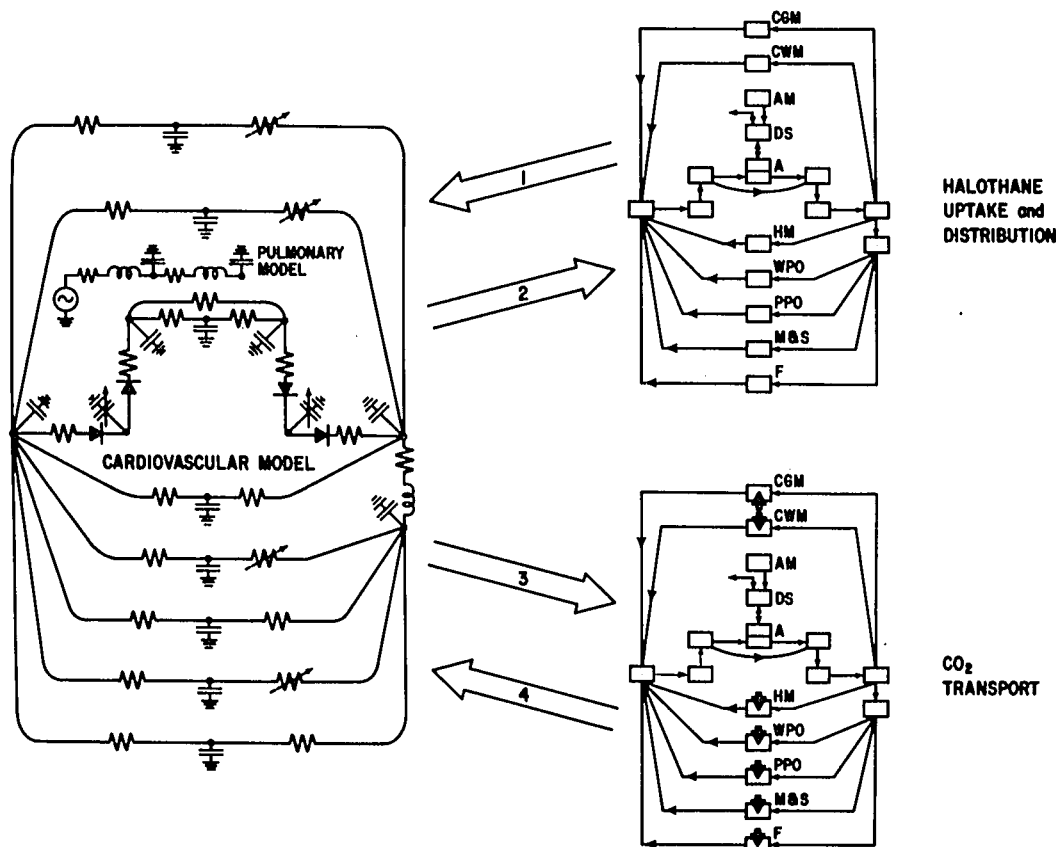


FIG. 1. The basic model,¹ plus the added CO₂-transport model (lower right). Arrow 1: changes in halothane concentration affect the cardiovascular and respiratory systems. Arrow 2: Changes in ventilation, as well as total blood flow and its distribution, affect halothane uptake and distribution. Arrow 3: Changes in ventilation, as well as total blood flow and its distribution, affect CO₂ transport. Arrow 4: Changes in P_{CO₂} affect the cardiovascular and respiratory systems. CGM = cerebral gray matter; CWM = cerebral white matter; AM = anesthesia machine; DS = dead space; A = alveolar; HM = heart muscle; WPO = well-perfused organs; PPO = poorly perfused organs; M & S = muscle and skin; F = fat. For more detail, see figure 1 in reference 1. This figure details the left and upper right sections. The lower right section, the CO₂-transport model, is similar to the halothane mass-transport model.

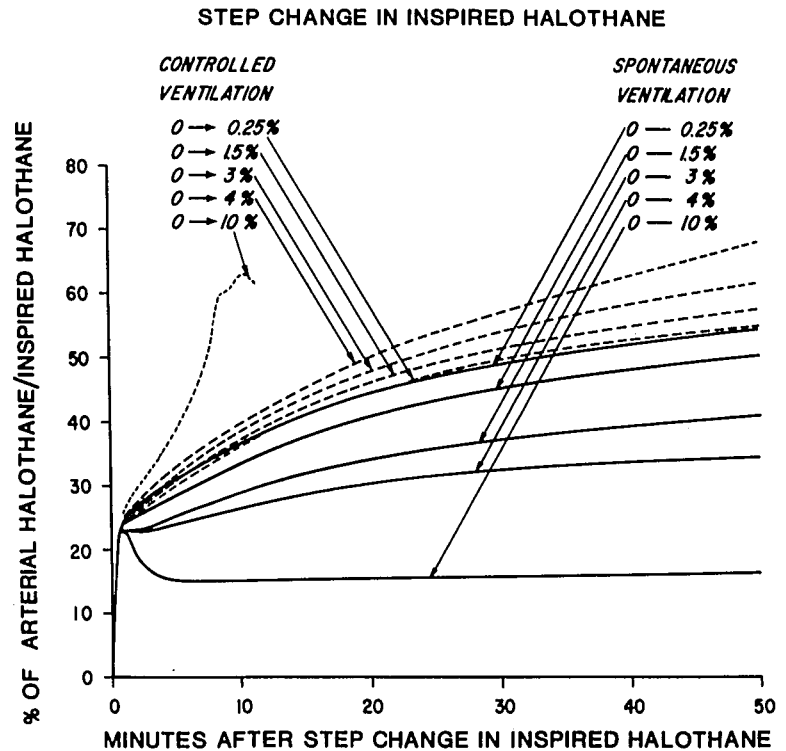
ized responses of the halothane concentration in arterial blood to step changes in inspired halothane concentration ranging from 0 → 0.25 per cent to 0 → 10 per cent. During controlled ventilation, the relative approach of the halothane concentration in arterial blood to equilibrium is more rapid when the inspired concentration is higher. The reverse is true during spontaneous ventilation. At any given inspired concentration, the uptake of halothane is slower during spontaneous than during controlled ventilation. With a 10 per cent inspired concentration during spontaneous ventilation, the concentration in arterial blood actually decreases from an early peak. This is due to the marked depression of ventilation, and hence uptake into the lungs, at high levels of inspired halothane, with continued, albeit slow, distribution of halothane to some of the compartments, particularly brain, whose blood flows are well preserved (see fig. 3, and fig. 3 in reference 1).

Figure 4 compares the cardiovascular responses to a step change in inspired halothane concentration

(0 → 4 per cent) during spontaneous ventilation and controlled ventilation. Arterial blood pressure and stroke volume show sharp initial decreases with both types of ventilation. However, with controlled ventilation the declines continue, while the values remain steady with spontaneous ventilation. Myocardial "contractility" soon begins to increase during spontaneous ventilation, while showing the expected continued decline during controlled ventilation. Right atrial pressure shows a much sharper late rise during controlled than during spontaneous ventilation. Cardiac output increases slightly during spontaneous ventilation and decreases during controlled ventilation.

In figure 5 can be seen the responses of regional blood flows to the same step change in inspired halothane concentration illustrated in figure 4 (0 → 4 per cent). The most striking differences between the two modes of ventilation are seen in blood flows in the cerebral gray matter and well-perfused organ compartments. During spontaneous ventilation, they show late increases; during controlled ventilation, late

FIG. 2. Responses of the halothane concentration in arterial blood to various step changes in inspired halothane concentration during controlled and spontaneous ventilation. Notice that these are relative arterial concentrations.

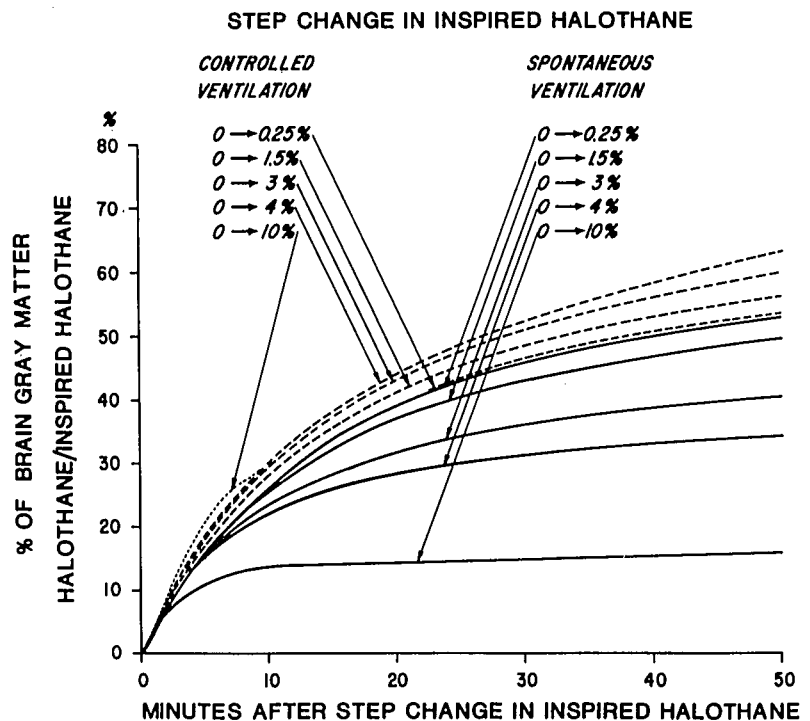


decreases. The significant reduction in peak airway flow during spontaneous ventilation can also be seen in figure 5.

Figure 6 shows the changes in selected compartmental CO₂ tensions and halothane concentrations. Arterial blood P_{CO₂} increases as expected during spontaneous ventilation, but actually decreases during controlled ventilation. That this reflects a reduction in

tissue P_{CO₂}, in turn resulting from decreased CO₂ production, is evident in the cerebral gray matter compartment. The uptakes of halothane into the various compartments are always more rapid during controlled ventilation, particularly during the later stages. However, the difference between the two types of ventilation is less in compartments with slower uptakes.

FIG. 3. Effects of the concentration of inspired halothane on the concentrations in the cerebral gray matter during spontaneous and controlled ventilation. Notice that these are relative concentrations (see fig. 2).



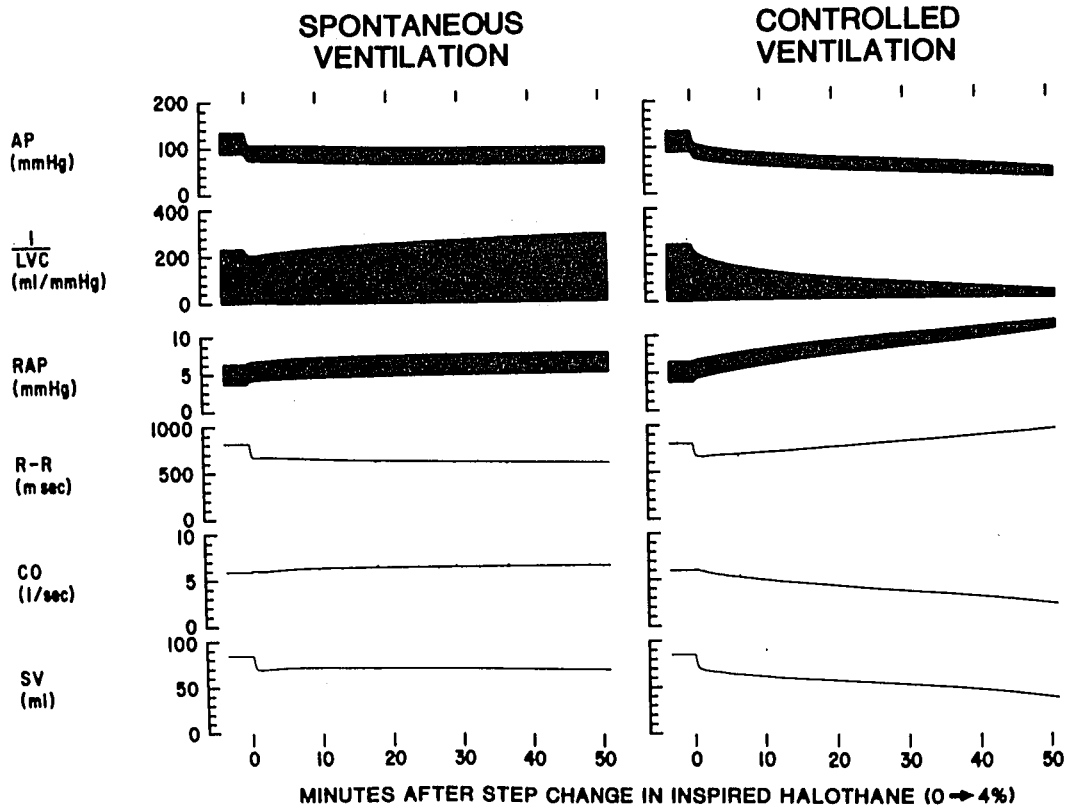


FIG. 4. Cardiovascular responses to a 0 → 4 per cent step change in inspired halothane concentration during spontaneous and controlled ventilation. AP = arterial pressure; 1/LVC = the reciprocal of left ventricular compliance = "myocardial contractility" of the left ventricle; CO = cardiac output; SV = stroke volume. Regional vascular resistances are modulated by the halothane concentration in arterial blood. Myocardial compliances are modulated by the halothane concentration in cerebral gray matter.

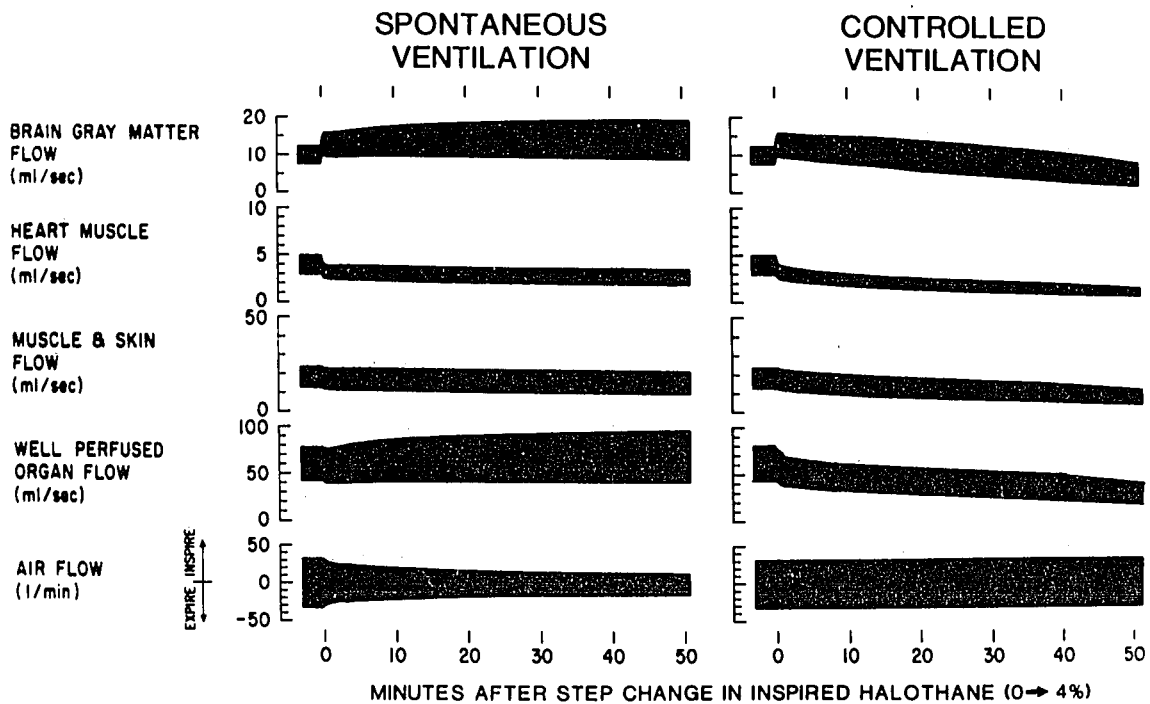


FIG. 5. Responses of regional blood flows to a 0 → 4 per cent step change in inspired halothane concentration during spontaneous and controlled ventilation. Regional vascular resistances are modulated by the halothane concentration in arterial blood. Myocardial compliances are modulated by the halothane concentration in cerebral gray matter.

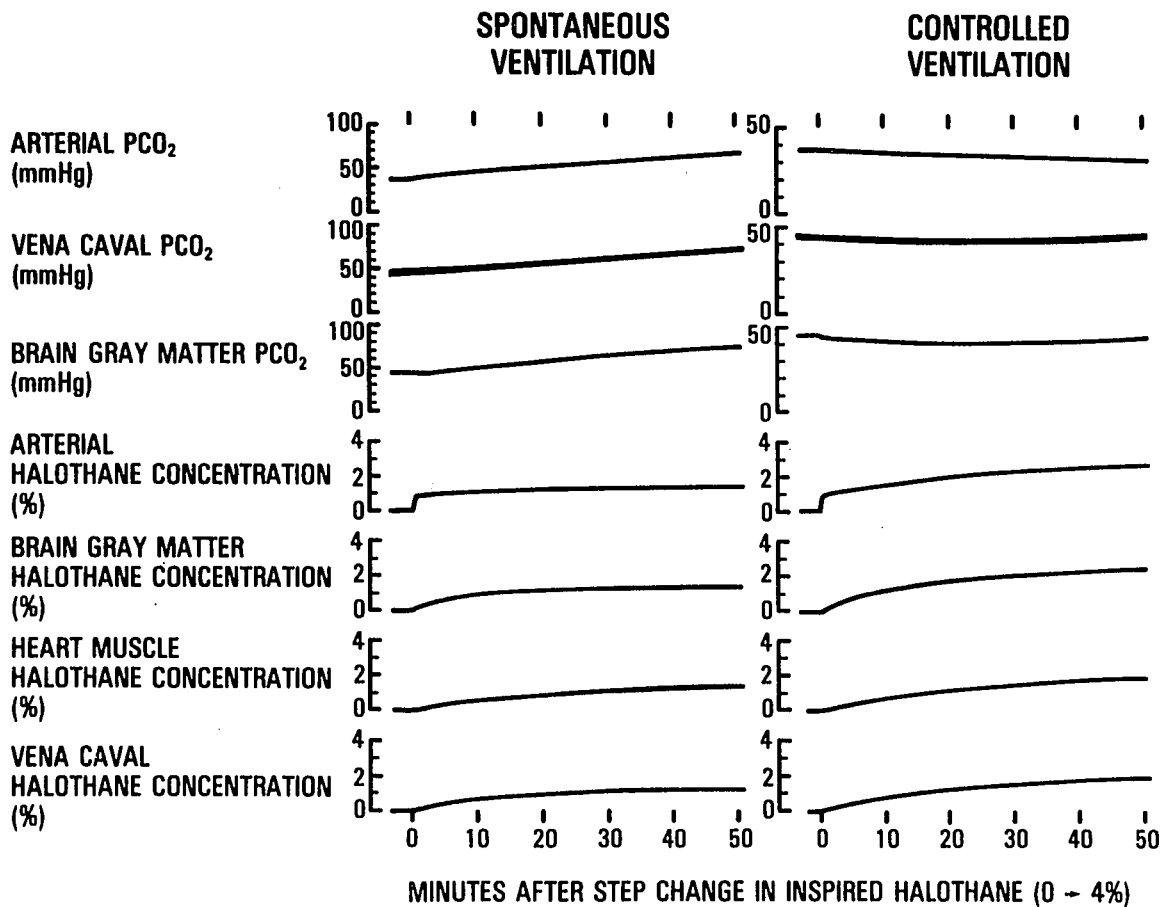


FIG. 6. Responses of selected compartmental CO₂ tensions and halothane concentrations. Regional vascular resistances are modulated by the halothane concentration in arterial blood. Myocardial compliances are modulated by the halothane concentration in cerebral gray matter. Notice that in the top three tracings the scales are different on the right and left sides.

Discussion

The uniqueness of the present model, combining the basic model with a CO₂-control loop, lies in several areas: the amalgamation of separate respiratory, circulatory, and uptake and distribution models; the pulsatile characteristics of both the pulmonary model and the circulatory model; the modulation of air flow by the partial pressure of CO₂ in the brain; the modulation of myocardial "contractility" and regional vascular resistances by halothane concentration; the ability to select and weight the compartments whose halothane concentrations modulate these variables; the modulation of "contractility" and resistances by the partial pressure of CO₂; the modification by halothane of the effect of CO₂; and the inclusion of a baroreceptor pressure-heart rate loop, whose slope and set point are influenced by the concentrations of both halothane and CO₂.

The model demonstrates quantitatively how the use of spontaneous ventilation during induction with halothane, as opposed to controlled ventilation, protects the patient in two ways, each related to the halothane-induced depression of ventilation. First, the de-

crease in ventilation retards the alveolar uptake of halothane (fig. 2). Second, the increased PaCO₂ increases myocardial "contractility," cardiac output, and arterial pressure, thereby partially antagonizing the circulatory depressant effects of halothane (fig. 4). Thus, a higher inspired concentration of halothane is possible during spontaneous ventilation. Countering these protective effects partially is the CO₂-induced stimulation of ventilation.

Our model supports the prediction of Munson *et al.* that the relative rate of increase of the alveolar or arterial blood halothane concentration during controlled ventilation increases with increasing inspired concentrations of halothane, but that just the opposite occurs during spontaneous ventilation.² However, the late, relatively steady-state values found after 30 min during spontaneous ventilation (fig. 2) are lower than those predicted by his model. The differences between models are probably due to a variable that is a function of halothane concentration, rather than to the initial (awake) parameters, since the differences are negligible at low inspired concentrations of halothane and increase with increasing inspired concentrations. The explanation could lie in at least three factors, two of

which are probably minor. 1) We allowed cardiac output to change, while Munson's model kept it constant. During induction with spontaneous ventilation and either 2 per cent¹ or 4 per cent (fig. 4) halothane, cardiac output changed very little, suggesting that cardiac output plays only a small role in the differences. 2) The differences could be due to the changes in regional blood flow distribution³⁻⁵; we permitted them to occur, but Munson *et al.* did not.² Again, this probably represents a small influence. 3) The most likely explanation lies in the modulation of ventilation by halothane. Munson's model used the mean cerebral concentration of halothane to modulate ventilation, while we used cerebral gray matter concentration. The uptake of halothane into the latter compartment is considerably more rapid (fig. 4 in reference 1). The differences between the two compartments are still large at 90 min, and noticeable at 120 min. Thus, an earlier and speedier depression of ventilation, and thus a slower uptake into the lungs, both initially and throughout the anesthetic course, are seen in our model. The greater the inspired concentration, the greater the depression of ventilation in our model, and the greater the difference between the two models.

The differences in circulatory responses to halothane produced by the two modes of ventilation are strikingly demonstrated in figures 4 and 5. In general, the early changes are very slightly slower during spontaneous ventilation. As anesthesia progresses with controlled ventilation, circulatory depression continuously increases, while during spontaneous ventilation, the circulatory variables either stabilize or actually improve.

In the companion paper,¹ we discussed the similarity between the early changes in cerebral blood flow (CBF) in our model and in goats studied by Albrecht *et al.*⁶ It was pointed out that, except for the final, steady-state values, the courses of events were similar in the two studies, even though ventilation was controlled in our model and spontaneous in their goats. The similarities between CBF changes demonstrated by our model and their studies are even greater with spontaneous ventilation. One would predict from figure 3 that, with 4 per cent inspired halothane, any differences between controlled and spontaneous ventilation would be magnified, particularly later in the course of a study. (We used 4 per cent inspired halothane in our model comparison of controlled and spontaneous ventilation because the differences were easier to see in a reduced illustration.)

The partial pressures of CO₂ shown in figure 6 are particularly interesting. Notice that while the anticipated increases in arterial blood, venous blood, and cerebral CO₂ are seen during spontaneous ventilation, CO₂ tensions in arterial blood and brain actually decrease during controlled ventilation. The decrease in

the brain is due to decreased CO₂ production during exposure to halothane, with constant elimination via the lungs and more than enough circulation to carry CO₂ away from the tissues. The decrease in arterial blood CO₂ stems from the decreases in production in the tissues and delivery to the lungs, the latter brought about by decreased venous return. The nearly steady vena caval P_{CO₂} confirms this explanation. The ability to demonstrate phenomena such as this is another unique feature of the model.

Finally, we can list some uses for such a model, both realized and potential. The former include teaching; developing further insight into drug action; predicting actions of new drugs, even before their testing in animals; setting up automatic control systems[§]; and "guiding" an automatic control system, in an *adaptive* system.^{**} The potential uses include a Link-type simulator for training anesthetists, a clinical examination system for educational testing organizations, a device for quantifying the clinical progress of trainees, and a new-generation monitor, which could estimate difficult-to-measure variables from easy-to-measure ones (parameter estimation). The simulator-trainer could simulate standardized emergency situations.

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