

The Effects of Changes in Cardiac Output and Distribution on the Rate of Cerebral Anesthetic Equilibration

Calculations Using a Mathematical Model

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The effects of alterations in cardiac output produced by differential distribution of tissue blood flow on the rates of rise of arterial and cerebral anesthetic partial pressures have been predicted using a mathematic model. Calculations show that circulatory changes associated with circulatory shock and excitement increase and decrease these rates of rise, respectively. The effects of changes in distribution of tissue blood flow are greatest with the more soluble anesthetics. The actual effects are probably much greater than predicted from models which assume that changes in cardiac output are produced by proportionately equal changes in blood flow to all tissues.

ANESTHESIA results from the development of an adequate cerebral partial pressure of anesthetic. This partial pressure is thought to follow closely the alveolar (arterial) partial pressure.¹⁻³ The effects of changes in cardiac output on the development of the arterial partial pressure have been predicted, but these predictions generally have assumed that changes in output were equally (proportionately) distributed among all tissues.²⁻⁴ This is an oversimplification. States of altered cardiac output, such as circulatory shock or excitement, may spare or increase flow to particular tissues relatively, that is, blood flow in tissues may be affected differentially. In shock, blood flow to brain may not be decreased as much as flow

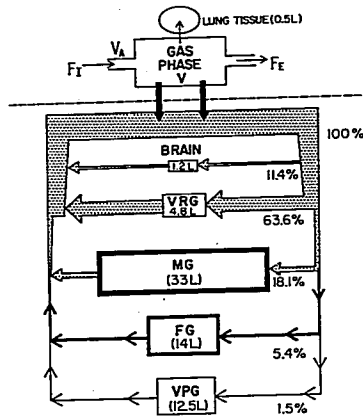


FIG. 1. Schematic of the mathematical model. The lung (V), alveolar ventilation (V_A), inspired (F_I) and alveolar (F_E) concentrations (partial pressures) are shown above the dashed line (alveolar-capillary membrane). The various body compartments are indicated (see text). Percentage figures refer to the normal distribution of cardiac output (see table 1). (Reprinted from E. S. Munson, M.D., and D. L. Bowers: Effects of hyperventilation on the rate of cerebral anesthetic equilibration, *ANESTHESIOLOGY* 28: 377, 1967.)

to other tissues. In excitement, as in exercise, muscle blood flow may be increased markedly while flow to other tissues remains unchanged. Through the use of a mathematical analog we examined the effects of proportional as opposed to differential changes in tissue blood flow on the rise of arterial and cerebral partial pressures of anesthetic.

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Method

Calculations of anesthetic uptake and distribution were made with a mathematical model patterned after Mapleson,⁵ Severinghaus⁶ and Eger.⁷ A diagram of the model is shown in figure 1. Anesthetic input in the gaseous phase is maintained at a constant inspired partial pressure. The blood volume is divided in proportion to the perfusion of the various tissues. The body is divided into compartments which are grouped according to blood flow per unit mass and/or by solvent characteristics. Five groups result: brain; the vessel-rich group (VRG), which includes heart, liver, and kidney; the muscle group (MG); the fat group (FG); and the vessel-poor group (VPG). A detailed description of the model and the equations representing uptake by the various body compartments may be found in a previous publication.¹ Mathematical calculations were performed with a Burroughs 5500 digital computer. Arterial and cerebral partial pressures of anesthetic were printed on a Cal-Comp plotter.[§]

Cyclopropane, halothane and methoxyflurane were selected as anesthetics representative of low, moderate and high solubility in tissues. The solubility characteristics of these drugs in human blood and tissues have been described.⁷⁻⁹ Arterial and cerebral anesthetic

partial pressures were calculated at cardiac outputs of 2.5, 5 and 10 liters per minute, as representing reasonable approximations of the conditions existing in circulatory shock, the normal resting state, and excitement. Alveolar ventilation was maintained constant at 4 liters per minute in all calculations. Two distributions were considered (table 1). In one, all changes in tissue perfusion were *proportional*, that is, if cardiac output were halved, this was accomplished by halving all tissue blood flows; if cardiac output were doubled, all tissue blood flows were doubled. This has been assumed in previous reports.²⁻⁴ In the second case, changes in cardiac output were achieved by *differential* changes in blood flow.¹⁰ For example, if shock were simulated by halving total cardiac output, the absolute blood flow to brain was unaltered while flows to muscle and fat were more than halved ($\frac{1}{2}$ and $\frac{1}{3}$, respectively). Similarly, during excitement, cardiac output was doubled by increasing blood flow to muscle and fat (six- and two-fold, respectively) while flow to brain and the VRG was unaltered.

Results and Discussion

SHOCK

Ventilation brings anesthetic into the lung and causes the alveolar (arterial) partial pressure of anesthetic to rise. Uptake in pulmonary capillary blood removes anesthetic from

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TABLE 1. Distribution of Blood Flow with Normal and Altered Cardiac Output

Tissue Volumes	Blood Flow to the Various Tissue Groups					
	Normal (control)	Altered				
		Proportional		Differential ^a		
		Shock	Excitement	Shock	Excitement	
Curves	C	SP	EP	SD	ED	
Cardiac output	5	2.5	10	2.5	10	
Brain	1.2	0.57	0.26	1.14	0.57	0.57
Vessel-rich group	4.8	3.18	1.59	6.36	1.59	3.18
Muscle group	33	0.90	0.45	1.80	0.30	5.55
Fat group	14	0.27	0.14	0.54	0.03	0.54
Vessel-poor group	12.5	0.08	0.04	0.16	0.01	0.16

Tissue volumes = liters. Blood flow = liters/minute. Curves shown in figures 2-5 are identified as follows: C = control; SP = shock, proportional; SD = shock, differential; EP = excitement, proportional; and ED = excitement, differential.

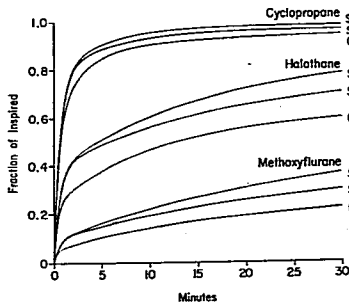


FIG. 2. Rate of rise of the alveolar (arterial) partial pressure of anesthetic plotted as a fraction of the inspired partial pressure for each agent. Alveolar ventilation is maintained constant at 4 liters/minute in all calculations. Curves represent arterial partial pressure when cardiac output is 5 liters/minute and distribution normal (C), output 2.5 liters/minute and tissue flow reduced proportionately (SP) and differentially (SD) (see table 1).

the lung and thus opposes or limits the rise produced by ventilatory input. As previously predicted by others^{4,11} the reduction in cardiac output found in shock reduces uptake. Since anesthetic removal from the alveoli is reduced, arterial partial pressure is permitted to rise more rapidly (curves SP and SD versus C, fig. 2). However, proportionate reduction of flow to all tissues (SP curves, fig. 2) leads to a considerably different picture than if the decrease in flow is greater in muscle and fat, and does not occur in brain (SD curves, fig. 2). Initially, curves SP and SD rise together because the returning venous blood at this point contains no anesthetic and uptake is simply a function of cardiac output, identical for both curves. Uptake beyond 1-2 minutes is increased when flow to muscle and fat is greater (*i.e.*, curve SP). The resultant arterial curve is therefore lower than curve SD, where flow to these large tissue depots is much more restricted. Although this difference is found with all anesthetics, it is proportionately greater with those that are more soluble. For example, at 30 minutes, curve SP is 98 per cent as high as curve SD for cyclopropane, 90 per cent for halothane, and 81 per cent for methoxyflurane. The arterial partial pressure achieved

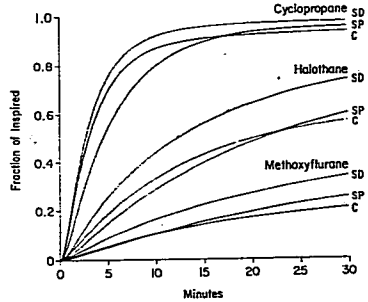


FIG. 3. Rate of rise of the cerebral partial pressure of anesthetic plotted as a fraction of the inspired partial pressure for each agent. The shapes and positions of these curves are similar to their corresponding arterial curves in figure 2. The identifying legends are the same. Note that the rate of rise of cerebral anesthetic is markedly accelerated with differential reduction in output (SD). This effect is greater with the more soluble anesthetics.

is important because it is the limit for the approach of partial pressures in all tissues. Thus, the diversion of flow to vital tissues in shock (as opposed to proportional reduction in flow) makes the more soluble agents capable of producing a more rapid and profound anesthesia if the agent is administered at "normal" concentrations.

The above considerations are also pertinent to the rate of rise of cerebral partial pressure of anesthetic (fig. 3). If flow to brain is reduced proportionately with other tissues, the rate of rise of cerebral partial pressure of anesthetic is delayed. In this situation, the initial rate of rise (SP curves) equals (methoxyflurane) or is less than (halothane, cyclopropane) that occurring normally (C curves), despite the higher alveolar partial pressure of anesthetic found in shock. However, if flow to brain in shock is preserved at the expense of other tissues (SD curves), then the rate of rise of partial pressure of anesthetic in brain is increased above normal and induction of anesthesia is accelerated. As with alveolar rate of rise, the effect is greatest with the more soluble agents. For example, if induction with cyclopropane normally is achieved in five minutes (*i.e.*, with cerebral partial pressure at 70

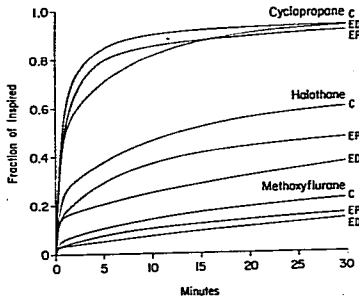


FIG. 4. Rate of rise of the arterial anesthetic partial pressure plotted as a fraction of the inspired partial pressure for each agent. Curves represent arterial partial pressure when output is 5 liters/minute and distribution normal (C), output 10 liters/minute and tissue flow distribution increased proportionately (EP) and differentially (ED).

per cent of inspired), then in shock and differential decreases in blood flow (fig. 3, SD curve) the same cerebral partial pressure is reached in a little more than four minutes, or 83 per cent of the time normally taken. If induction with halothane normally requires five minutes, then shock reduces induction time to 70 per cent of normal; with methoxyflurane the figure is 62 per cent.

In reality the model apparently does not depict either of the extremes of proportional or differential changes in flow.¹² In shock there is reduction in flow to all tissues. Blood flow to brain is not spared, although it is reduced less than flow to less vital tissues. Therefore, the rise of arterial and cerebral partial pressures of anesthetic in shock probably lies somewhere between the two courses described above (SP and SD curves).

EXCITEMENT

The increase in cardiac output and anesthetic uptake that accompanies excitement slows the rise in arterial partial pressure of anesthetic (fig. 4, curves EP and ED versus C), in agreement with predictions by previous workers.⁴⁻¹¹ However, the distribution of the increased flow is also of importance. If blood flow is increased proportionately to all tissues (EP curves) then the arterial rise is retarded less (at least during the first 15 minutes) than

the rise found when muscle flow alone is increased (ED curves). This results from the great capacity of muscle for anesthetic. The greater the diversion of blood to muscle, the greater the uptake and the lower the arterial partial pressure of anesthetic. As in shock, the more soluble the anesthetic the greater the influence of differential as opposed to proportional changes in flow. The early effect of a differential increase in muscle flow on the halothane curves is less, but close to that seen with methoxyflurane. This similarity, despite the dissimilarity of the blood solubilities, results from the high muscle/blood partition coefficient of halothane (3.5⁶) which compensates for the lower blood solubility.

The rise in cerebral partial pressure of anesthetic follows that in the blood (fig. 5). However, if cerebral blood flow is increased (EP curves), this produces the closest approach of brain to arterial partial pressure. In the first few minutes of anesthesia, this compensates for the lower arterial partial pressures seen with proportionate increase in cardiac output. The result is that, during this time, the normal (C) and excitement (EP and ED) curves overlap and, in fact, with cyclopropane the cerebral curve in excitement exceeds the normal curve.

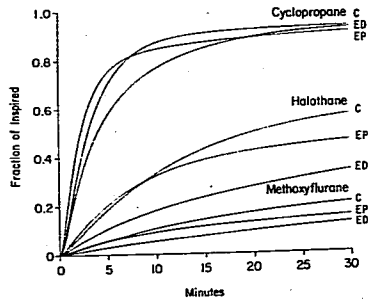


FIG. 5. Rate of rise of the cerebral anesthetic partial pressure plotted as a fraction of the inspired partial pressure for each agent. The shapes and positions of these curves are similar to the corresponding curves in figure 4. The identifying curve legends are the same. Note that the rate of rise of cerebral anesthetic is always slower than normal with differential increase in flow (ED). As observed in shock (fig. 3) this effect is greater with the more soluble anesthetics.

This is not the case when a differential increase in blood flow occurs. If the additional flow goes principally to muscle, then excitement produces a cerebral anesthetic rise which is always slower than normal (curves ED versus C). The difference between these curves parallels the difference seen among the arterial curves. As with the arterial curves the difference is greatest with the more-soluble inhalation anesthetics.

The design of the mathematical model for the simulation of drug uptake and distribution is based on many assumptions.¹³ The model considers variables such as ventilation, cardiac output, and tissue flows as linear (static) parameters. In reality, these values may change during the progress of anesthesia and furthermore, the effects of anesthesia may alter the sensitivity of ventilatory and circulatory responses. Increase in alveolar ventilation which might accompany early shock or excitement would tend to accelerate further the rate of rise of arterial and cerebral anesthetic. Despite these limitations, our predictions of cerebral anesthetic equilibration have obvious clinical implications. For example, in shock induction of anesthesia with "normal" inspired concentrations of anesthetic would produce a more rapid and relatively deeper level of anesthesia. Likewise, in excitement induction of anesthesia would be delayed unless the usual inspired concentrations were increased. This would be particularly applicable to young patients in whom induction of anesthesia may be associated with crying and increased muscular activity. Similar situations would include febrile and hypermetabolic states.¹⁴ The effects of changes in distribution of tissue flow are greatest with the more soluble anesthetic agents. Our calculations suggest that in these circumstances the least variable, and hence most predictable, induction of anesthesia is obtained with a less soluble anesthetic such as cyclopropane.

Summary

The effects of alterations in cardiac output produced by differential tissue distribution on the rate of rise of arterial and cerebral anesthetic partial pressures have been predicted using a mathematical model. Calculations show that the circulatory changes associated

with shock and excitement increase and decrease these rates of rise, respectively. The effects of changes in distribution of tissue blood flow on rise in arterial and brain partial pressure are greatest with the more soluble anesthetics. These effects are probably much greater than predicted from models which assume that changes in cardiac output are produced by proportionately equal changes in blood flow to all tissues.

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