• Miller-Volatile Agents (+Eger's Tutorial on Pharmacokinetics of Volatile Agents (from CD))

INTRODUCTION

The modern anesthetist expeditiously develops and then sustains a brain anesthetic concentration sufficient for surgery, doing so with agents and techniques that usually permit a rapid recovery from anesthesia. Producing an adequate brain anesthetic concentration for surgery requires sufficient anesthetic delivery to the patient that does not impose excessive depression. Knowledge of the factors that govern the relationship between the delivered and brain (or heart or muscle) concentrations is indispensable to the optimum conduction of anesthesia.

THE INSPIRED TO ALVEOLAR ANESTHETIC RELATIONSHIP

Of the steps between delivered and brain anesthetic partial pressures, none is more pivotal than that between the inspired and alveolar gases. The alveolar partial pressure governs the partial pressures of anesthetic in all body tissues: all must approach and ultimately equal the alveolar partial pressure. By use of high inflow rates (and hence conversion to a nonrebreathing system), the anesthetist can precisely control the partial pressure of anesthetic that is inspired.

The Effect of Ventilation

Two factors determine the rate at which the alveolar concentration of anesthetic (FA) rises toward the concentration being inspired (FI): the inspired concentration (see **The Concentration Effect**) and alveolar ventilation. Ventilation exerts a powerful effect. On induction, the unopposed effect of ventilation rapidly increases the alveolar concentration (i.e., FA/FI quickly approaches 1). This occurs with preoxygenation to achieve high alveolar concentrations of oxygen. Normally, a 95 percent or greater washin of oxygen occurs in 2 minutes or less when a nonrebreathing (or high inflow rate) system is used **(Fig. 4–1)**.

FIGURE 4–1 The washin of oxygen was determined in two patients breathing from a mask. Note that a 63% change is obtained in about a half minute, an 86% change in about a minute, and a 95– 98% change in 2 minutes. (From Eger [unpublished data])

However, inhaled anesthetics do not mimic the rapid washin of oxygen. The solubility of anesthetics is far higher than that of oxygen (or nitrogen), and the higher solubility causes the transfer of substantial quantities of anesthetic to the blood passing through the lung. This uptake opposes the effect of ventilation to increase the alveolar anesthetic concentration. At low inspired concentrations, the FA/FI ratio is ultimately determined by the balance between the delivery of anesthetic by ventilation and its removal by uptake. The relationship is a simple one. For example, if uptake removes one-third of the inspired anesthetic molecules, FA/FI equals two-thirds; if uptake removes two-thirds of the inspired molecules, FA/FI equals one-third.

Anesthetic Uptake Factors

Anesthetic uptake itself is the product of three factors: solubility (?), cardiac output (Q), and alveolar to venous partial pressure difference (PA–PV). **1** That is:

Uptake = (?) X (Q) X (PA–PV) divided by barometric pressure

The fact that uptake is a product of the three factors rather than a sum means that if any factor approaches zero, uptake must approach zero, and ventilation is free to rapidly drive the alveolar concentrations upward. Thus, if solubility is small (as in the case of oxygen), if cardiac output approaches zero (as in profound myocardial depression or death), or if the alveolar to venous difference becomes inconsequential (as might occur after an extraordinarily long anesthetic), uptake would be minimal, and FA/FI would quickly equal 1.

Solubility

The blood/gas partition coefficient (?, or "blood solubility") describes the relative affinity of an anesthetic for two phases and hence how that anesthetic partitions itself between the two phases when equilibrium has been achieved. For example, isoflurane has a blood/gas partition coefficient of 1.4, indicating that at equilibrium, isoflurane's concentration in blood is 1.4 times its concentration in the gas (alveolar) phase. "Equilibrium" means that no difference in partial pressure exists (i.e., a blood/gas partition coefficient of 1.4 does not indicate that the partial pressure in blood is 1.4 times that in the gas phase). The partition coefficient may be thought of in another way—it indicates the relative capacity of the two phases. Thus, a value of 1.4 means that each milliliter of blood holds 1.4 times as much isoflurane as a milliliter of alveolar gas.

A larger blood/gas partition coefficient produces a greater uptake and hence a lower FA/FI ratio. Because the anesthetic partial pressure in the alveoli is transmitted to the arterial blood and thence to all tissues (especially the brain), the development of an adequate brain anesthetic partial pressure may be delayed in the case of highly blood-soluble agents, such as ether and methoxyflurane **(Table 4–1)** **1** . Indeed, the delay in development of an anesthetizing cerebral partial pressure contributed to the elimination of such highly blood-soluble agents from anesthetic practice. Even the moderate solubility of enflurane, isoflurane, or halothane would slow induction of anesthesia with these agents were it not for the use of anesthetic overpressure—that is, we compensate for the uptake of anesthetic by delivering a higher concentration than we hope to achieve in the alveoli. For example, on induction of anesthesia, we may use 4 to 5 percent halothane to produce an alveolar concentration of 1 percent. The use of overpressure can eliminate differences among anesthetics that otherwise would result as a consequence of differences in solubility. For example, induction of anesthesia with 5 percent halothane is essentially as rapid as induction with 8 percent sevoflurane, despite a nearly fourfold greater solubility of halothane. **2**

TABLE 4–1. Partition Coefficients at 37°C

Cardiac Output

The effect of altering cardiac output is intuitively obvious. A greater passage of blood through the lungs removes more anesthetic and thereby lowers the alveolar anesthetic concentration. To the beginning student of uptake and distribution, this may appear to produce a conflict. It would seem that if more agent were taken up and delivered more rapidly to the tissues, the tissue anesthetic partial pressure should rise more rapidly. In one sense this is true: an increase in cardiac output does hasten the equilibration of tissue anesthetic partial pressure with the partial pressure in arterial blood. **3** What this reasoning ignores is the fact that the anesthetic partial pressure in arterial blood is lower than it would be if cardiac output were normal.

The effect of a change in cardiac output is analogous to the effect of a change in solubility. As already noted, doubling solubility doubles the capacity of the same volume of blood to hold anesthetic. Doubling cardiac output also would double capacity, but in this case by increasing the volume of blood exposed to anesthetic.

The Alveolar to Venous Anesthetic Gradient

The alveolar to venous anesthetic partial pressure difference results from tissue uptake of anesthetic. Were there no tissue uptake, the venous blood returning to the lungs would contain as much anesthetic as it had when it left the lungs as arterial blood. That is, the alveolar (which equals arterial) to venous partial pressure difference would be zero. The presumption that alveolar and arterial anesthetic partial pressures are equal is reasonable in normal patients who have no barrier to diffusion of anesthetic from alveoli to pulmonary capillary blood and who do not have ventilation/perfusion ratio abnormalities. Later, we shall consider the effect of ventilation/perfusion ratio abnormalities on anesthetic uptake.

The factors that determine the fraction of anesthetic removed from blood traversing a given tissue parallel the factors that govern uptake at the lungs: tissue solubility, tissue blood flow, and arterial to tissue anesthetic partial pressure difference. Again, uptake is the product of these three factors. If any one factor approaches zero, uptake by that tissue becomes inconsequential. The succeeding paragraphs discuss the characteristics of each of these factors and then how uptake by individual tissues can be summed to give the venous component of the alveolar to venous anesthetic partial pressure difference.

Blood/gas partition coefficients span a range of values extending from 0.45 for desflurane to 15 for methoxyflurane (see **Table 4–1**). In contrast, tissue/blood partition coefficients (i.e., tissue solubility) for lean tissues are close to 1, ranging from slightly less than 1 to a maximum of 3.4 (see **Table 4–1**) —that is, different lean tissues do not have greatly different capacities per milliliter of tissue. Put another way, a given anesthetic has roughly the same affinity for lean tissues and blood. As with blood/gas partition coefficients, tissue/blood partition coefficients define the concentration ratio of anesthetic at equilibrium. For example, a halothane brain/blood partition coefficient of 1.9 means that 1 mL of brain can hold 1.9 times as much halothane as 1 mL of blood having the same halothane partial pressure.

Lean tissues differ in the volume of tissue relative to the volume of blood passing that tissue. A larger volume of tissue relative to flow has two implications. First, the large tissue capacity increases the transfer of anesthetic from blood to tissue. Second, it takes longer to fill up a tissue with a large capacity (i.e., it takes longer for the tissue to equilibrate with the anesthetic partial pressure being delivered in arterial blood). That is, a large tissue volume relative to blood flow sustains the arterial to tissue anesthetic partial pressure difference (and hence uptake) for a longer time. With its high perfusion per gram, brain equilibrates rapidly with the anesthetic partial pressure brought to it in arterial blood. Per milliliter of tissue, muscle has about one-twentieth the perfusion of brain, and thus muscle takes about 20 times as long as brain to equilibrate. Uptake of anesthetic by muscle continues long after uptake by brain has ceased.

Fat has a tissue/blood coefficient that is significantly greater than 1, particularly for more potent anesthetics (see **Table 4–1**). Fat/blood coefficients range from 2.3 (nitrous oxide) to 51 (halothane) to 61 (methoxyflurane). That is, each milliliter of fat tissue contains 2.3 times more nitrous oxide or 51 times as much halothane than a milliliter of blood having the same nitrous oxide or halothane partial pressure. This enormous capacity of fat for anesthetic means that most of the anesthetic contained in the blood perfusing fat is transferred to the fat. Although most of the anesthetic moves from the blood that perfuses fat into the fat, the anesthetic partial pressure in that tissue rises very slowly. Both the large capacity of fat and the low perfusion per milliliter of tissue prolong the time required to narrow the anesthetic partial pressure difference between arterial blood and fat.

Tissue Groups

The algebraic sum of uptake by individual tissues determines the alveolar to venous partial pressure difference and hence the uptake at the lungs. However, we do not need to analyze the effect of individual tissues to arrive at the algebraic sum; instead, we can group tissues in terms of their perfusion and solubility characteristics (i.e., in terms of those features that define the duration of a substantial arterial to tissue anesthetic partial pressure difference). Four tissue groups result from such an analysis **(Table 4–2**). **1**

TABLE 4–2. Tissue Group Characteristics

The vessel-rich group (VRG) is composed of the brain, heart, splanchnic bed (including liver), kidney, and endocrine glands. These organs make up less than 10 percent of the body weight but receive 75 percent of the cardiac output. This high perfusion confers several features. Access to a large flow of blood permits the VRG to take up a relatively large volume of anesthetic in the earliest moments of induction. However, the small volume of tissue relative to perfusion produces a rapid equilibration of this tissue group with the anesthetic delivered in arterial blood. The time to half equilibration (i.e., the time at which the VRG anesthetic partial pressure equals half that in arterial blood) varies from about 1 minute for nitrous oxide to 2 minutes for halothane. The longer time to equilibration with halothane results from its higher tissue/blood partition coefficients (see **Table 4–1**). Equilibration of the VRG with the anesthetic partial pressure in arterial blood is over 90 percent complete in 4 to 8 minutes. Thus, after 8 minutes, uptake by the VRG is too small (i.e., the arterial to VRG anesthetic partial pressure difference is too small) to significantly influence the alveolar concentration. For a substantial period after 8 minutes, uptake is principally determined by the muscle group.

Muscle and skin, which make up the muscle group, have similar blood flow and solubility (lean tissue) characteristics. The lower perfusion (about 3 mL of blood per 100 mL of tissue per minute) sets this group apart from the VRG (70 mL per 100 mL per minute). Although about half of the body bulk is muscle and skin, this volume receives only 1 L/min blood flow at rest. That is, this tissue group receives one-quarter the amount of anesthetic delivered to the VRG and initially takes up only approximately one-quarter as much anesthetic. The large bulk relative to perfusion means two things: (1) during induction, most of the anesthetic delivered to the muscle group is removed from the muscle group blood flow, and (2) the muscle group continues to remove anesthetic from its blood supply for a long time. The time to half equilibration ranges from 20 to 25 minutes (nitrous oxide) to 70 to 80 minutes (sevoflurane or halothane). Thus, long after equilibration of the VRG has taken place, muscle continues to take up substantial amounts of anesthetic. This tissue approaches equilibration in 2 to 4 hours.

Once equilibration of muscle is complete, only fat (i.e., the fat group) continues to serve as an effective depot for uptake. In a normal lean patient, fat occupies one-fifth of the body bulk and receives a blood flow of about 400 mL/min (i.e., the perfusion per 100 mL of fat nearly equals the perfusion per 100 mL of resting muscle). Thus, during the initial delivery of anesthetic to tissues, fat has access to only 40 percent of the anesthetic that is delivered to the muscle group (i.e., blood blow to the fat group is 40 percent of that to the muscle group). Fat also differs from muscle in its higher affinity for anesthetic, a property that greatly lengthens the time over which it absorbs anesthetic. The half-time to equilibration of fat ranges from 70 to 80 minutes for nitrous oxide to 30 hours for sevoflurane and halothane. Equilibration with fat does not occur in the course of an ordinary halothane or enflurane anesthetic.

One tissue group, the vessel-poor group, remains to be defined. This group consists of ligaments, tendons, bone, and cartilage (i.e., those lean tissues that have little or no perfusion). The absence of a significant blood flow means that this group does not participate in the uptake process despite the fact that it makes up one-fifth of the body mass.

Synthesis of the Factors Governing the Rise of the FA/FIRatio

We may now consider the combined impact of ventilation, solubility, and distribution of blood flow on the development of the alveolar anesthetic partial pressure. The initial rate of rise of FA/FI is rapid for all agents, regardless of their solubility **(Fig. 4–2)** **4**, **5** . The rapidity of this upswing results from the absence of an alveolar to venous anesthetic partial pressure difference (there is no anesthetic present in the lung to create a gradient) and hence

the absence of uptake in the first moment of induction. Thus, the effect of ventilation to generate a sudden rise in FA/FI is unopposed. Obviously, delivery of more and more anesthetic to the alveoli by ventilation produces a progressively greater alveolar to venous partial pressure difference. The resulting increase in uptake increasingly opposes the effect of ventilation to drive the alveolar concentration upwards. Ultimately, a rough balance is struck between the input by ventilation and the removal by uptake. The height of the FA/FI ratio at which the balance is struck depends on the solubility factor in the uptake equation (see equation for anesthetic uptake, earlier). A higher solubility produces a greater uptake for a given alveolar to venous partial pressure difference. Hence, the initial rapid rise in FA/FI is halted at a lower level with a more soluble agent. This results in the first "knee" in the curve—higher for desflurane than for sevoflurane, higher for sevoflurane than for isoflurane, and higher for isoflurane than for halothane. The position of nitrous oxide is discussed later (see **The Concentration Effect**).

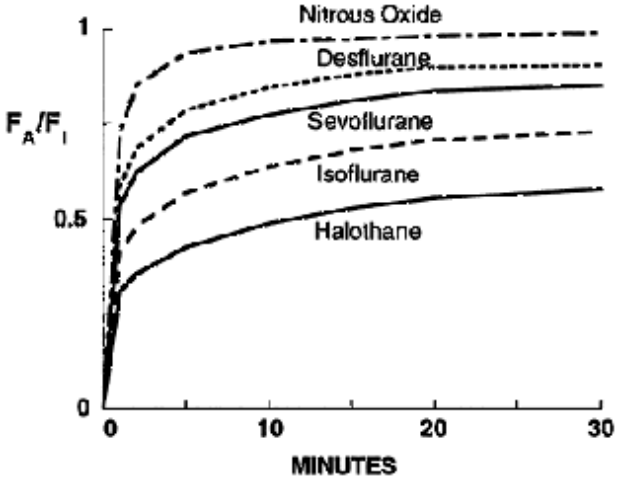


FIGURE 4–2 The rise in alveolar (FA) anesthetic concentration toward the inspired (FI) concentration is most rapid with the least soluble anesthetics, nitrous oxide and desflurane, and slowest with the most soluble anesthetic, halothane. All data are from human studies. (Data from Yasuda et al**1,** ,**5**)

The balance struck between ventilation and uptake does not remain constant. FA/FI continues to rise, albeit at a slower rate than seen in the first minute. This rise results from the progressive decrease in uptake by the VRG, a decrease to an inconsequential amount after 8 minutes. Thus, by about 8 minutes, three-quarters of the cardiac output returning to the lungs (i.e., the blood from the VRG) contains nearly as much anesthetic as it had when it left the lungs. The consequent rise in venous anesthetic partial pressure decreases the alveolar to venous partial pressure difference and hence the uptake, allowing ventilation to drive the alveolar concentration upward to the second knee at roughly 8 minutes.

With the termination of effective uptake by the VRG, muscle and fat become the principal determinants of tissue uptake. The slow rate of change of the anesthetic partial pressure difference between arterial blood and muscle or fat produces the relatively stable terminal portion of each curve in **Figure 4–1** . In fact, this terminal portion gradually ascends as muscle and, to a lesser extent, fat progressively equilibrate with the arterial anesthetic partial pressure. If the graphs were extended for several hours, a third knee would be found that indicates equilibration of the muscle group. Uptake after that time would principally depend on the partial pressure gradient between arterial blood and fat.

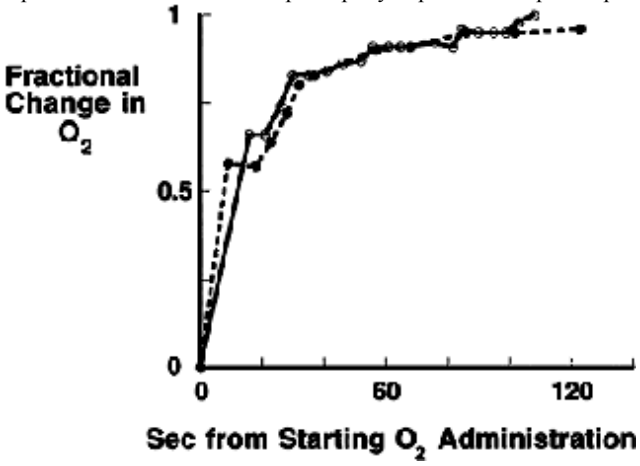


FIGURE 4–1 The washin of oxygen was determined in two patients breathing from a mask. Note that a 63% change is obtained in about a half minute, an 86% change in about a minute, and a 95– 98% change in 2 minutes. (From Eger [unpublished data])

The Concentration Effect

The aforementioned analysis ignores the impact of the concentration effect on FA/FI. The inspired anesthetic concentration influences both the alveolar concentration that may be attained and the rate at which that concentration may be attained. **6**, **7** Increasing the inspired concentration accelerates the rate of rise. At an inspired concentration of 100 percent, the rate of rise is extremely rapid because it is dictated solely by the rate at which ventilation washes gas into the lung; that is, at 100 percent inspired concentration, uptake no longer limits the level to which FA/FI may rise. The cause of this extreme effect is readily perceived. At 100 percent inspired concentration, the uptake of anesthetic creates a void, which draws gas down the trachea. This additional inspiration replaces the gas taken up. Because the concentration of the replacement gas is 100 percent, uptake cannot modify the alveolar concentration. This explains why the rise of nitrous oxide shown in **Figure 4–2** is more rapid than the rise of desflurane, despite the identity of their blood/gas partition coefficients.

FIGURE 4–2 The rise in alveolar (FA) anesthetic concentration toward the inspired (FI) concentration is most rapid with the least soluble anesthetics, nitrous oxide and desflurane, and slowest with the most soluble anesthetic, halothane. All data are from human studies. (Data from Yasuda et al**1,** ,**5**)

The concentration effect results from two factors, a concentrating effect and an augmentation of inspired ventilation. **8** Both are illustrated in **Figure 4–3** . The first rectangle represents a lung containing 80 percent nitrous oxide. If half of this gas is taken up, the residual 40 volumes of nitrous oxide exist in a total of 60 volumes, yielding a concentration of 67 percent **Figure 4–3** A. That is, uptake of half the nitrous oxide does not halve the concentration, because the remaining gases are "concentrated" in a smaller volume. If the void created by uptake is filled by drawing more gas into the lungs (an augmentation of inspired ventilation), the final concentration equals 72 **Figure 4–3** B.

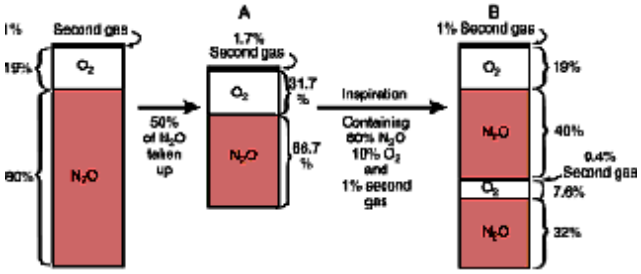


FIGURE 4–3 The rectangle to the left represents a lung filled with 80% nitrous oxide plus 1% of a second gas. (A) Uptake of half the nitrous oxide does not halve the concentration of nitrous oxide, and the reduction in volume thereby increases the concentration of the second gas. (B) Restoration of the lung volume by addition of gas at the same concentration as that contained in the left-most rectangle will increase the nitrous oxide concentration and add to the amount of the second gas present in the lung. (Modified from Stoelting and Eger**8**)

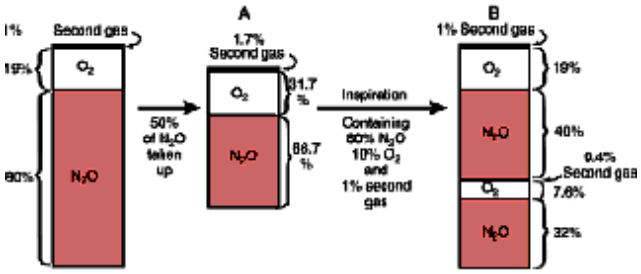
This explanation has been criticized as overly simplistic, as ignoring the realities of some aspects of ventilation. **9** For example, if ventilation is controlled with a volume-limited respirator, an augmentation in inspired ventilation is limited to the period of the expiratory pause. If ventilation is spontaneous, this limitation is minimized. In any event, the reader needs to be aware that although **Figure 4–3** describes the basic factors governing the concentration (and second gas effects—see later), the actual situation is more complex.

The impact of the concentration effect on FA/FI may be thought of as identical to the impact of a change in solubility **10** ; as the inspired concentration increases, the effective solubility decreases. Thus, at 50 percent inspired nitrous oxide, the FA/FI rises as rapidly as the FA/FI of an anesthetic that has half the solubility of nitrous oxide and is given at 1 percent inspired concentration, and 75 percent inspired nitrous oxide acts as does an anesthetic given at 1 percent that has one-quarter the solubility of nitrous oxide.

The Second Gas Effect

The factors that govern the concentration effect also influence the concentration of any gas given concomitantly. **8**, **11** This second gas effect applies to halothane or enflurane when it is administered with nitrous oxide. The loss of volume associated with the uptake of nitrous oxide concentrates the halothane or enflurane (see **Fig. 4–3** A). Replacement of

the gas taken up by an increase in inspired ventilation augments the amount of halothane or enflurane present in the lung (see **Fig. 4–3** B).



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Both the concentration effect and the second gas effect were demonstrated by the following experiments. **11** Dogs were given 0.5 percent halothane in either 10 percent nitrous oxide or 70 percent nitrous oxide. The FA/FI for nitrous oxide rose more rapidly when 70 percent nitrous oxide was inspired than when 10 percent was inspired (the concentration effect) **(Fig. 4–4)**. Similarly, the FA/FI ratio for halothane rose more rapidly when 70 percent nitrous oxide was inspired than when 10 percent was inspired (second gas effect).

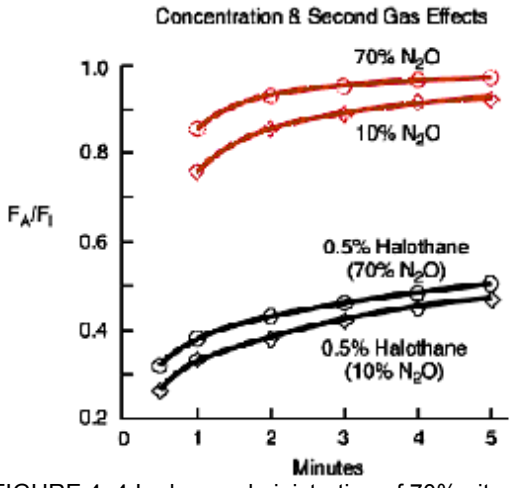


FIGURE 4–4 In dogs, administration of 70% nitrous oxide produces a more rapid rise in the FA/FI ratio of nitrous oxide than administration of 10% (concentration effect, upper two curves). The FA/FI ratio for 0.5% halothane rises more rapidly when given with 70% nitrous oxide than when given with 10% (second gas effect, lower two curves). (Modified from Epstein et al**11**)

FACTORS MODIFYING THE RATE OF RISE OF FA/FI

Alteration of those factors that govern the rate of delivery of anesthetic to the lungs or its removal from the lungs alters the alveolar concentration of anesthetic. We have seen the importance of differences in solubility (see **Fig. 4–2)**. The succeeding sections examine the impact of differences in ventilation and circulation and the interaction of these differences with factors such as solubility.

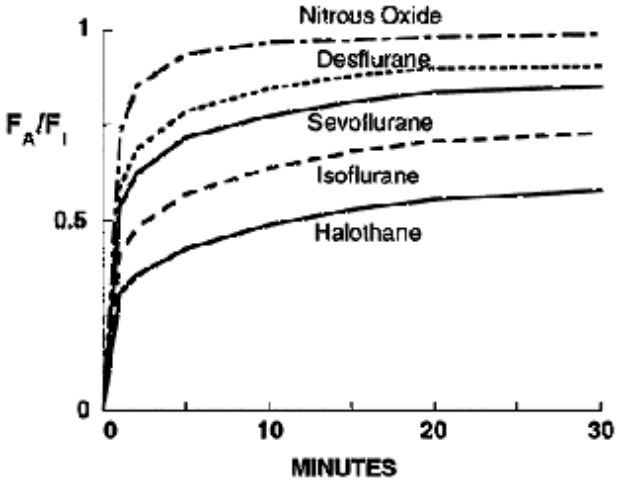


FIGURE 4–2 The rise in alveolar (FA) anesthetic concentration toward the inspired (FI) concentration is most rapid with the least soluble anesthetics, nitrous oxide and desflurane, and slowest with the most soluble anesthetic, halothane. All data are from human studies. (Data from Yasuda et al**1,** ,**5**)

The Effect of Ventilatory Changes

By augmenting delivery of anesthetic to the lungs, an increased ventilation accelerates the rate of rise of FA/FI**1**, **25 (Fig. 4–5)**. A change in ventilation produces a greater relative change in FA/FI with a more soluble anesthetic. In **Figure 4–5**, an increase in ventilation from 2 to 8 L/min triples the ether concentration at 10 minutes, only doubles the halothane concentration, and scarcely affects the nitrous oxide concentration.

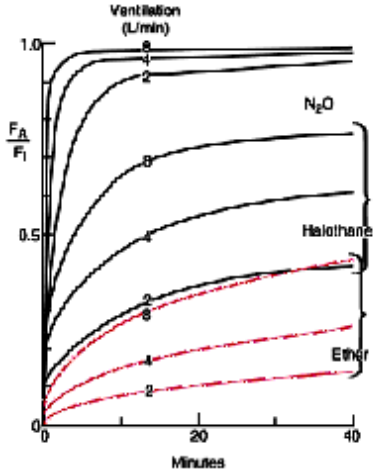


FIGURE 4–5 The FA/FI ratio rises more rapidly if ventilation is increased. Solubility modifies this impact of ventilation: the effect on the anesthetizing partial pressure is greatest with the most soluble anesthetic (ether) and least with the least soluble anesthetic (nitrous oxide). (Modified from Eger**90**)

The impact of solubility may be explained as follows. With a poorly soluble agent, such as nitrous oxide, the rate of rise of FA/FI is rapid, even with hypoventilation. Because FA normally cannot exceed FI, there is little room for an augmentation of ventilation to increase FA/FI. With a highly soluble agent, such as ether and methoxyflurane, most of the anesthetic delivered to the lungs is taken up, so that if the uptake at 2 L/min ventilation equaled X, the uptake at 4 L/min would approach 2X. Thus, if cardiac output is held constant, ventilation of 4 L/min produces an arterial ether concentration that is nearly twice the concentration produced by a ventilation of 2 L/min. Because arterial and alveolar concentrations are in equilibrium, our example suggests that doubling ventilation must nearly double the concentration of a highly soluble anesthetic in lung or blood.

These observations imply that imposed alterations in ventilation (e.g., an increase produced by conversion from spontaneous to controlled ventilation) produce greater changes in anesthetic effect with more soluble agents. Because such effects include both anesthetic depth and depression of circulation, greater caution must be exercised when ventilation is augmented during anesthesia produced with a highly soluble agent.

Anesthetics themselves may alter ventilation and thereby alter their own uptake. **3**, **26** Modern potent agents (desflurane, enflurane, halothane, isoflurane, sevoflurane) are profound respiratory depressants, whose depression of ventilation is inversely related to anesthetic dose. **27**, **28**, **29**, **30**, **31** At some dose, all inhaled anesthetics probably produce apnea, a feature that must limit the maximum alveolar concentration that can be obtained if ventilation is spontaneous.

Thus, administration of an anesthetic concentration that produces significant respiratory depression progressively decreases delivery of anesthetic to the alveoli. **3**, **32** As a result, doubling the inspired concentration does not double the alveolar concentration attained at a given point in time. At high inspired concentrations, further increases in inspired concentration produce little absolute change in the alveolar concentration **(Fig. 4–6)**. Anesthetics can thereby exert a negative feedback effect on their own alveolar concentration, an effect that increases the safety of spontaneous ventilation by limiting the maximum concentration that is attained in the alveoli.

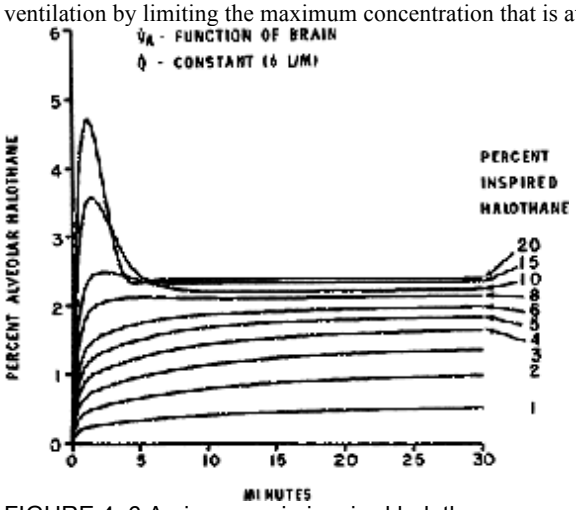


FIGURE 4–6 An increase in inspired halothane concentration does not produce a proportional increase in the alveolar concentration because of the progressively greater depression of ventilation which occurs as alveolar halothane is increased. The initial "overshoot" seen with 10 to 20% inspired halothane results from the delay in the transfer of alveolar halothane partial pressure to the brain. (From Munson et al**3**)

The Effect of Changes in Cardiac Output

The discussion in the previous section assumed a constant cardiac output and examined the effect of changes in ventilation. In this section, the reverse process is discussed. An increase in cardiac output augments uptake and thereby hinders the rise in FA/FI. **1**, **33** As with a change in ventilation, a change in cardiac output scarcely affects the alveolar concentration of a poorly soluble agent; the alveolar concentration of a highly soluble agent is much more influenced **(Fig. 4–7)**. The reason for the impact of a change in solubility is similar to the reason explaining the effect of a change in ventilation. A decrease in cardiac output can do little to increase the FA/FI ratio of a poorly soluble agent because the rate of rise is rapid at any cardiac output. In contrast, nearly all of a highly soluble agent is taken up, and a halving of blood flow through the lungs must concentrate the arterial (equals alveolar) anesthetic, nearly doubling its partial pressure in the case of an extremely soluble agent.

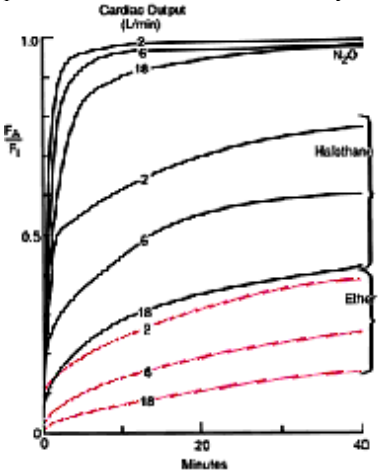


FIGURE 4–7 If unopposed by a concomitant increase in ventilation, an increase in cardiac output will decrease alveolar anesthetic concentration by augmenting uptake. The resulting alveolar anesthetic change is greatest with the most soluble anesthetic. (Modified from Eger**90**)

This effect of solubility suggests that conditions that lower cardiac output (e.g., shock) may produce unexpectedly high alveolar anesthetic concentrations if highly soluble agents are used. The higher FA/FI ratio should be anticipated and the inspired anesthetic concentration lowered accordingly to avoid further depression of circulation. Shock presents a two-pronged problem: (1) an increase in ventilation usually accompanies the circulatory depression, and (2) both an increase in ventilation and a decrease in cardiac output accelerate the rise in FA/FI. Perhaps this is why such heavy reliance is placed on the use of nitrous oxide in patients in shock. In contrast to more soluble anesthetics (e.g., halothane), the alveolar concentration of nitrous oxide would be little influenced by the associated cardiorespiratory changes.

Anesthetics also affect circulation. Usually, they depress cardiac output, **34**, **35** although stimulation may occur with some agents (e.g., nitrous oxide). In contrast to the negative feedback that results from respiratory depression, circulatory depression produces a positive feedback: depression decreases uptake, and this increases the alveolar concentration, which in turn further decreases uptake. A potentially lethal acceleration of the rise in FA/FI results from the depression of cardiac output **(Fig. 4–8)** **3**, **26**, **32** . The impact of this acceleration increases in importance with increasing anesthetic solubility. High inspired concentrations of agents such as enflurane and halothane should be administered with considerable caution, particularly if ventilation is controlled.

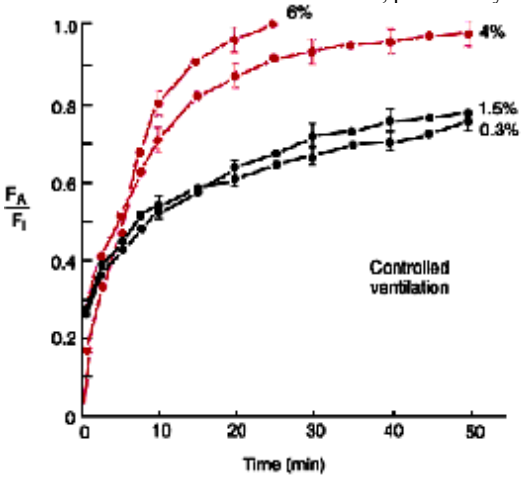


FIGURE 4–8 Dogs given a constant ventilation demonstrate different rates of rise of FA/FI. The rates of rise depend on the inspired halothane concentration. The two higher concentrations accelerated the rate of rise by depressing cardiac output and thereby decreasing uptake. (Modified from Gibbons et al**32**)

The Effect of Concomitant Changes in Ventilation and Perfusion

The preceding considerations of the effects of ventilatory and circulatory alterations presume that only one of these variables was changed while the other was held constant. In fact, both may change concomitantly. If both ventilation and cardiac output increase proportionately, an intuitive expectation might be that FA/FI would be little altered. After all, uptake equals the product of solubility, the cardiac output, and the alveolar to venous anesthetic partial pressure difference (see anesthetic uptake equation, earlier). In the absence of other changes, doubling cardiac output doubles uptake, and this should exactly balance the influence of doubling of ventilation on FA/FI. That is, a doubling of both delivery of anesthetic to the lungs and removal of anesthetic from the lungs should produce no net change in the alveolar concentration.

This reasoning ignores one other factor in the equation that defines uptake. By accelerating the rate at which tissue equilibration occurs, an increase in cardiac output accelerates the narrowing of the alveolar to venous partial pressure difference **36** and thereby reduces the impact of the increase in cardiac output on uptake. Thus, a proportional increase in ventilation and cardiac output increases the rate of rise of FA/FI.

The magnitude of the acceleration of rise in FA/FI depends in part on distribution of the increase in cardiac output. If the increase is distributed proportionately to all tissues (e.g., if a doubling of output doubles flow to all tissues), the increase is fairly small **(Fig. 4–9)** **36**, **37** . Thus, conditions such as hyperthermia and thyrotoxicosis would only slightly influence the development of an anesthetizing anesthetic concentration through their influence on FA/FI. However, if the increase in cardiac output is diverted to the VRG, a greater effect is seen. Perfusion of the VRG is

normally high and results in rapid equilibration. Further increases in perfusion only hasten the rate of equilibration. Because blood returning from the VRG soon has the same partial pressure as it had when it left the lungs, it cannot remove more anesthetic from the lungs. Thus, after a few seconds or minutes, the increase in ventilation is not matched, even in part, by an increase in uptake. The result is a considerable acceleration in the rise in FA/FI. This effect may be seen in a comparison of the FA/FI curves for children and adults **(Fig. 4–10)**. Children (especially infants) have a relatively greater perfusion of the VRG and consequently show a significantly faster rise in FA/FI **(Ch. 59**). **38** A clinical result of this accelerated rise is a more rapid development of anesthesia in young patients. The higher perfusion of the brain further accelerates the development of anesthesia.

Ventilation/Perfusion Ratio Abnormalities

Up to this point, I have assumed that alveolar and arterial anesthetic partial pressures are equal (i.e., that the alveolar gases completely equilibrate with the blood passing through the lungs). For normal patients, this assumption is approximately correct, but diseases such as emphysema and atelectasis, as well as congenital cardiac defects, produce substantial deviations from equilibration. The associated ventilation/perfusion ratio abnormality does two things: (1) increases the alveolar (end-tidal) anesthetic partial pressure and (2) decreases the arterial anesthetic partial pressure (i.e., a partial pressure difference appears between alveolar gas and arterial blood). The relative change depends on the solubility of the anesthetic. With a poorly soluble agent, the end-tidal concentration is slightly increased, but the arterial partial pressure is significantly reduced. The opposite occurs with a highly soluble anesthetic. **39**

The considerable decrease in the arterial anesthetic partial pressure that occurs with poorly soluble agents may be explained as follows. Ventilation/perfusion ratio abnormalities increase ventilation relative to perfusion of some alveoli, whereas in other alveoli, the reverse occurs. With a poorly soluble anesthetic, an increase in ventilation relative to perfusion does not appreciably increase alveolar or arterial anesthetic partial pressure issuing from those alveoli (see effect for nitrous oxide in **Fig. 4–5)**. However, when ventilation decreases relative to perfusion, a significant effect can occur, particularly when ventilation is absent, as in a segment of atelectatic lung. Blood emerges from that segment with no additional anesthetic. Such anesthetic-deficient blood then mixes with the blood from the ventilated segments containing a normal complement of anesthetic. The mixture produces an arterial anesthetic partial pressure that is considerably below normal.

FIGURE 4–5 The FA/FI ratio rises more rapidly if ventilation is increased. Solubility modifies this impact of ventilation: the effect on the anesthetizing partial pressure is greatest with the most soluble anesthetic (ether) and least with the least soluble anesthetic (nitrous oxide). (Modified from Eger**90**)

With highly soluble agents, a different situation results from similar ventilation/perfusion ratio abnormalities. In alveoli receiving more ventilation relative to perfusion, the anesthetic partial pressure rises to a higher level than usual (see **Fig. 4–5** for effect with diethyl ether). That is, blood issuing from these alveoli has an increased anesthetic content, the increase being nearly proportional to the increased ventilation. Assuming that overall (total) ventilation remains normal, this increase in the anesthetic contained by blood from the relatively hyperventilated alveoli compensates for the lack of anesthetic uptake in unventilated alveoli.

These effects are illustrated in **Figure 4–11** for a condition that may be iatrogenically produced, endobronchial intubation. Because all ventilation now is directed to the intubated lung, this lung is hyperventilated relative to perfusion. FA/FI for this lung is slightly increased (above that obtained in the absence of endobronchial intubation) with the poorly soluble cyclopropane and greatly increased with the highly soluble ether. As indicated earlier, the increase with ether compensates for the absence of uptake from the unventilated lung, a compensatory mechanism that is not available with cyclopropane. The result is that the cyclopropane arterial partial pressure is well below normal, whereas the ether arterial partial pressure is scarcely changed.

FIGURE 4–11 When no ventilation/perfusion abnormalities exist, the alveolar (PA or PET) and arterial (Pa) anesthetic partial pressures rise together (continuous lines) toward the inspired partial pressure (PI). When 50% of the cardiac output is shunted through the lungs, the rate of rise of the end-tidal partial pressure (dashed lines) is accelerated while the rate of rise of the arterial partial pressure (dot-dashed lines) is retarded. The greatest retardation is found with the least soluble anesthetic, cyclopropane. (From Eger and Severinghaus**39**)

These concepts have been confirmed experimentally by comparing the rate of arterial anesthetic rise with and without endobronchial intubation in dogs. **40** Endobronchial intubation significantly slowed the arterial rate of rise of cyclopropane but did not influence the rise with methoxyflurane. An intermediate result was obtained with halothane **(Fig. 4–12)**. These data suggest that in the presence of ventilation /perfusion ratio abnormalities, the anesthetic effect of agents such as nitrous oxide, desflurane, and sevoflurane may be delayed more than the anesthetic effect of isoflurane or halothane.

THE EFFECT OF NITROUS OXIDE ON CLOSED GAS SPACES

Volume Changes in Highly Compliant Spaces

During the course of anesthetic administration, appreciable volumes of nitrous oxide can move into closed gas spaces. Although this transfer does not influence FA/FI, it may have important functional consequences. There are two types of closed gas spaces in the body, those enclosed by compliant walls and those enclosed by noncompliant walls. The former (bowel gas, pneumothorax, or pneumoperitoneum) are subject to changes in volume secondary to the transfer of nitrous oxide into these spaces. **41** These spaces normally contain nitrogen (from air), a gas whose low solubility (blood/gas partition coefficient, 0.015) limits its removal by blood. Thus, the entrance of nitrous oxide (whose solubility permits it to be carried by blood in substantial quantities) is not countered by an equal loss, and the result is an increase in volume. The theoretical limit to the increase in volume is a function of the alveolar nitrous oxide concentration, because it is this concentration that is ultimately achieved in the closed gas space. That is, at equilibrium, the partial pressure of nitrous oxide in the closed gas space must equal its partial pressure in the alveoli. An alveolar concentration of 50 percent might double the gas space volume, and a 75 percent concentration might produce a fourfold increase.

These theoretic limits may be approached if equilibrium is rapidly achieved, as with pneumothorax or gas emboli. Administration of 75 percent nitrous oxide in the presence of a pneumothorax may double the pneumothorax volume by 10 minutes and may triple it by 30 minutes **(Fig. 4–13)** **41** . This increase in volume may seriously impair cardiorespiratory function, **42** and the use of nitrous oxide is contraindicated in the presence of a significant pneumothorax.

FIGURE 4–13 The volume of a pneumothorax created by air injection is little affected when oxygen subsequently is breathed (filled triangle and circles). However, if 75% nitrous oxide is breathed, the volume doubles in 10 minutes and triples in a half-hour (open circles, squares, and triangles). (From Eger and Saidman**41**)

A still more rapid expansion of volume occurs if air is inadvertently allowed to enter the blood stream in a patient anesthetized with nitrous oxide. Expansion may be complete in seconds rather than minutes. Munson and Merrick **43** demonstrated that the lethal volume of an air embolus was decreased in animals breathing nitrous oxide as opposed to air **(Fig. 4–14)**. The difference could be entirely explained by expansion of the embolus in the animals breathing nitrous oxide (i.e., the predicted total volume of air plus nitrous oxide in the embolus equaled the volume of air needed to produce death in animals breathing only air). These studies suggest caution in the use of nitrous oxide for procedures in which air embolization is a risk (e.g., posterior fossa craniotomies, laparoscopy). They also suggest that if air embolization is suspected, nitrous oxide administration should be immediately discontinued. Conversely, a nitrous oxide "challenge" may be used to test whether air embolization has occurred. **44**

FIGURE 4–14 An air embolus equaling 0.55 mL/kg killed 50% of rabbits breathing oxygen. If the inspired gas mixture contained 75% nitrous oxide, only 0.16 mL/kg was required to kill half the animals. (Modified from Munson and Merrick**43**)

The endotracheal tube cuff normally is filled with air. It, too, is susceptible to expansion by nitrous oxide **45** ; the presence of 75 percent nitrous oxide surrounding such a cuff can double or triple the volume of the cuff. The result may be an unwanted increase in pressure exerted on the tracheal mucosa. Similarly, nitrous oxide may expand the cuffs of balloon-tipped (e.g., Swan-Ganz) catheters **46**, **47** when the balloons are inflated with air. The expansion is rapid, and a doubling of volume may occur within 10 minutes.

Pressure Changes in Poorly Compliant Spaces

Pressure can be produced by the entrance of nitrous oxide into gas cavities surrounded by poorly compliant walls. Unwanted increases in intraocular pressure may be imposed by nitrous oxide administration after intravitreal sulfur hexafluoride injection. **48** Other examples include the gas space created by pneumoencephalography (now rare as a deliberate procedure) and the natural gas space in the middle ear. Pressures in the head or middle ear may rise by 20 to 50 mm Hg owing to the ingress of nitrous oxide at a faster rate than air can be removed. **49**, **50** Recognition of this problem has decreased the use of nitrous oxide for tympanoplasty because the increased pressure may displace the graft. Increase in middle ear pressure may cause adverse postoperative effects on hearing. **51** The capacity of nitrous oxide to expand the gas in the middle ear has also been used to elevate an adherent atelectatic tympanic membrane off the promontory and the ossicles. **52**

Washin of the Circuit

To begin anesthesia, anesthetic must be washed into the volume of the circuit. At inflow rates of 1 to 5 L/min and a circuit volume of 7 L (3-L bag, 2-L carbon dioxide absorber, and 2 L of corrugated hoses and fittings), the washin of the circuit is 75 to 100 percent complete in 10 minutes **(Fig. 4–15)**. Higher inflow rates produce a more rapid rise in the

inspired concentration, which suggests that induction can be accelerated and made more predictable by use of high inflow rates.

Anesthetic Loss to Plastic and Soda Lime

Uptake of anesthetic by several depots also constitutes a hindrance to the development of an adequate inspired anesthetic concentration. The rubber or plastic components of the circuit may remove agent **53**, **54** this was a significant problem with the obsolete anesthetic methoxyflurane, which has a high solubility in rubber and plastic **(Table 4–3**). A minor problem exists for halothane and isoflurane, and no problem results from the solution of nitrous oxide, desflurane, or sevoflurane. **55**

TABLE 4–3. Rubber/Gas and Plastic/Gas Partition Coefficients

Normal (moist) carbon dioxide absorbents containing 13 to 15 percent water can slightly increase the sevoflurane, and, to a lesser extent, the halothane requirement by degrading each of these anesthetics. **56** Degradation results in the removal of hydrogen fluoride and the production of unsaturated compounds. Nitrous oxide, desflurane, and isoflurane are not materially degraded. For sevoflurane and halothane, degradation is of concern because the unsaturated compounds produced are toxic (e.g., compound A from sevoflurane is nephrotoxic). **57**

In contrast to normal (moist) carbon dioxide absorbents, desiccated absorbents materially degrade all potent inhaled anesthetics. **58** Degradation of sevoflurane materially increases anesthetic requirement. **59** In addition, dehydration of Baralyme increases compound A production from sevoflurane, but dehydration of soda lime does the opposite. **59** Desiccated absorbents degrade all anesthetics containing the CHF2-O- moiety (i.e., desflurane, enflurane, and isoflurane), the degradation product of concern being carbon monoxide. **58** Degradation by soda lime is minimal at hydrations approximately one-tenth those found in normal soda lime.

The Effect of Rebreathing

Inspired gas actually consists of two gases: that delivered from the anesthetic machine and that previously exhaled by the patient and subsequently rebreathed. Because the patient has removed (taken up) anesthetic from the rebreathed gas, the amount taken up and the amount rebreathed influence the inspired anesthetic concentration. An increase in uptake or rebreathing lowers the inspired concentration of a highly soluble gas more than the inspired concentration of a poorly soluble gas. This effect of uptake can be diminished by decreasing rebreathing, which is accomplished by increasing the inflow rate. With a ventilation of 5 L/min, rebreathing can be essentially abolished by use of a 5-L/min inflow rate. **60**

High inflow rates (i.e., 5 L/min or greater) have the advantage of increasing the predictability of the inspired anesthetic concentration, but they have the disadvantages of being wasteful and of increasing atmospheric pollution. High inflow rates may be unacceptably costly because of the attendant greater consumption of expensive volatile anesthetics. High inflow rates also may result in drier inspired gas and greater difficulty in estimating ventilation from excursions of the rebreathing bag. These several disadvantages lead us to consider techniques that avoid the use of high inflow rates.

THE LOW-FLOW OR CLOSED-CIRCUIT TECHNIQUE

Much of the previous discussion assumed the use of a nonrebreathing system and a fixed inspired concentration of anesthetic. Although this approach does not invalidate the principles described earlier, it also does not reflect the variety of approaches applied in practice. Practice often deviates in two ways: (1) most anesthetists use lower inflow (fresh gas flow) rates in order to provide a more economical delivery of anesthesia, and (2) most anesthetists apply a constant alveolar, rather than a constant inspired, concentration because a constant alveolar concentration more closely reflects a constant level of anesthesia.

A low inflow rate results in several advantages and a few disadvantages, the latter particularly applying to kinetics. The advantages of low inflow administration (defined as fresh gas flows of less than half the minute volume, usually less than 3 L/min) or closed-circuit anesthesia (defined as delivery of gases in amounts sufficient to replace the gases—oxygen and anesthetic—removed by the patient) include lower cost, increased humidification, reduced heat loss, decreased release of anesthetic to the environment, and better capacity to assess physiologic variables, such as ventilation. On the debit side, one must be more concerned about oxygen levels (especially if nitrous oxide is used, but the patient also contributes nitrogen from stores in the body, and such nitrogen can slightly decrease the inspired concentration of oxygen), about increasing concentrations of carbon monoxide, and about rebreathing of toxic products from the breakdown of volatile anesthetics. Regarding this last point, carbon dioxide absorbents can degrade both halothane and sevoflurane to toxic unsaturated compounds. **61**, **62** However, the debit of most immediate concern is the lack of control that low flows and, especially, closed circuits offer.

Closed-Circuit Anesthesia

The use of a closed circuit represents an extreme of anesthetic administration, one that is infrequently accomplished because few systems completely eliminate leakage of gas from the circuit. Indeed, anesthetists often apply a deliberate leak of approximately 200 mL/min by sampling gases for oxygen, carbon dioxide, and anesthetic analyses.

Usually, closed-circuit anesthesia requires replacement of three gases: (1) oxygen, (2) nitrous oxide, and (3) a potent volatile anesthetic. Each replacement implies somewhat different considerations. Oxygen replacement remains constant unless metabolism changes as a consequence of sympathetic response to stimulation, alteration in body temperature, or shivering. Replacement of nitrous oxide follows a fairly predictable course, in part because the concentration applied does not usually vary. Furthermore, it is the least soluble of anesthetics, especially in fat, and is the most prone to percutaneous loss (a constant value). Of most interest and potential variability are the uptakes of the potent inhaled anesthetics.

Uptake of potent anesthetics may be estimated from the values (constants) obtained by Yasuda et al **4**, **5** in human volunteers. These values may be applied to obtain uptake at a constant alveolar concentration. To provide an appropriate level for comparison, I have assumed an alveolar concentration equal to the minimum alveolar concentration (MAC). The resulting figure **(Fig. 4–16)** reveals parallel shapes for each anesthetic, shapes dictated by the perfusion and solvent characteristics of the three major tissue compartments (plus intertissue diffusion). Thus, a large initial uptake rapidly decreases to a much lower level in 5 to 10 minutes, reflecting the high initial uptake of the VRG (high because of its large perfusion) and the rapid decrease in uptake imposed by a short time constant. The subsequent slower decrease primarily results from the longer time constant of the muscle group, which dominates this period until its uptake declines below that provided by fourth compartment and fat groups.

FIGURE 4–16 The uptake (in milliliters per minute), as illustrated in this graph, resulted from the application of the constants calculated by Yasuda et al**4,** ,**5** from their measurements in human volunteers. The application also assumes that the alveolar concentration equals maximum alveolar concentration (MAC). Uptake is a function of both MAC and solubility of the anesthetic in blood and tissues. Thus, the fivefold higher MAC for desflurane versus isoflurane is offset by a threefold lower solubility, producing less than a twofold difference in uptake at any point in time. Uptake for all anesthetics initially declines rapidly as a function of the rate at which the vessel-rich group equilibrates. The further decline after 5 to 10 minutes is a function of the approach to equilibration of the muscle group. (Data from Yasuda et al**4,** ,**5**

Although the curves for each anesthetic do not differ in shape, they differ in position. The height of each curve (i.e., uptake) is directly proportional to two factors: (1) solubility and (2) MAC. This relationship tends to minimize differences among anesthetics because solubility and MAC tend to move inversely. For example, although the MAC for desflurane is five times that for isoflurane, its uptake is less than twice that of isoflurane because of its lower solubility in both blood and tissues.

Uptake may be estimated from the "square-root-of-time rule," first proposed by Severinghaus **63** and expanded greatly by Lowe and associates **64**, **65** in their classic descriptions of closed-circuit anesthesia. This rule states that uptake at any point in time may be estimated as uptake during the first minute of anesthesia divided by the square root of time in minutes. Making certain assumptions permits an estimate of uptake during the first minute. In general, uptake equals the product of blood solubility, cardiac output, and alveolar to venous anesthetic partial pressure difference. Several sources supply standard values for solubility and cardiac output, and alveolar to venous anesthetic partial pressure difference may be estimated if we determine what alveolar partial pressure we wish and assume that venous anesthetic partial pressure is inconsequential. An inconsequential venous partial pressure is reasonable because no anesthetic can appear in venous blood before recirculation (about a half a minute) and even the anesthetic that appears is small because tissue uptake is maximal during the first minute. Thus, we might estimate isoflurane uptake in a normal adult as 1.4 times 5,400 times 0.0115, or 87 mL, where 1.4 is the blood/gas partition coefficient; 5,400 is a reasonable cardiac output, and 0.0115 is MAC as a fraction of one atmosphere (1 atm). By 4 minutes, uptake would equal 87 mL/2; by 9 minutes 87 mL/3; and by 64 minutes 87 mL/8.

Hendrickx et al **66** questioned the accuracy of the square root of time rule, suggesting that the rule overestimates the decrease in uptake with the passage of time. Eger **67** considered whether the evidence provided by Hendrickx overturns the square root of time rule, and the matter continues to be debated.

Replacement of anesthetic taken up may be accomplished by infusion of liquid anesthetic directly into the anesthetic circuit, either continuously or as boluses. A continuous infusion requires a pump of some sort, and an elegant solution uses a computer to direct a progressive decrease in infusion rate as a function of time. Bolus injection from a syringe has an elegant simplicity but has two disadvantages: (1) the circuit concentration modestly oscillates, and (2) the anesthetist is required to remember when and how much to inject. A further disadvantage accrues to the injection of

desflurane by either pump or syringe. The high vapor pressure of desflurane (about 1 atm at room temperature) results in the unpredictable formation of bubbles of desflurane gas and a potential for a marked variability in the rate of infusion or injection, especially when smaller volumes of liquid are to be injected.

An alternative solution to injection of liquid applies a variable bypass (Tec-type) vaporizer, one capable of accurate delivery of a range of concentrations at low inflow rates (e.g., 200 mL/min). This solution may not be applicable in the initial delivery of anesthesia, because the demand for vapor may exceed the capability of presently available vaporizers. For example, the maximum output of a conventional isoflurane vaporizer is 5 percent, and at a 200 mL/min flow of oxygen, only approximately 10 mL of isoflurane vapor can be produced per minute, far less than the 87 mL estimated earlier. Even after 1 hour of anesthesia, an isoflurane vaporizer is barely capable of meeting the demand for anesthetic **(Fig. 4–17** A). This difficulty may be overcome in several ways. If a concentration less than MAC is acceptable, a lesser delivery of vapor is required. Thus, the concurrent use of nitrous oxide decreases the demand on the vaporizer. In addition, the use of nitrous oxide also increases the total fresh gas flow to compensate for the considerable uptake of nitrous oxide. If the fresh gas flow increases to 1,500 mL/min, 79 mL of isoflurane vapor can be produced. Another solution is to select an anesthetic having a vaporizer capability closer to demand. Such a solution tends to be available for less soluble anesthetics. For example, we calculate the uptake for desflurane in the first minute of anesthesia to be 0.45 Å~ 5,400 Å~ 0.06, or 146 mL. At a 200-mL/min flow of oxygen, the 18 percent maximum output of a desflurane vaporizer permits delivery of 44 mL. Although still inadequate to meet demand in the first minute, this figure is 2.6 times closer to meeting that demand than the isoflurane vaporizer, and within 10 minutes, the desflurane vaporizer can supply the required volume (see **Fig.4–17** A).

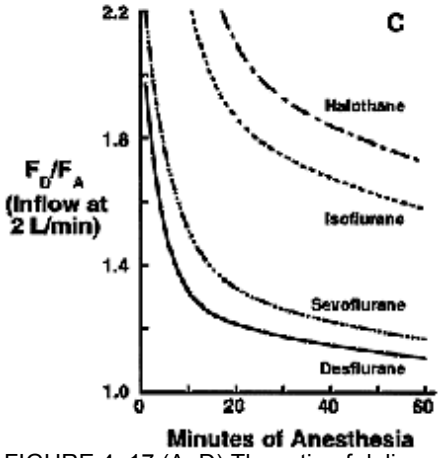


FIGURE 4–17 (A–D) The ratio of delivered to alveolar concentrations (FD/FA) required to sustain the alveolar concentration constant at, for example, MAC, is a function of several factors. First, it is determined by uptake (see Fig. 4–16). Second, it is determined by rebreathing. Thus, the ratio decreases with increasing inflow rates. Although these graphs have the same shape, notice the progressive decrease in the scale on the ordinate as inflow rate increases. The lowest values for any anesthetic result from a nonrebreathing system (i.e., when the inflow rate equals minute ventilation).

Figure 4–17 A suggests one of the major difficulties associated with the closed-circuit approach, namely, control. Clearly, there is an enormous difference between delivered (i.e., vaporizer dial) and alveolar concentrations. The differences decrease with less soluble anesthetics, but even with an anesthetic such as desflurane and even after the initial high-uptake period is passed, the dialed concentration markedly exceeds the alveolar concentration that it sustains. This means that changes in uptake (e.g., secondary to the increase in cardiac output that may result from surgical stimulation) can cause considerable alterations in alveolar concentration unless the delivered concentration is altered. The alveolar concentration changes for two reasons: (1) assuming a constant ventilation, the difference between the alveolar and inspired concentrations varies directly with uptake (e.g., a greater uptake increases the difference), and (2) because of the rebreathing, the inspired concentration varies inversely with the uptake (e.g., an increased uptake lowers the inspired concentration). Thus, the sum of these effects either decreases or increases the alveolar concentration. A closed circuit has an inherent element of instability not present in an open circuit.

Low-Flow Anesthetic Delivery

The instability of the closed circuit may be greatly mitigated by the use of low-flow (less than half the minute ventilation) anesthetic delivery. Low-flow delivery may provide most of the advantages of closed systems without the attendant instability while retaining considerable advantages over open systems in economy, maintenance of

humidification and temperature, and limited atmospheric pollution. Low-flow delivery also diminishes the disadvantages of the closed circuit in the areas of constancy of oxygen and anesthetic levels and elimination of carbon monoxide and toxic anesthetic breakdown products.

In a low-flow delivery system, two factors control the relationship between the concentration delivered from a vaporizer (FD) and that in the alveoli (FA), a relationship that may best be described as the ratio (FD/FA) of the two variables. First, we have already seen that uptake governs this ratio in a closed system (see **Fig. 4–17** A). Thus, FD/FA is higher for more soluble anesthetics, and regardless of solubility, the ratio is highest early in anesthetic administration and decreases rapidly in the first 5 to 10 minutes of anesthesia (as uptake by the VRG of tissues decreases to the point of near-equilibration) and more slowly thereafter (as uptake by tissue groups with longer time constants, such as muscle, the fourth compartment, and fat decreases).
FIGURE 4–17 (A–D) The ratio of delivered to alveolar concentrations (FD/FA) required to sustain the alveolar concentration constant at, for example, MAC, is a function of several factors. First, it is determined by uptake (see Fig. 4–16). Second, it is determined by rebreathing. Thus, the ratio decreases with increasing inflow rates. Although these graphs have the same shape, notice the progressive decrease in the scale on the ordinate as inflow rate increases. The lowest values for any anesthetic result from a nonrebreathing system (i.e., when the inflow rate equals minute ventilation).

Second, inflow rate also governs FD/FA. The relationship is inverse: the higher the inflow rate, the lower the ratio (compare Figs. **4–17** B–D with **Fig. 4–17** A). An increase in inflow rate decreases FD/FA by decreasing rebreathing. Rebreathing is important because uptake of anesthetic depletes the anesthetic concentration in rebreathed gases, and the concentration in the delivered gases (FD) must be sufficient to compensate for this depletion. The higher the inflow rate, the less the compensation required because rebreathing is less.

However, increases in inflow rate do not produce proportional decreases in FD/FA (compare Figs. **4–17** A–D). The greatest reduction in FD/FA comes with but modest increases in inflow rate. Thus, a large decrease occurs when the inflow rate is changed from that needed for a closed circuit to a 1-L/min inflow rate, whereas only a small decrease occurs when the inflow rate is increased from 2 to 4 L/min. Once the inflow rate exceeds minute ventilation (i.e., a nonrebreathing system exists), further increases in inflow rate have no effect on FD/FA, and FD/FA is the same as the ratio of inspired (FI) to alveolar concentrations (i.e., FD/FA = FI/FA).

I have used the term anesthetic tether as a metaphor for the FD/FA ratio. **68** A large ratio equates to a long tether, one permitting considerable freedom or variability in the alveolar concentration. With a long tether, changes in uptake secondary to changes in physiologic variables (e.g., an increase in cardiac output consequent to surgical stimulation) can appreciably alter the alveolar concentration and thus the level of anesthesia. In the example just cited, there is positive feedback because by increasing uptake, surgical stimulation decreases the alveolar concentration and thereby increases the perception of that stimulation. Most anesthetists prefer a short anesthetic tether because a short tether provides a tighter control over the level of anesthesia. A shorter tether is produced by the use of less soluble anesthetics and higher inflow rates.

Another benefit to a short tether accrues to the anesthetist who does not have access to an agent-specific analyzer. In the absence of such an analyzer, some anesthetists would rely on the dial setting of the vaporizer to indicate the concentration of anesthetic in the patient‘s lungs (i.e., would assume that FD equaled FA). Although the vaporizer setting may correlate with the concentration in the lungs, the correlation may be a distant one. The correlation is poor: (1) early in anesthesia for all agents, (2) later in anesthesia for closed circuits or very low inflow rates, and (3) later in anesthesia for more soluble agents, such as isoflurane, even at higher inflow rates. Note that with poorly soluble anesthetics, such as sevoflurane and desflurane, by 30 to 60 minutes after the inception of anesthetic administration, the delivered concentration from the vaporizer may be less than 20 percent greater than that in the alveoli (i.e., the FD/FA ratio is 1.2), even at inflow rates of 1 to 2 L/min (**Figs. 4–17 B and C**).

Economic concerns increasingly dictate the practice of anesthesia. The reader may wish to appreciate the differences in anesthetic consumption as a function of the choice of inflow rate, the duration of anesthesia, and the choice of anesthetic. The reports by Yasuda et al **4**, **5** provide constants that may be used to estimate the uptake of commonly available potent inhaled anesthetics. By using the gas laws and published values for specific gravities, the values for uptake of vapor may be converted to milliliters of liquid taken up. Combining this information with a knowledge of the function of circuit rebreathing systems **60** allows an estimate of the amounts of liquid in milliliters that must be delivered at various inflow rates to provide a constant alveolar concentration equal to MAC **(Table 4–4)**. **69** The relative costs of anesthesia may be estimated by applying the price of the anesthetic of interest to the number of milliliters needed to sustain anesthesia.

TABLE 4–4. Milliliters of Liquid Anesthetic at Various Inflow Rates Needed to Sustain an Alveolar Concentration Equal to Minimum Alveolar Concentration

If both economy and a low FD/FA ratio are desirable, the aforementioned considerations suggest that a good compromise is the use of a low-flow delivery system after an initial period of higher flows. Higher flows (4 to 6 L/min) might be applied early in anesthesia (i.e., at the times of highest uptake) and then decreased progressively as uptake decreases. Flows of 2 to 4 L/min might be given for the period from 5 to 15 minutes after inducing anesthesia, and flows of 1 to 2 L/min may be given thereafter. If the average inflow rate were 2 L/min, 1 hour of anesthesia with the four potent anesthetics listed in **Table 4–4** would require administration of 9.0 to 46.0 mL of liquid. This fivefold range of values is smaller than the eightfold range of potency (MAC) values because the amount of anesthetic delivered must account for more than potency. The amount delivered also must compensate for uptake and losses of anesthetic through the overflow valve. The relatively smaller uptake and losses of the less soluble desflurane and sevoflurane are what account for the reduction from eightfold to fivefold. An even smaller range is found at lower inflow rates, decreasing to about twofold for a closed circuit. However, such flows should not be used with sevoflurane because of the greater concentrations of compound A that result.

RECOVERY FROM ANESTHESIA

General Principles

Nearly all the factors that govern the rate at which the alveolar anesthetic concentration rises on induction apply to recovery. Thus, the immediate decline is extremely rapid because the washout of the functional residual capacity by ventilation is as rapid as the washin. Only 2 minutes is required to eliminate 95 to 98 percent of nitrogen from the lungs when pure oxygen is breathed.

Nitrogen, however, is a poorly soluble gas relative to the inhaled anesthetics. As ventilation sweeps anesthetic from the alveoli, an anesthetic partial pressure gradient develops between that partial pressure in the returning venous blood and the partial pressure in the alveoli. This gradient drives anesthetic into the alveoli, thereby opposing the tendency of ventilation to lower the alveolar concentration. The effectiveness of the venous to alveolar gradient in opposing the tendency of ventilation to decrease the alveolar anesthetic partial pressure is in part determined by the solubility of the anesthetic. A highly soluble agent, such as methoxyflurane, opposes the elimination produced by ventilation more effectively than does a poorly soluble agent, such as nitrous oxide, because a greater reserve exists in blood for the highly soluble agent—that is, far more methoxyflurane is available at a given partial pressure for transfer to the alveoli. Thus, the fall in the alveolar partial pressure of methoxyflurane is slower than the fall with halothane, and the latter, in turn, is less rapid than the fall with nitrous oxide. The rate at which recovery occurs is similarly affected: it is rapid with nitrous oxide and may be slow with methoxyflurane. The rapidity of recovery thus largely depends on the solubility of the anesthetic. **70**

Differences Between Induction and Recovery

Recovery differs from induction in two crucial ways. First, on induction, the effect of solubility to hinder the rise in alveolar anesthetic concentration could be overcome by increasing the inspired anesthetic concentration (i.e., by applying overpressure). No such luxury is available during recovery; the inspired concentration cannot be reduced below zero. Second, on induction, all the tissues initially have the same anesthetic partial pressure—zero. On recovery, the tissue partial pressures are variable. The VRG has a pressure that usually equals that required for anesthesia; that is, the VRG has come to equilibrium with the alveolar anesthetic partial pressure. The muscle group may or may not have the same partial pressure as that found in the alveoli. A longer anesthetic (2 to 4 hours) might permit equilibrium to be approached, but a shorter case would not. The high capacity of fat for all anesthetics except nitrous oxide precludes equilibration of the fat group with the alveolar anesthetic partial pressure with hours or even days of anesthesia.

The failure of muscle and fat to equilibrate with the alveolar anesthetic partial pressure means that these tissues initially cannot contribute to the transfer of anesthetic back to the lungs. In fact, as long as an anesthetic partial pressure gradient exists between arterial blood and tissue blood, that tissue will continue to take up anesthetic. Thus, for the first several hours of recovery from halothane anesthesia, fat continues to take up halothane and by so doing accelerates the rate of recovery. Only after the alveolar (equals arterial) anesthetic partial pressure falls below that in a tissue can the tissue contribute anesthetic to the alveoli.

The failure of several tissues to reach equilibration with the alveolar anesthetic partial pressure means that the rate of decrease of alveolar anesthetic on recovery is more rapid than its rate of increase on induction, and that recovery depends in part on the duration of anesthesia **(Fig. 4–18)**. **71**, **72** A longer anesthetic puts more anesthetic into the slowly filling muscle and fat depots. Obviously, these reservoirs can supply more anesthetic to the blood returning to the lungs when they are filled than when they are empty and thereby can prolong the time to recovery. **70**

FIGURE 4–18 Both solubility and duration of anesthesia affect the fall of the alveolar concentration (FE) from its value immediately preceding the cessation of anesthetic administration (FEO). A longer anesthetic slows the fall, as does a greater solubility. (From Stoelting and Eger**72**)

Solubility influences the effect of duration of anesthesia on the rate at which the alveolar anesthetic partial pressure declines. **72** The decline of the partial pressure of a poorly soluble agent such as nitrous oxide is rapid in any case, and thus the acceleration imparted by a less than complete tissue equilibration cannot significantly alter the rate of recovery. The approach to equilibration becomes important with halothane and becomes even more important with methoxyflurane (see **Fig. 4–18)**. Recovery may be rapid after a short methoxyflurane anesthetic but may be slow after a prolonged anesthetic. This is one of the reasons why nitrous oxide is usually a component of an inhaled (or for that matter, an injected) anesthetic regimen. The rapid elimination of this component permits at least a portion of recovery to be rapid. The recovery from anesthesia with desflurane and sevoflurane is more rapid than with more soluble agents, such as isoflurane and halothane. **70**

The importance of solubility and duration of anesthesia to the rate of recovery may be appreciated by the use of context-dependent times to reach particular levels of washout. **73** Regardless of duration of anesthesia, the alveolar concentrations of poorly soluble anesthetics (nitrous oxide, desflurane, sevoflurane) and moderately soluble anesthetics (isoflurane, halothane) decrease by 50 percent in roughly the same period of time. If recovery were reached at a 50 percent decrease, the choice of anesthetic would matter little to the time to recovery from anesthesia. The impact of solubility and anesthetic duration becomes evident if greater levels of washout are required to achieve recovery. If 80 percent washout is required, then increasing duration of anesthesia markedly affects recovery from isoflurane, but little affects recovery from desflurane and sevoflurane **(Fig. 4–19)**. If 90 percent washout is required, then increasing duration of anesthesia affects both isoflurane and sevoflurane but not the less soluble desflurane (see **Fig. 4–19)**. Indeed, the 90 percent washout may be of importance if anesthesia is maintained primarily with the potent inhaled anesthetic. After 2, 4, or 8 hours of anesthesia with 1.25 MAC sevoflurane versus desflurane, initial **(Fig. 4–20)** and later **(Fig. 4–21)** recovery is nearly twice as rapid with desflurane, and the difference between the recovery times appears to increase with increasing duration of anesthesia. **24**

FIGURE 4–19 The time to decrease the partial pressure in the alveoli or vessel-rich group by a certain fraction directly depends on several factors, primary among which are the solubility of the anesthetic and the duration of anesthesia. If between 80% of the anesthetic must be elimination to permit awakening, awakening from isoflurane will be delayed for progressively longer times as the duration of anesthesia is increased, but awakening from desflurane or sevoflurane will be minimally affected. If 90% of the anesthetic must be eliminated, awakening from both sevoflurane and isoflurane will be delayed more and more as the duration of anesthesia increases (isoflurane more than sevoflurane), but awakening from desflurane will be minimally affected. (Modified from Bailey**73**)

FIGURE 4–20 The possibility of a differential time to awakening suggested by the analysis in Figure 4–19 is shown to occur after 2, 4, or 8 hours of anesthesia at 1.25 MAC for desflurane versus sevoflurane. Awakening to response to command or to orientation is nearly twice as rapid after anesthesia with the less soluble desflurane. (From Eger et al**24**)

FIGURE 4–21 The differential suggested by Figure 4–19 extends to measures of more subtle degrees of awakening such as the digit symbol substitution test (DSST), a measure of judgment and cognition. Note that there appears to be a greater spread between the results after 2 versus 8 hours of anesthesia. (From Eger et al**24**)

Can I Have My Cake and Eat It Too?

The less soluble new inhaled anesthetics desflurane and sevoflurane offer a more rapid recovery from anesthesia than the more soluble older agents, such as isoflurane. However, this rapid recovery comes at a price: the new anesthetics are more expensive. Might it be possible to have the best of both worlds by using isoflurane for the major portion of anesthesia, reserving desflurane (or sevoflurane) for the final minutes? The premise would be that such an approach would provide the economy of isoflurane and the rapid recovery of desflurane. Neumann et al **74** tested this premise. Volunteers were anesthetized for 2 hours on three occasions: once with 1.25 MAC of isoflurane; once with 1.25 MAC of desflurane; and once with 1.5 hours of 1.25 MAC of isoflurane followed by 0.5 hours of a combination of desflurane and isoflurane ("crossover"). The combination provided a total of 1.25 MAC (i.e., desflurane was added as the isoflurane was eliminated, the addition being sufficient to sustain a total of 1.25 MAC). To ensure economy, all anesthetics were delivered at a 2 L/min inflow rate.

The premise was not realized. Recovery after the crossover was no faster than recovery after isoflurane alone **(Fig. 4–22)**. Recovery after desflurane alone was considerably faster than recovery after either isoflurane or the crossover from isoflurane to desflurane.

FIGURE 4–22 Volunteers were anesthetized for 2 hours on three occasions: once with 1.25 MAC isoflurane; once with 1.25 MAC desflurane; and once with 1.5 hours of 1.25 MAC isoflurane followed by 0.5 hours of a

combination of desflurane and isoflurane ("crossover"). The combination provided a total of 1.25 MAC (i.e., desflurane was added as the isoflurane was eliminated, the addition being sufficient to sustain a total of 1.25 MAC). All anesthetics were delivered at a 2-L/min inflow rate. At the end of 2 hours, anesthetic administration was discontinued and a nonrebreathing system applied. The digit symbol substitution test (DSST) was applied at 15-minute intervals, and the results are displayed as a percentage of the control (preanesthesia) results. Recovery of judgment and cognition as defined by the DSST was more rapid at 15, 30, and 45 minutes with desflurane given alone (asterisks indicate significant differences from isoflurane or crossover results). (Data from Neumann et al**74**

Impact of Metabolism

Saturation of the enzymes responsible for the metabolism of anesthetics may limit the ability of metabolism to significantly alter the rate at which the alveolar anesthetic partial pressure rises. This limitation does not exist on recovery, and metabolism may be an important determinant of the rate at which the alveolar anesthetic partial pressure declines. The importance of metabolism to recovery is implied by results from Munson et al, **75** who showed that contrary to what might be predicted from their respective solubilities, the alveolar washout of halothane is more rapid than that of enflurane, a result later confirmed by Carpenter et al. **18**, **19** This agrees with the relative ease with which these two agents are metabolized: 15 to 20 percent of the halothane taken up during the course of an ordinary anesthetic can be recovered as urinary metabolites, **76** whereas only 2 to 3 percent of enflurane can similarly be recovered. **77** Thus, there are two major routes by which halothane can be eliminated, the lung and the liver. With enflurane, elimination via the liver is relatively minor, which explains why Munson et al **75** found a more rapid fall in alveolar halothane. These results also apply to desflurane, isoflurane, and sevoflurane. Metabolism of desflurane and isoflurane is too small to accelerate their elimination, but metabolism of sevoflurane is sufficient to narrow the difference between its washout and that of desflurane. **24**

Diffusion Hypoxia

The uptake of large volumes of nitrous oxide on induction of anesthesia gives rise to the concentration and the second gas effects. On recovery from anesthesia, the outpouring of large volumes of nitrous oxide can produce what Fink **78** called diffusion anoxia. These volumes may cause hypoxia **(Fig. 4–23)** in two ways. First, they may directly affect oxygenation by displacing oxygen. **78**, **79**, **80** Second, by diluting alveolar carbon dioxide, they may decrease respiratory drive and hence ventilation. **80** Both of these effects require that large volumes of nitrous oxide be released into the alveoli. Because large volumes of nitrous oxide are released only during the first 5 to 10 minutes of recovery, this is the period of greatest concern. This concern is enhanced by the fact that the first 5 to 10 minutes of recovery also may be the time of greatest respiratory depression. For these reasons, many anesthetists administer 100 percent oxygen for the first 5 to 10 minutes of recovery. This procedure may be particularly indicated in patients with preexisting lung disease or in those in whom postoperative respiratory depression is anticipated (e.g., after a nitrous oxide–narcotic anesthetic).

Impact of the Anesthetic Circuit

The anesthetic circuit may limit the rate of recovery just as it limits induction. If the patient is not disconnected from the circuit on cessation of anesthetic delivery, the patient may continue to inspire anesthetic. To reduce the inspired level to zero or near-zero, several factors must be taken into account. The anesthetic within the circuit must be washed out. In addition, the rubber or plastic components of the circuit and the soda lime within the circuit will have absorbed anesthetic (see **Table 4–3**) that can be released back into the gas phase, **54** and this, too, must be washed out. Finally, the patient's exhaled air contains anesthetic that cannot be rebreathed if the inspired anesthetic concentration is to approach zero. The effect of each of these factors to raise the inspired anesthetic concentration can be overcome by the use of high inflow rates of oxygen (i.e., 5 L/min or greater).

• Eger's Tutorial on Pharmacokinetics of Volatile Agents (from CD)

Potency
MAC Bar – minimal alveolar concentration that blocks the adrenergic response
MAC Awake - minimal alveolar concentration at which 50% of patients respond to command appropriately.
Above this concentration, you guarantee suppression of remembrance.
At 25% - relaxation of upper esoph sphincter.

We use 50% because compared to 90%, there is much less variablility ($1/10^{th}$) (and therefore less subjects needed to study). Also, 90% is just above 50% (because the curve is a steep "S").

Spinal cord mediates the capacity of CNS to decrease mobility to stimulation. If you cut connections between the brain and spinal cord in the rat, it doesn't alter the MAC.

IV anaesthetic – ex. propofol works mainly on the brain.
It takes about 10 minutes for equilibration between alveolus and spinal cord concentration of inhalational agent.

MAC (30-60 yr old)

	O2	50% N2O
Halothane	0.75	0.29
Isoflur	1.15	0.59
Sevo	1.85	0.57
Des	6.00	3.00
N2O	105	-

Factors that don't change MAC:
Body mass
Species
Gender
Duration

Factors that Do change MAC:
Age
Temperature (50% decrease for every 10 degrees)
Pregnancy
Decreased Na concent.
Chronic alcoholism (increases)
Acute alcoholism (decreases)

Opioids are synergistic and decrease MAC, but won't get to MAC on own, but even small doses considerably reduce MAC.

Benzos decrease MAC (difficult to get anaesthetised with just benzos – i.e., no movt – with just benzos).

Volatile pharmacokinetics

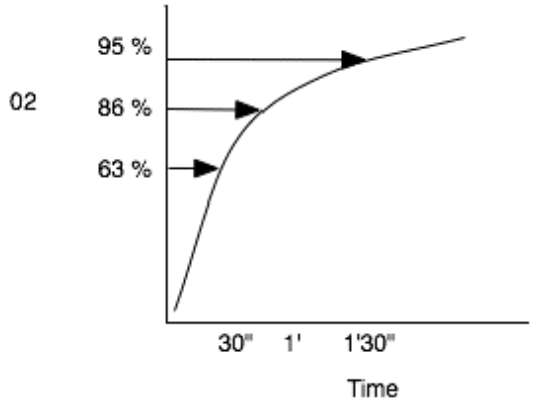
Different position for different agents, but the same shape.

Tau (time constant) = Capacity/Flow

Time that results is the time for a 63% change in the concentration of whatever we are deliverying to that system.

Ex. the lungs - Capacity/Flow = FRC/Ventil. = 2 L/4L/min = 0.5 min (i.e., tau for lungs is ½ min, i.e., the time it would take to reach a 63% change in same newly introduced gas.)

Ex. in 30 sec there will be 63% equilibrium.



1 Tau = 63%
2 Tau = 86%
3 Tau = 95%
4 Tau = 98%

But rise in Fa/FI not as fast as O2 because of uptake.

Uptake = solubility * C.O. * A-V difference
(arterial-venous is same as Alveolar – venous, if no V/Q abnormalities nor barrier to diffusion).

1) solubility – Blood/gas partition coeff. (the bigger the coeff., the greater the uptake).

Des	0.45
N20	0.47
Sevo	0.65
Iso	1.4
Enflur	1.9
Halo	2.5

Ether	12
Methoxy	15

Tissue solubility governs the A-V difference (i.e., it stands between the arterial and venous side).

Tissue/Gas P.Coeff.

Tissue	N20	Des	Sevo	Iso
Blood	0.46	0.45	0.65	1.4
Brain	0.49	0.54	1.2	2.1
Fat	1.1	12	34	64
	(greater fat sol. Is why its more potent)			

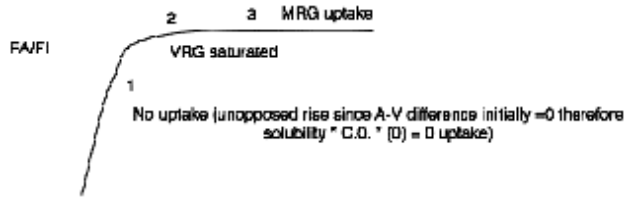
4 Tissue groups

	VRG /	Muscle/	Fat/	Vessel Poor (no uptake in practice)
% body mass	9/	50/	19/	22
L/70 kg	6/	33/	14/	12
%CO	75/	18/	7/	0
L/min	4.0/	1.0/	0.4/	0
Tau	2-4 min/	120-240 min/	-/	-

(4 tissue groups defined by tau = capacity/flow)

So the VRG has short Tau, therefore 98% saturated in 8 min (ex. brain will equilibrate with alveolar concentration in 8 min). Therefore the A-V difference will become minimal and uptake stops.

Fat G has same mass/flow as muscle group, but volatiles much more soluble in fat, therefore capacity is much larger causing increased tau.



Pungency – significant differences between des, iso, sevo at 2 MAC. No difference at 1 MAC.

Opioids decrease perception of pungency.

Recovery Factors:

-Solubility
MAC awake/MAC N20 -60%
Sevofl -33%
Desfl -33%
Propofol -20% (need to get rid of 80% to awaken).
(compared awakening of above, propofol is longer wake up cf. to Des/Sevofl).

NB. Hyperalgesia at 0.1 MAC

On recovery, the ex. muscle group elutes its volatile, but a very soluble agent "likes" being in blood rel. to alveoli, therefore longer recovery (poorly sol. will be cleared from lung quicker, therefore duration of anaesthesia has less effect in less soluble agent.).

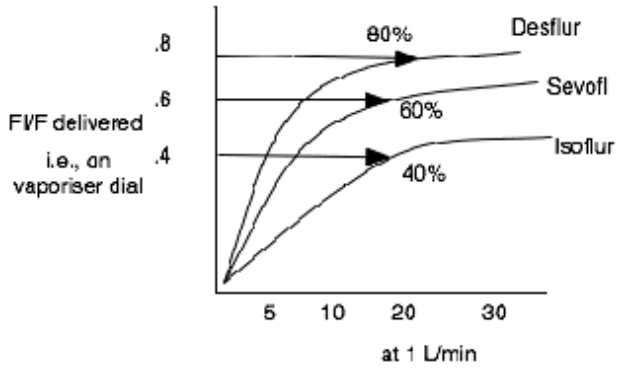
-Obesity
Fat reservoir, even in long anaesthesia, will not be filled and will extract anaesthetic from blood, hastening recovery

Visceral (well perfused, ex. peri renal fat) fat has short Tau (200') it does saturate, therefore will prolong delay.

Combining Isoflur (maintenace) and desflurane (at end, ex. last 30') to get quick wake up at lower cost. But it doesn't work! (i.e., same long wake up as Isoflur alone).

-Circuits influence on uptake
Volume of circuit
Only halothane is really absorbed in circuit
Flow through circuit – influencing rebreathing

At induction, using low flow, if volatile v. soluble, much is taken up in blood. Upon exhaling, there is less volatile, therefore this dilutes the volatilein the circuit more than if little is taken up.



i.e., at 30 min, if we have a FGF of 1L/min, if we dial up 1%, we have 0.4% at 30'. Of course FA will be lower still (about 25% of FI) at 30'.

With Desflurane, the vaporiser dial % is a poor man's gas analyser, i.e., if % is 1 on dial, it is 0.8%% inspired, and 0.7% alveolar.

The lower flow rate, the more exaggerated the difference in the uptake curves because of rebreathing.

N20
MAC is 105
Therefore needs to be delivered at high concentration. Amount of N20 carried in blood, substantial compared to Desfl (with the same solubility) because of much higher partial pressure. Therefore has effects on cavities in body (i.e., large quantities of gas taken to a cavity causing an increase in volume or pressure). Esp. if gas in cavity is rel poorly soluble (ex. N2 or sulfur hexafluride) which cannot be carried away from that cavity. i.e., solubility of N20 is much greater then N2.

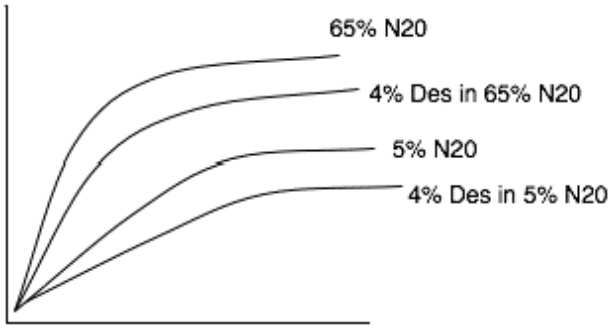
Uptake/Elimination
Diffusion Hypoxia-theoutpouring of N20 in large volumes dilutes the 02.

Induction-
2 phenomenon
1) Concentration effect
2) 2nd gas effect
Both are really the same thing but applied to different gases.

Ex. 65% N20 vs 5% N20

Concentration effect-the 65% N20 induces a more rapid rise compared to 5% N20.

2nd gas effect-the 65% induces a greater rise of ex. desflurane compared to 5% N20 .



PONV and N20
Minimise PONV by using 50% N20 or less-it is minimal.