Inhalation Anesthesia Kinetics

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Introduction

The kinetics of inhaled anesthetics is fundamental to the clinical practice of anesthesia. It explains the time course of anesthetic movement from the vaporizer and flow meters to the patient’s brain.

In 1950 and 1951, Kety wrote a pair of seminal articles on this subject, one for anesthesiologists\(^1\) and one for mathematicians\(^2\). Interest in those articles led Edmund I Eger II to direct his career toward verifying and extending Kety’s thinking and teaching\(^3\) to the unified and apparently complete science we call “uptake and distribution” or “pharmacokinetics” of inhaled gases and vapors.

Following Kety’s approach, the measure of anesthetic in each location is anesthetic tension. In equilibrium, anesthetic tension in all connected compartments is equal. At the same time, anesthetic concentrations in compartments differ according to drug solubility in each compartment.

This text is modified from my original work, submitted for my section of the Atlas of Clinical Anesthesiology\(^4\). This work follows Kety’s development and explains the subject using a set of figures created with the computer simulation I created for this purpose, Gas Man\(^5\). Some of these figures have been directly simulated in Gas Man for Macintosh\(^6\), extracted, and annotated while others have been copied directly from pictures, graphs, and overlays from Gas Man Version 2 for Windows\(^7\) or Version 4 for all platforms\(^8\). Gas Man is introduced in Figures 3 and 4.

I welcome comments and suggestions by e-mail sent to jphilip@bwh.harvard.edu or jim@lifename.com.


The Gas Man\(^®\) Computer Program and Workbook are available at www.medmansimulations.org and www.gasmanweb.com or by writing to Med Man Simulations Inc., PO Box 67-160, Chestnut Hill MA 02467 USA or +1 508 314 1103. The current version is Version 4 for Windows and Macintosh.

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Figure 1. The alveolar tension curve dissected; a description of the alveolar tension curve in response to a step change in inspired tension or concentration. The alveolar tension curve in response to a step change in inspired concentration or partial pressure (tension) has a characteristic shape. First described by Kety in 1950, the curve is comprised of three phases. The initial rapid exponential rise results from anesthetic "washing in" to the patient's lungs with a time constant equal to the ratio of lung volume (FRC = function residual capacity) divided by alveolar ventilation (VA),

$$\tau = V/F = FRC / V_A$$  \hspace{1cm} (1).

Numerically, its approximate value is $$\tau = 2 L / (4 L/min) = 0.5 \text{ min}.$$ A Pseudo-plateau (first plateau) interrupts the curve at a height that reflects the balance between alveolar ventilation bringing anesthetic to the lungs and cardiac output taking drug away. The Pseudo-plateau height or ratio is:

$$P_e/P_i = 1 / (1 + (CO \cdot \lambda) / V_A)$$  \hspace{1cm} (2)

We call the term CO • λ the effective cardiac output. By effective we identify the additional effect of blood/gas solubility ratio, $\lambda$, more properly called $\lambda_{B/G}$.

Emerging from this first pseudo-plateau, the alveolar tension curve demonstrates an up-going tail. The tail has three portions as it rises as three exponentials with three time constants. The first time constant represents wash-in to the fastest tissue group which is well perfused with blood. This tissue group is termed the vessel-rich group (VRG, or R for rich). Its time constant ($\tau$) is equal to the ratio of effective tissue volume (V) to effective tissue blood flow (F). In the case of the tissue is the vessel-rich tissue group; we designate these parameters $\tau_{VRG}$, $\lambda_{VRG}$, and $V_{VRG}$. Analogous subscripts apply to the Muscle and Fat compartments. By effective, we again mean that solubility has been considered and its effects accounted for. Specifically,

$$\tau_{tissue} = (V_{tissue} \cdot \lambda_{tissue/blood}) / F_{tissue}$$  \hspace{1cm} (3)

The time constant for the VRG is between 1.5 and 4 minutes for most inhalants.

The next, slower exponential portion of the tail of the curve represents "wash in" to a tissue group of intermediate speed. Since muscle comprises most of this tissue group, the second group is termed the muscle group (MUS, or M). Muscle time constant is several hours.

The final, slow exponential portion barely rises at all during most anesthetics. It represents "wash-in" to fat (FAT, or F) and other very poorly perfused tissues. The time constant is so long that this tissue group can be considered an infinite sink which completely removes anesthetic from the small amount of blood (5%) perfusing it.

The heights of portions of the alveolar tension curve (ATC) are quantified as plateaus or asymptotes. Their heights are determined by blood flow to "unanesthetized" tissues. The 1st plateau occurs before VRG wash-in. The 2nd plateau occurs after VRG wash-in but before muscle wash-in. The 3rd plateau (after muscle but before fat) and 4th plateau (after fat) exist but are only seen during extremely long anesthetics. In each case, the fraction of blood flow to unanesthetized tissues is designated F.

The four panels of Figure 1 show 1) Gas Man Graph, 2) Gas Man Graph with curves labeled, 3) Alveolar tension curve (ATC) with features identified, and 4) ATC with features quantified.
Figure 1. Alveolar Tension Curve Dissected

- **Isoflurane %**
  - Gas Man® Graph
  - $I = \text{inspired}$
  - $A = \text{alveolar tension curve (ATC)}$
  - $R = \text{vessel-rich group}$
  - $F = \text{muscle}$
  - $M = \text{fat}$

- **Relative %**
  - Gas Man Graph with curves labeled
  - $A = \text{alveolar tension curve (ATC)}$
  - $R = \text{vessel-rich group}$
  - $M = \text{muscle}$
  - $F = \text{fat}$

- **Alveolar tension curve (ATC) with features identified**
  - Initial rise
  - Knee
  - 2nd plateau
  - Tail (VRG portion)
  - Pseudo-plateau

- **Alveolar tension curve (ATC) with features quantified**
  - $\tau_{VRG} = \frac{\text{Vol}}{\text{Flow}}$
  - $2nd\ plateau = \frac{V_{VRG}}{F_{VRG}}$
  - $\tau_{l lung} = \frac{\text{Vol}}{\text{Flow}} = \frac{FRC}{V_A}$
  - $P_E = \frac{1}{1 + \frac{F \cdot CO \cdot \lambda_{AVG}}{V_A}}$
  - $P_I = \frac{1}{1 + \frac{CO \cdot \lambda_{AVG}}{V_A}}$
Figure 2. **Derivation of the Alveolar/Inspired Plateau Ratio**, the A/I tension ratio established before anesthetic returns to the lungs in venous blood. The fully-mixed lung compartment is depicted as a box representing the lung(s) with volume $V = \text{FRC}$, the patient’s functional residual capacity. On the left, alveolar ventilation ($V_A$) carries gas with inspired partial pressure $P_I$ into the lung while the same alveolar ventilation ($V_A$) removes gas with Alveolar partial pressure ($P_A$). On the right side of the lung, effective flow removes anesthetic. The removal rate is termed effective flow which is equal to cardiac output (CO) times blood/gas solubility ($\lambda_{B/G}$). If venous blood returned anesthetic agent to the lungs, then the return would be $P_V \cdot \lambda$. However, for the situation of interest here, no anesthetic yet returns in venous blood and $P_V = 0$. Since equilibrium requires the amount of substance entering and leaving the lung to be equal, we can equate the two sides of the lung picture as an equation.

$$P_I \cdot V_A - P_A \cdot V_A = P_a \cdot CO \cdot \lambda - P_V \cdot CO \cdot \lambda.$$  
Then, since $P_V = 0$,

$$P_I \cdot V_A - P_A \cdot V_A = P_a \cdot CO \cdot \lambda.$$  
Then, when $P_a = P_A$ (alveolar and arterial tensions are equal),

$$P_I \cdot V_A - P_A \cdot V_A = P_A \cdot CO \cdot \lambda.$$  
Rearranging terms,

$$P_I \cdot V_A = P_A \cdot CO \cdot \lambda + P_A \cdot V_A.$$  
Reversing sides and grouping $P_A$s,

$$P_A \cdot CO \cdot \lambda + P_A \cdot V_A = P_I \cdot V_A.$$  
Rearranging terms,

$$\frac{P_A}{P_I} = \frac{\dot{V}_A}{\dot{V}_A + CO \cdot \lambda}.$$  
Rearranging again,

$$\frac{P_A}{P_I} = \frac{1}{1 + \frac{CO \cdot \lambda}{\dot{V}_A}}.$$  

This is the common form of the alveolar/inspired plateau ratio.
Figure 3. **Gas Man Picture shows the behavior superimposed on the structure of the pharmacokinetic model for inhalants.** Annotations label each of the components. The model **structure** is represented by the compartments and the connections that link them. The model’s **behavior** is represented by the compartments filling to heights which represent anesthetic tension (partial pressure) in the various locations. Anesthetic travels from left to right in the top half of the figure, along the path from vaporizer (DEL) to breathing circuit (CKT), to lungs (ALV), to arterial blood (ART), to tissues (VRG [e.g., brain, heart], MUS, FAT) and to mixed venous blood (VEN). Each of these compartments along the anesthetic tension path imparts a delay and possibly a gradient (actually a ratio) in anesthetic tension. The end result is a system that behaves in a reasonably predictable and measurable manner. Simulation provides special benefit by allowing clinically-impossible but theoretically-important insightful experiments to be performed.

**Figure 3.**
Figure 4. Gas Man Graph shows the time course of anesthetic tensions in various locations from vaporizer to tissues. Locations include Vaporizer output (DEL), Circuit (CKT) or Inspired (I), Alveolar (A) or Exhaled (E), Vessel-rich tissue group (VRG) including brain, heart, and other well-perfused tissues, Muscle (MUS, M), and Fat (F). Annotations label each of the lines. The figure shows the response of each of these locations to a step change in isoflurane tension delivered from the vaporizer (DEL) with a fresh gas flow (FGF) equal to 8 L/min. The dotted line represents MAC, the minimum alveolar concentration (tension) for anesthetization. This is discussed later in the text.
Figure 5. Gas Man correctly depicts expired gas concentrations during induction, maintenance, and emergence from anesthesia. Bouillon and Shafer demonstrated that Gas Man® accurately predicts the expired anesthetic concentration observed in patients. They assessed accuracy during the first 15 minutes of induction (Panel A), 6 hours of maintenance (Panel A-1), and during emergence from anesthesia lasting 1 hour (Panel B), 2 hours (Panel C), 4 hours (Panel D) and 12 hours (Panel E).
Figure 6. The **Initial Rise of the Alveolar Tension Curve is an exponential curve.** For simplicity, we introduce a drug of solubility zero and call it zerothane. Because blood/gas solubility is zero, there is no uptake into blood with this agent. Thus, the A/I or \( \frac{P_A}{P_I} \) plateau ratio is \( \frac{P_A}{P_I} = 1/ [(1 + CO \lambda)/VA] = 1/1 = 1 \). Alveolar tension thus approaches Inspired Tension. The relationship between Alveolar Tension \( (P_A(t)) \) and Inspired Tension \( (P_I(t)) \) is \( P_A(t) = P_I(t) \left(1 - e^{-t/\tau}\right) \). The time constant, \( \tau \), measures the speed of this natural process of gas mixing.

For all fully mixed natural processes, the time constant equals the ratio of volume to flow. In this case the volume of interest is lung volume or FRC. Flow is lung gas flow, equal to alveolar ventilation. Thus, \( \tau = FRC/VA = 2 L / (4 L/min) = 0.5 \) minutes. The exponential wash in curve is plotted in Figure 6. At 0.5 minutes \((1\tau)\), expired tension equals 63% of inspired. At the end of 2 minutes \( (4\tau) \), expired reaches 98% of inspired and the process is complete.

We now apply this theory to the clinical situation. At the beginning of anesthesia, most clinicians remove nitrogen by administering oxygen for two minutes before inducing general anesthesia. This allows alveolar oxygen tension to come close to its maximum and provides the greatest oxygen reserve. Oxygen tension rises as nitrogen tension falls. We use the terms preoxygenation and dentrogenation interchangeably to describe this practice. The appropriate dentrogenation time, of course, varies with each of the determinants of tau. Thus, if FRC is halved and alveolar ventilation is doubled in the parturient, dentrogenation time is shortened by a factor of four from two minutes down to one-half minute. At the other extreme, if FRC is doubled as a result of chronic obstructive pulmonary disease and alveolar ventilation is halved by the respiratory depression from pre-operative opioid, dentrogenation requires four times as long or 8 minutes to complete.
Figure 7. The Knee of the Alveolar Tension Curve is formed as Alveolar Tension breaks away from the uptake-free Alveolar Tension wash in curve. A plateau is formed. The plateau height is related to alveolar ventilation, cardiac output, and blood/gas solubility, as depicted in the figure.

When drug solubility in blood is other than zero, during what would have been exponential wash in to the lungs, cardiac output and blood/gas solubility combine (multiply) to remove anesthetic agent. This causes alveolar tension to "break away" from the uptake-free lung wash in curve. Here, the plateau is flat because cardiac output takes anesthetic away as alveolar ventilation brings anesthetic in. To simplify and clarify, venous return of anesthetic to the lungs is set to zero. As can be seen from the figure, alveolar plateau height is inversely related to blood/gas solubility ratio.

Figure 7.
Figure 8. **Venous return converts the flat plateau into the up going tail** of the alveolar tension curve. As anesthetic returns from body tissues, first from VRG, much later from muscle and still later from Fat, venous return of anesthetic to the lungs produces the slow rise in alveolar tension in what is called the tail of the alveolar tension curve.

![Figure 8. Venous Return Converts Plateau --> Tail](image-url)
Figure 9. **Expired Tension curves obtained from patient data**, redrawn from Yasuda, Lockhart, and Eger 1991\(^{10}\) with overlaid theoretical values. The numbers labeled “knee” at the left of the figure are the theoretical knee-heights of the alveolar tension curves. These values closely approximate the expired tension knee heights. The numbers labeled “Tail” at the right are the theoretical Alveolar/Inspired tension ratios after the vessel-rich tissue group is fully equilibrated with arterial blood and before Muscle or Fat develop an appreciable anesthetic tension. Blood flow to VRG is 76% of cardiac output in this example. Numerical values are computed as

\[
\frac{P_A}{P_I} = \frac{1}{1 + \frac{F_T CO \lambda}{V_A}}
\]

where \(F_T\) is the fraction of cardiac output going to other than the vessel-rich tissue group. These tail height values closely approximate the expired tension tail heights after 30 minutes of anesthesia administration. The small curve at the left is the theoretical curve for zerothane with time constant 0.5 minutes.
Figure 10. **Inspired Overpressure** Ratio and Inspired Concentration to achieve one MAC. Inspired overpressure ratio is computed as the inverse of the plateau ratio at the knee of the alveolar tension curve. For example, for isoflurane, this is $1/0.38 = 2.6$. If one MAC alveolar tension is desired, the inspired concentration to achieve one MAC is computed as the overpressure ratio multiplied by the MAC of each drug.

Inspired Overpressure ratio to Maintain one MAC is lower than the Inspired Overpressure to Achieve one MAC. This is because anesthetic is returning in venous blood from fast tissues. Inspired Overpressure ratio to Maintain one MAC is computed as the inverse of the A/I ratio at the tail of the alveolar tension curve for each drug in the figure. For isoflurane, for example, this is $1/0.71 = 1.4$. Inspired Concentration to Maintain one MAC is computed as the tail overpressure ratio multiplied by the MAC of each drug. For isoflurane this is $= 1.4 * 1.1 = 1.5\%$.

This figure was created using Gas Man Version 2 by using the Overlay Screen, selecting "Show Inspired over MAC", and adding annotations.
Figure 11. Alveolar tension achieved using overpressure ratios shown in Figure 10 with a 1 MAC target. Note that in each case, the alveolar tension "knee" occurs at 1 MAC and alveolar tension rises a bit higher. After 3 minutes of anesthesia, inspired tension is reduced. This figure was created using Gas Man Version 2 (Ref, please) by using the Overlay Screen, selecting “Show Alveolar over MAC”, and adding annotations.

Figure 11.
Figure 12. **VRG (Brain) tension achieved with inspired overpressure** ratios shown in Figure 10, alveolar tension values shown in Figure 10, and a 1 MAC target. This figure was created using Gas Man Version 2 (Ref, please) by using the Overlay Screen, selecting “Show VRG over MAC”, and adding annotations.
Vital Capacity Induction with Sevoflurane results explained with Gas Man. Inspired, Alveolar, and Brain (Vessel Rich Group or VRG) levels of sevoflurane and nitrous oxide for the first minute after a vital capacity inhalation induction. Anesthetic levels are tensions (partial pressures) expressed in fractions or multiples of MAC. Curves were obtained by computer simulation using Gas Man with the data obtained in 32 patients\textsuperscript{11}. The 0.33 MAC line indicates the reported value for sevoflurane MAC-awake \textsuperscript{11}. The dotted lines reflect the expected kinetics if nitrous oxide were not present in inspired gas.

In each case, the patient performed a vital capacity (VC) maneuver from a breathing circuit primed with 8% sevoflurane in 75% N2O/O2. Fifty-nine percent (59%) of patients lost consciousness in one breath, taking 39 ± 3 seconds. The average for all 34 patients was 51 ± 4 seconds. This corresponds to a brain tension of approximately 0.5 MAC.

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Figure 14. **Bolus up and bolus down with Sevoflurane is explained with Gas Man and an agent monitor.** This figure depicts a Gas Man® simulation overlaid on the graphic trend displayed on an anesthetic agent monitor. A one hour anesthetic is depicted. The top and bottom ends of the vertical black lines represent inspired and end-expired agent concentration recorded by the Agent Monitor, part of the RGM (Respiratory Gas Monitor) in the Ohmeda Modulus 2 Central Display Anesthesia Delivery System. The thick black scale applies to the monitored inspired and expired concentrations. It is aligned with the thin black scale from the Gas Man screen. Gas Man curves show Circuit = inspired = light green, Alveolar = expired = dark green, VRG = Brain = red, Muscle = brown, and Fat = yellow.

From time = 0 to time = 3 min, the circuit outflow is sealed loosely with a glove, the sevoflurane vaporizer is set to 8%, and fresh gas flows is 4 l/min. The 3 liter reservoir bag is emptied into the waste anesthetic gas system (scavenger) each time it becomes full. At Time = 3 min, the bag has been emptied three times and is again full. Prior to time = 3 min, inspired (light green) shows that circuit concentration has risen although this value is not yet sensed by the Agent Monitor (black).

At time = 3 min (Anesthesia Time = AT = 0 min), the patient takes a deep breath from the circuit. The agent monitor (upper end of black line) shows Inspired = 6 %, and Expired (lower end of black line) rapidly reaches 4 and then 5 %. Inspired (light green) and Expired (dark green) simulated concentrations follow the same time course. At the same time, the Brain level (red) begins to rise. The patient then continues to breath at 4 l/min.

At time = 4 min (AT = 1 min), the patient has breathed sevoflurane for one minute and the brain has reached 1%. At AT = 2 minutes, Brain = 2%, the 1 MAC level depicted by the dotted line. At Time = 9 min (AT = 6 min), Brain = 4 % = 2 MAC and the real patient was intubated without the aid of an IV neuromuscular blocking drug. Immediately after intubation, with the patient anesthetized adequately for intubation but excessively for surgical prep, the vaporizer is set to 0 (Anesthesia machine and Gas Man), and Inspired and Expired fall rapidly. The Brain falls slowly to 1 MAC three minutes later and the vaporizer is set to 3 % at time = 12 min or AT = 9 min).

At time = 45 min (AT = 43 min), surgery is complete. The Vaporizer is set to 0 and FGF is set to 10 L/min. Inspired falls rapidly to zero, Expired falls rapidly to 0.5 %, and brain reaches 0.7% or 0.33 MAC 3 minutes later. At this time, the patient’s eyes open, the anesthesiologist removes the tracheal tube, and Expired agent is monitored as it continues to leave the patient’s body.
Table 1. **Maximum Effect - Vaporizer to the Top.** This table depicts the expected response to breathing the maximum concentration each agent-specific vaporizer can deliver. For nitrous oxide, 75% is chosen as a rational safety limit. For the other agents, the maximum dial setting routinely available is listed. The Alv % column shows alveolar concentration after 30 seconds of breathing with normal minute ventilation. By this time, a stable alveolar tension plateau is established. The Alv MAC fraction column shows the alveolar and blood anesthetic tension at this time. The brain anesthetic tension approaches this value with time. The note is an assessment of the clinical effect of the result predicted.

<table>
<thead>
<tr>
<th>Agent Name</th>
<th>Max % Setting</th>
<th>Alv %*</th>
<th>Alv MAC fraction</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2O</td>
<td>75</td>
<td>51</td>
<td>0.5</td>
<td>Slight effect</td>
</tr>
<tr>
<td>Enf</td>
<td>5</td>
<td>1.7</td>
<td>1.0</td>
<td>Small effect</td>
</tr>
<tr>
<td>Halo</td>
<td>5</td>
<td>1.5</td>
<td>1.7</td>
<td>Moderate effect Used in peds</td>
</tr>
<tr>
<td>Iso</td>
<td>5</td>
<td>2.2</td>
<td>1.9</td>
<td>More Potent than halothane</td>
</tr>
<tr>
<td>Des</td>
<td>18</td>
<td>13</td>
<td>2.1</td>
<td>Don’t use it and avert sympathetic act.</td>
</tr>
<tr>
<td>Sevo</td>
<td>8</td>
<td>4.8</td>
<td>2.3</td>
<td>Very Potent, well tolerated</td>
</tr>
</tbody>
</table>

* Alv = Alveolar tension 30 sec after breathing maximum agent begins.
Figure 15. **Theoretical curve of alveolar tension during wake up** from infinite length 1 MAC anesthetics with several agents. These curves are obtained by inverting the curves in Figure 9. Knee and Tail heights are computed as one minus the Knee and Tail heights during induction.

The value 0.33 MAC is designated with a dotted line in the figure. This MAC fraction is important since it corresponds to “MAC Awake” for desflurane\(^\text{13}\) and sevoflurane\(^\text{14}\). MAC Awake for isoflurane is 0.4 MAC\(^\text{15}\) while MAC Awake for Halothane is 0.52 MAC\(^\text{16}\).

With the insoluble agents sevoflurane and especially desflurane, alveolar tension falls below the MAC Awake line very quickly. Indeed, this threshold is crossed during lung wash out. Thus, no matter how long anesthesia is administered at one MAC, wake up time is quite short with these insoluble agents.

Of course, if other concomitant medications provide excessive analgesia or sedation, their effect is added to that of the inhalant, and MAC Awake for the inhalant appears lower. Lines representing lowered MAC Awake are not shown in the figure.

There is an important difference between the clinical kinetics of anesthesia induction and emergence. During induction, overpressure can be used to rapidly produce 1 MAC alveolar tension using any of the agents as long as the vaporizer can be set sufficiently high to compensate for blood/gas solubility. However, during wake up, underpressure cannot be provided since the vaporizer cannot be set below zero. Thus, anesthetic tension in body tissues can at best exponentially approach the desired end point, 0, but only if this 0 level is achieved in arterial blood. Thus, wake up is usually slower than induction.

For shorter anesthetic administrations, alveolar tension initially falls to a level which is lower than after a long anesthetic. The observed short-anesthetic plateau or knee is lowered by blood returning from slow tissues (muscle and fat) with low anesthetic tensions. This is not shown in the figure but can be shown with the Gas Man Simulation.
Common Misinterpretations of MAC

We must recognize that it is not anesthetic level in the alveolar gas or blood that is of interest clinically. We only use these data because we can measure them more readily than anesthetic level in the target organ, the brain. Furthermore, the level that counts is anesthetic partial pressure or tension, not anesthetic concentration. Tension is important because it equalizes in all compartments while concentration merely equilibrates, producing constant concentration ratios which do not equal one. Typically, brain tension lags behind that in arterial blood by the blood-to-brain time constant, about two minutes. One or two time constants are required for brain-blood equilibrium if alveolar tension does not fall too rapidly, otherwise four time constants are required. This is shown in Figure 15, above.

Thus, if we analyze the term MAC representing minimum alveolar concentration (for anesthetization), we find that all three letters (MAC) are in error. To correctly use MAC, we must recognize that M is the median level for anesthetization; it divides the population in half. Next, it is brain not alveolar level that causes anesthetization. Finally, it is partial pressure or tension, not concentration, that affects the brain. A more correct term than MAC might be MBT, Median Brain Tension (for anesthetization).

Figure 16. The Breathing Circuit in schematic form shows the interaction of breathing circuit, expired gas, and fresh gas, in the composition of inspired gas.

Fresh Gas Flow (FGF) carries Agent into the breathing circuit where Inspired gas is formed. Inspired gas goes to the patient who then exhales expired gas. Expired gas returns to the CO2 Absorber assembly where it either exits out the “pop-off valve” or passes through the CO2 absorber to mix with Agent-containing Fresh gas to produce Inspired Gas.

When FGF into the circuit greatly exceeds patient ventilation around the circuit, the composition of inspired gas closely mimics that of the FGF. However, when FGF is much less than patient ventilation, the dominant component of inspired gas is the patient’s own expired gas. Inspired gas is composed of an appropriately weighted average of expired gas and fresh gas.

The PE/Pi ratio and agent tension in exhaled gas has a tremendous impact on the clinician’s ability to reduce fresh gas flow and reduce agent expense. Agents with low solubility provide high expired concentrations which do not significantly dilute the composition of fresh gas. Thus, low solubility facilitates low flow which reduces the cost of anesthesia administration. The quantitative measure of this dilution is the difference between the tail height and one. Thus, from Figure 9, for isoflurane this value is 1 - 0.71 = 0.29. For desflurane this value is 1 - 0.88 = 0.12. The relative dilution by exhaled isoflurane compared with exhaled desflurane is thus 0.29/0.12 = 2.4.

Figure 16.
Figure 17. Low fresh gas flow and high vaporizer setting produce a controlled gentle rise in inspired desflurane and provide excellent clinical control with reduced cost and waste. The original papers and Package Insert for Desflurane suggest it be administered to patients after IV induction and that inspired and expired concentration should be made to rise slowly over several minutes\textsuperscript{19}. To this end, desflurane is usually administered at high fresh gas flow (e.g., 5 L/min) with progressively increasing vaporizer setting, beginning at 3 %. When this is done, there is much opportunity for variation in technique and much waste of agent. A smooth rise of inspired and expired desflurane can be achieved with low FGF and high vaporizer setting, specifically 1 L/min and vaporizer set to 18\%\textsuperscript{20}. The figure shows desflurane administration at 5 L/min and 1 L/min with vaporizer settings as described above.

Panel A = Gas Man graph with FGF = 5 L/min and adjusted vaporizer setting. Panel B = Gas Man graph with FGF = 1 L/min and Vaporizer = 18\% until 1 minute after Alv = 1 MAC = 6 \%. Panel C shows an agent monitor trend depicting the same anesthetic as Panel B.

**Figure 17.**

A (5 L/min FGF)  
B (1 L/min FGF, 18\%)

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**Panel A**

**Panel B**

**Panel C**
Figure 18. **Fully mixed and Ideal breathing Circuits.** Graphs show Inspired isoflurane concentration in a semi-closed breathing circuit with vaporizer set to 5% with fresh gas flow 2 liters per minute. The two lines depict two circuits, the fully mixed circuit and the ideal circuit.

In the perfectly mixed breathing circuit, fresh and exhaled gas mix in proportion to their flows to produce inspired gas. However, the presence of valves in the breathing circuit allows it to behave in a more ideal manner. In an ideal breathing circuit, fresh gas would be comprised of inspired gas in preference to exhaled gas which would leave the circuit first. If FGF exceeded patient ventilation, Inspired tension would equal Delivered Tension from the vaporizer. Real circuits behave in a manner somewhere between the two extremes of Ideal and Fully Mixed.

**Figure 18.**
Economics of Low Solubility and Low Flow

A brief discussion of economics is in order here. The manufacturing process for desflurane begins with manufacturing isoflurane. Then, a single fluorine atom substitutes a chlorine atom and desflurane results. At the time of desflurane's introduction, its manufacturer (Ohmeda Pharmaceutical Products Division, formerly Anaquest) priced 1 mL of liquid desflurane at $0.27, compared with generic isoflurane at $0.79. This would have resulted in desflurane anesthetic administrations costing twice as much as isoflurane if both were used the same fresh gas flow. However, desflurane's low solubility allows FGF to be reduced to 1/3 that of isoflurane to maintain the same degree of control. When flow was reduced to this level, desflurane was 33% less costly than isoflurane. And, at still lower flows, desflurane became even more economical. Since desflurane's introduction, the price of generic isoflurane has halved, making desflurane 30% more costly than isoflurane at fresh gas flows that provide equal levels of control. However, greater relative overpressure is required with low flow isoflurane during deepening and maintenance of anesthesia and desflurane's control during emergence can never be equaled by isoflurane because the minimum vaporizer setting with both agents is zero. Figure 19 provides a cost comparison of three agents as a function of fresh gas flow. In clinical practice, after IV induction and tracheal intubation, starting with a FGF of 1 L/min with the desflurane vaporizer set to 18% provides a smooth slow rise in inspired tension (to avert sympathetic activity) while controlling cost of administration. Vaporizer setting or FGF is reduced after about 5 minutes, when expired desflurane concentration has reached the desired level, around 1 MAC.

In a closed circuit, where fresh gas flow equals metabolic oxygen need plus anesthetic storage requirement and there is no waste, desflurane costs $2.70/hr while isoflurane costs $1.64/hr; both costs are quite small even when administered at 1 MAC alveolar concentration here. In addition, because of desflurane's low solubility, the 18% (3 MAC) maximum vaporizer dial setting is sufficient to maintain anesthesia. This is not true for isoflurane where the maximum dial setting of 5% (4 MAC) fails to deliver sufficient anesthetic to maintain adequate depth. While liquid injection or excess flow and waste is a necessity with isoflurane in closed circuit, desflurane allows closed circuit anesthesia using only the standard (Ohmeda Tec 6) vaporizer with little excess flow or waste.

Figure 19. Comparison of hourly cost of sevoflurane, desflurane, and isoflurane as a function of fresh gas flow. Bottle prices are in parentheses. Equations are regression lines relating cost to FGF while maintaining 1 MAC alveolar concentration of each agent. Costs are computed using Gas Man Version 2.1 for Windows1.
Dangers of Low Flow

When fresh gas flow is low, inspired oxygen is significantly affected by fresh gas flow. One must recognize that the concentration of gases in the breathing circuit approaches the concentration of the net flow of gases into the circuit. But, the net flow must include flows into the circuit and flow out of the circuit. And, flow out of the circuit must include uptake of oxygen, nitrogen, and nitrous oxide. After equilibrium is established, net flow of nitrogen is zero. If nitrous oxide is employed, nitrous oxide uptake is approximately 100 mL/min after the first 30 minutes of stable anesthesia. Thus, the uptake of oxygen is greater than that of nitrogen or nitrous oxide. Therefore, the inspired concentration of oxygen will always be lower than that of the fresh gas flow.

A useful example to help understand the impact of oxygen uptake on inspired oxygenation is to consider administering 1 L/min of air and no oxygen to a semi-closed breathing circuit with patient awake and breathing. The inflow is 1 L of oxygen comprised of approximately 200 mL of oxygen and 800 mL of nitrogen per minute. But, oxygen uptake is 200 mL per minute and nitrogen uptake is 0 mL/min. Thus, the net inflow of oxygen is 200 mL/min FGF minus 200 mL/min uptake = 0 mL/min. The net inflow of nitrogen is 800 mL/min - 0 mL/min uptake = 800 mL/min nitrogen. Thus, the breathing circuit composition will approach 0% oxygen and 100% nitrogen and result in certain death.

The danger of inspired hypoxia is averted by always adding the patient’s oxygen consumption to the oxygen flow setting.

Figure 20. Graphic trend of inspired oxygen and Pulse Oximeter Saturation as a volunteer breaths 1 L/min air. Inspired oxygen first falls as an exponential curve. Later, inspired oxygen concentration falls linearly until the experiment is discontinued with FIO2 = 8% and Saturation = 82% after 7 minutes of breathing.
Figure 21. Anesthetic control in the future. Here we see a possible control panel for inhalation anesthesia. Rather than our conventional mechanical control of a vaporizer, we see adjustments for Agent Name, Setting Units (% or MAC), Setting Value, and Location. The Location choices are Vaporizer (traditional), Inspired (few in 2000), Expired, and Brain. The anesthesiologist determines the depth (MAC) or concentration (%) of anesthesia he desires in the patient’s brain and then decides how to get there and what controls to employ. Whether different levels of training will be required to use different control locations is an interesting question. Across the range from beginners to experts, who should be allowed to use the brain control and who should be allowed to use the vaporizer control? It may be that vaporizer control is reserved for experts and novices could only use Brain Control. It is possible that novices could provide safe and effective anesthesia if allowed to ignore the interactions of vaporizer setting, fresh gas flow, and ventilation and control the important variable - anesthetic depth. When they became proficient with “automatic” mode, they could develop their skills with “manual” mode - vaporizer and fresh gas flow control.
Recap

This document shows and explains the relationship between anesthetic tensions in various locations and how they vary over time. Examples are taken from Gas Man® and from clinical experience documented by gas monitors. A more complete understanding of inhalant kinetics can be obtained by creating these and numerous advanced graphs using the same simulation program, Gas Man®. The current version is Version 3.1.8 for many computer platforms.

References


3. Personal communication, Edmund I Eger II


17 Weiskopf RB Eger EI II. Comparing the costs of inhaled anesthetics. Anesthesiology 79:1413-8, 1993

