

Pharmacokinetics of inhaled anesthetics and the general anesthetic equation – a reappraisal

J. F. A. HENDRICKX

Potent inhaled anesthetics are administered in a variety of ways. For many practitioners, the choice of the breathing system and fresh gas flow (FGF) may depend in part on habit and on how they have been taught to administer these agents. Lucien Morris, inventor of the copper kettle, has reviewed many of the reasons “why anaesthetics are given by habit instead of individual plan and thoughtful reasoning” (1). Many anesthesiologists have been reluctant to incorporate low FGF techniques into their clinical practice, even though (1) the advantages of lower FGF are well described (less waste and consequently costs and pollution, conservation of heat and humidity, educational value) ; (2) technology has evolved up to a point where most of the clinically relevant gases in a circle system can be monitored online ; and (3) the theoretical principles of low-flow anesthesia have been described in extensu by LOWE and ERNST more than 2 decades ago (2).

Over the last ten years, we have explored the pharmacokinetics of modern inhaled anesthetics in a circle system with the use of technology that is currently available to every clinician. Many of our studies are based on the theoretical framework of LOWE and ERNST, the general anesthetic equation (GAEq). In this mini-review, we highlight some aspects of our clinical research that may help the clinician understand what happens when the FGF is lowered (especially at and below 1 L/min). We emphasize, however, that we do not aim to present an uptake model that can be used to construct rigid administration schedules to be used in blind faith by the interested anesthesiologist. Rather, we present principles and monitoring techniques that allow the clinical application of many of the observations we have in made regarding low-flow anesthesia. Lucien Morris has said that “Safe anesthesia requires the dedicated attention to the patient by a safe anesthesiologist no matter which method, device, or kind of apparatus is in vogue” (1).

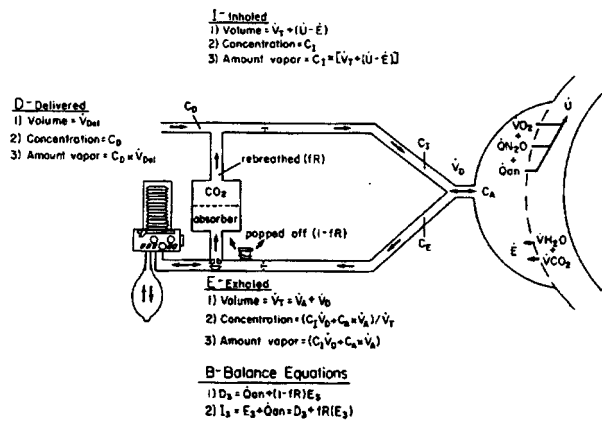
THE CONCEPTS OF THE GENERAL ANESTHETIC EQUATION (GAEq)

According to LOWE and ERNST, the delivered concentration (vaporizer dial setting) required to attain and maintain a constant end-expired concentration in a circle system can be predicted for any FGF if the following are known : (1) uptake of O₂, N₂O, and potent inhaled anesthetic ; (2) CO₂ and H₂O production ; and (3) alveolar and deadspace ventilation. Figure 1 displays the circle system, with the patient attached (2). The amounts of gases delivered (common gas outlet), inhaled, and exhaled can mathematically be quantified. By rearranging the components of these equations, a formula can be derived that mathematically expresses the vaporizer dial settings over time required to attain and maintain a constant end-expired concentration with a range of FGF : the GAEq (Fig. 1) (2). Even though many more factors are involved, and a more complex description can be used (incorporating factors like nitrogen wash-out, physiological versus anatomical dead-space ventilation, generalization to STPD conditions, etc.), this equation has didactic value and can be used as a first approach to study the kinetics of gases and vapors in a circle system.

A three-dimensional plot can be constructed that displays the “anesthetic continuum”, the vaporizer dial settings over time for any FGF for every agent at every desired end-expired concentration (Fig. 2) (2, 3). Of all these factors, the uptake pattern is of paramount importance : the uptake pattern will reflect itself in the way the anesthesiologist has to adjust the vaporizer dial setting (or liquid injection rate during closed-circuit anesthesia) over time. It should be clear that uptake of a

J. F. A. HENDRICKX, M.D.

Department of Anesthesiology/CCM, OLV Hospital, Aalst, Belgium.



- V_{del} = fresh gas flow (L/min)
- C_{del} = delivered (common gas outlet) concentration (%)
- VT = minute ventilation (L/min)
- VD = minute dead space ventilation
- VA = minute alveolar ventilation
- U = uptake of O_2 (V_{O_2}), N_2O (Q_{N_2O}), and anesthetic vapor (Q_{an}) (L/min)
- E = minute elimination of CO_2 (V_{CO_2}) and water vapor (V_{H_2O}) (L/min)
- fR = fraction rebreathed
- 1-fR = fraction of exhaled vapor exhausted from the system

Amount of vapor delivered = $C_{del} \times V_{del}$
 Amount of vapor inhaled = $C_1 \times (V_T + (U - E))$
 Amount of vapor exhaled = $C_1 \times V_D + C_A \times V_A$

By rearranging these factors, the general anesthetic equation can be derived :

$$C_D = \frac{Q_{an} [V_T + (U - E) - V_D \times fR] + (1 - fR) C_A \times V_A [V_T + (U - E)]}{V_A + (U - E) V_{del}}$$

Fig. 1. — Amounts of gases (= concentration x volume) delivered to the circle system and inhaled and exhaled by the patient. Modified after LOWE and ERNST (2).

potent inhaled anesthetic by the individual patient is the same regardless of the method employed to deliver it (assuming the same end-expired concentration is obtained) (2). Whether an open, semi-closed, or closed system is employed, a quantitative relationship exists between the desired arterial or alveolar concentration and the required delivered concentrations at any specific FGF (2). What determines end-expired concentration is patient uptake, alveolar minute ventilation, and inspired concentration of the anesthetic. How you get the desired inspired concentration depends on the FGF : in a circle system, with high FGF (> minute ventilation), the dial setting is virtually identical to the inspired concentration. With lower FGF, because of rebreathing, the dial setting will have to be higher than with high FGF to get the desired inspired concentration : the lower the FGF, the more the exhaled gas (with the lower expired concentration secondary to uptake) will dilute the inspiratory mixture. To maintain the end-expired concentration constant, the vaporizer dial setting has to be increased accordingly. The lower the FGF, the more the uptake pattern will therefore be reflected in the vaporizer dial settings (Fig. 3). In the extreme of FGF, during closed-circuit anesthesia, the liquid injection rate will exactly match uptake if we ignore leaks from the circuit and if we assume gases being sampled by the gas analyzer [± 200 ml/min] are redirected to the anesthesia circuit.

UPTAKE PATTERNS OF INHALED ANESTHETICS

Two uptake patterns have dominated the anesthesia literature : the square root of time (SqRT)

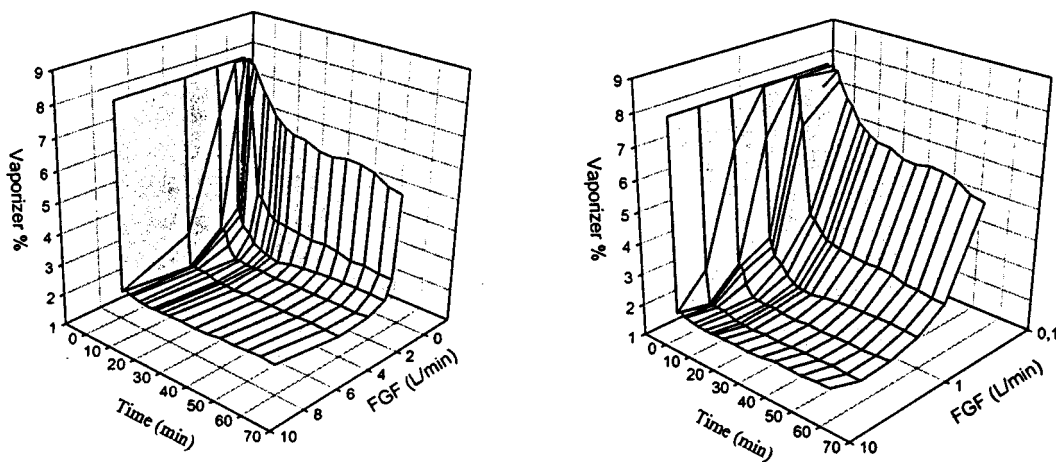
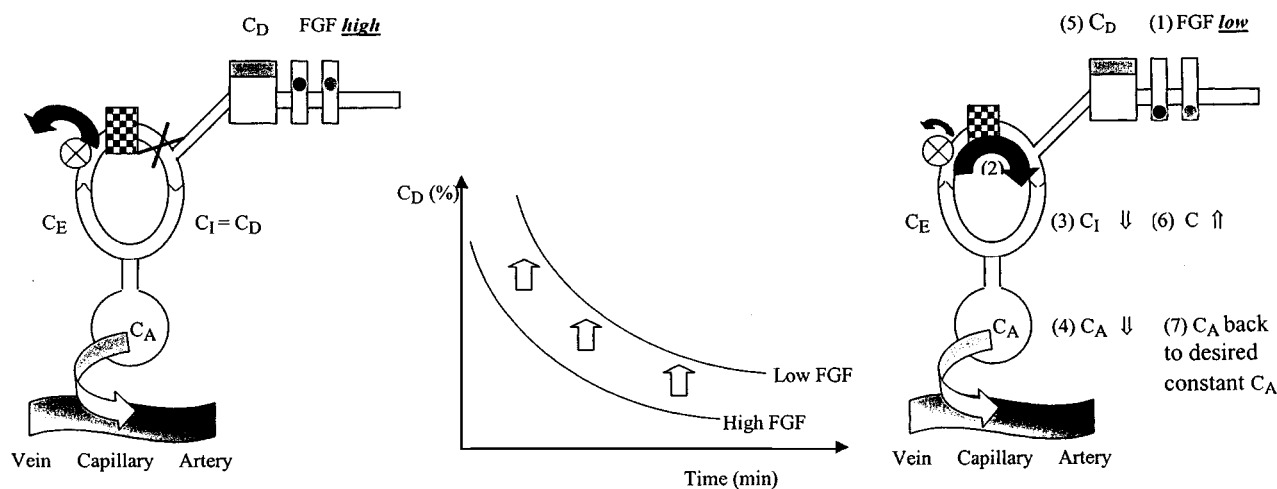


Fig. 2. — The general anesthetic equation for sevoflurane in O_2 at 0.6 MAC. Figure on the left uses a linear scale for fresh gas flow (FGF), figure on the right a logarithmic scale. The latter highlights the increase in vaporizer dial settings needed with lower fresh gas flows. Time (min) on X-axis ; sevoflurane vaporizer dials setting on Y-axis ; and FGF (L/min) on the Z-axis. Modified from ref 3.



With high FGF (FGF higher than minute ventilation) (left), all gases and vapor not being taken up by the patient escape via the pop-off valve. Because there is no rebreathing, C_D will equal C_I . The course of C_D required to attain and maintain a constant C_A is presented by the lower curve (in the middle) labeled "High FGF". With lower FGF (FGF lower than minute ventilation) (1), rebreathing occurs (2). The exhaled gas with the lower expired concentration (C_E) (due to uptake from the alveoli) dilutes the inspiratory mixture (3). Consequently, C_A will decrease (4). To maintain the same C_I and consequently C_A , C_D will have to be increased (5), increasing C_I , restoring the desired C_A . The C_D course over time is presented by the curve labelled "low FGF".

FGF = fresh gas flow ; C_D = delivered or vaporizer concentration ; C_I = inspired agent concentration ; C_A = alveolar agent concentration ; C_E = expired agent concentration. \otimes = pop-off valve ; \boxtimes = sodalime absorber

Fig. 3. — Effect of lowering fresh gas flows on vaporizer dial settings required to maintain a constant alveolar concentration of a potent inhaled anesthetic.

model and the more familiar four compartment (4C) model, recently modified to the five compartment (5C) model (2, 4-8). Note that, when uptake patterns are compared in this paper, it is always assumed that the end-expired concentration is maintained constant.

According to the SqRT model, the rate of uptake is inversely proportional to the square root of time (Vt) (2). The model was developed by LOWE and ERNST to predict vaporizer dial settings or liquid injection rates during closed-circuit anesthesia. An identical amount of agent (called the "unit dose") is taken up during each successive SqRT interval (0-1, 1-4, 4-9, 9-16, 16-25, etc). This unit dose is calculated as the product of cardiac output, blood/gas solubility and the fraction of the MAC administered. In addition, a "prime dose" is given to obtain the desired concentration in the circle system, FRC and the blood.

The original 4C model grouped tissues in 4 groups according to their time constants and capacity to absorb anesthetic agent : the vessel-rich group, muscle group, fat group and vessel-poor group. More recently, the 4C has been changed to a five compartment model : the lung has been introduced as the first compartment from which uptake occurs, the vessel-poor group which absorbs negligible amounts of vapor has been deleted and a-fifth "intertissue diffusion" compartment has been

added (9). Uptake by the individual organ can be predicted if organ volume, organ blood flow and tissue solubility of the agent is known. The model assumes that no alveolar-arterial gradient exists and that uptake is perfusion-limited.

Using liquid injection closed-circuit anesthesia to determine uptake, we found that both models overestimate initial uptake (first 15 minutes), and underestimate uptake thereafter (10-11). Uptake varied significantly between patients, and there were no consistent correlations between uptake and patient demographic parameters. These findings were confirmed when we used Fick's method to measure uptake (Fig. 4) (12-14). The reasons for the discrepancies between our data and the models are multiple and have been reviewed elsewhere (10). The almost constant rate of uptake (= uptake per unit of time) between 15 min and 60 min should facilitate low-flow techniques because there may be less of a need for frequent vaporizer dial setting changes, and therefore no need to continuously titrate the injection rate or vaporizer dial settings according to a complex mathematical model.

CLINICAL EVALUATION OF THE GENERAL ANESTHETIC EQUATION (GAEQ) IN O_2

The uptake pattern of a potent inhaled anesthetic should be reflected in its GAEq, in 2 particular

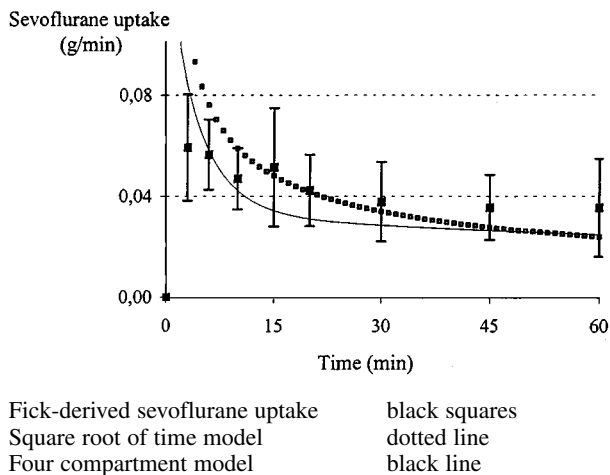


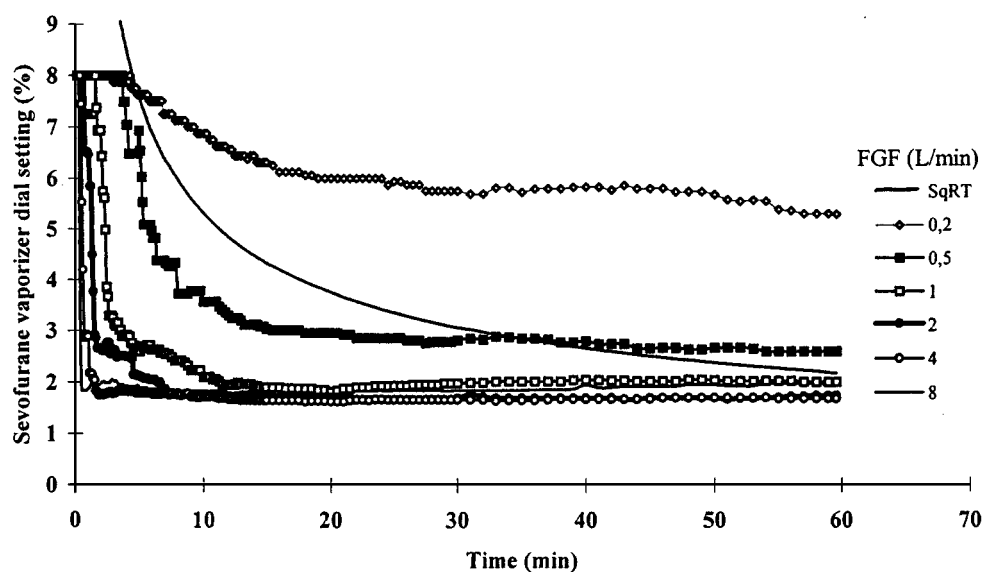
Fig. 4. — Fick-derived sevoflurane uptake

in that part of the GAEq presenting dial settings with low FGF (2). We have clinically evaluated the GAEq for halothane, isoflurane, sevoflurane, and desflurane using O_2 as the carrier gas at 0.65 MAC (3, 15-17). We previously determined the accuracy of the vaporizer used in this study, and we solved the problem of N_2 accumulation when redirecting gas sampled by the gas analyzer to the circle system to allow the use of FGF below 400 ml/min. (18-19). Figure 5 illustrates the delivered (= vaporizer dial setting) sevoflurane concentration into a circle system required to provide an end-expired sevoflurane concentration (Et_{sevo}) of 0.65 MAC (1.3%) for 6 different FGF. This graph contains the same information as figure 2. Several important findings deserve mention.

First, a similar pattern emerges for each FGF. After 15 min, no or only a limited number of further vaporizer dial settings are needed during the ensuing 45 min. For example, at a FGF of 1 L/min, the vaporizer dial setting to maintain the Et_{sevo} at 1.3% is not different at 60 min than at 15 min ($1.9 \pm 0.3\%$ at 15 min and 2.0 ± 0.3 at 60 min).

Secondly, the lower the FGF, the higher the vaporizer dial setting. This can be explained by rebreathing (see above). Similarly, rebreathing explains why the uptake pattern is more reflected in the vaporizer dial settings with lower FGF. Compare the uptake pattern from figure 4 with figure 5 : the uptake pattern is reflected in the vaporizer dial settings during the use of lower FGF. At one extreme of FGF, closed-circuit anesthesia, the vaporizer dial setting will closely match the uptake pattern (assuming a constant end-expired concentration, and no or minimal loss of gas through leaks and gas analyzer). At the other extreme, 8 L/min FGF (FGF \gg minute ventilation), the uptake pattern is hardly recognizable in the vaporizer dial settings except during periods of high anesthetic requirements (= first few minutes of the anesthetic).

Third, vaporizer settings at 0.2 L/min were very different from those predicted by LOWE and ERNST for closed-circuit anesthesia, with sevoflurane rate of uptake decreasing less than predicted. Similarly, the vaporizer dial settings according to the 4C model were found to consistently under-predict halothane vaporizer dial settings because the 4C model underestimates uptake after 15 min. (17).



SqRT = Vaporizer concentrations predicted by the square root of time model for closed-circuit anesthesia.

Fig. 5. — The general anesthetic equation of sevoflurane in O_2 at 0.65 MAC (1.3% end-tidal)

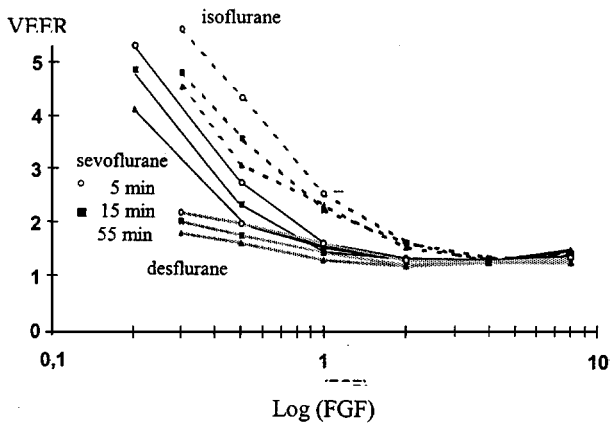


Fig. 6. — Vaporizer/end-expired ratio's (VEER) at 10, 15 and 55 min for isoflurane, sevoflurane, and desflurane in O₂ to maintain 0.65 MAC.

Fourth, vaporizer setting variability increases with lower FGF : the lower the FGF, the more the uptake will influence the composition of the inspiratory mixture (see comments above) and therefore the vaporizer dial setting (20). Because uptake differs up to 50% between patients, vaporizer setting variability increases with lower FGF (10, 20).

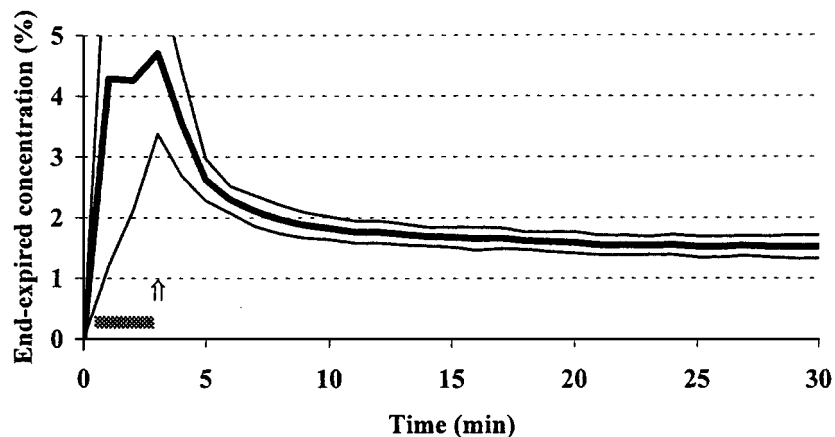
The GAEq patterns differ between agents : agents with lower blood/gas solubilities have lower vaporizer/end-expired ratios (VEER). Agents can be compared based on their VEERs. We constructed such a plot, the log(flow) – VEER plot (Fig. 6) (21). In this figure, the VEERs after 10, 15 and 55 min for a wide range of FGF (hence the logarithmic scale) are presented for 0.65 MAC. The FGF at which the VEER starts to increase significantly is lower for agents with a lower blood/gas

partition coefficient. It has been suggested that the agents with a lower blood/gas partition coefficient would be more “user-friendly” because their VEER is lower – there is less of a discrepancy between the vaporizer dial setting and the end-expired concentration.

LOW-FLOW ANESTHESIA AFTER OVERPRESSURE INDUCTION WITH SEVOFLURANE (22)

Our GAEq data can be used to construct simple administration schedules. The GAEq for sevoflurane indicates that, after the end-expired concentration has been maintained at 1.3% for 15 min, a vaporizer dial setting of 1.9% will maintain Et_{sevo} at approximately 1.3% during the ensuing 45 min with a FGF of 1 L/min (Fig. 7). We hypothesized that, after overpressure induction with sevoflurane in O₂/N₂O, enough sevoflurane would have been administered to increase the concentration of sevoflurane in the tissues responsible for the high initial uptake phase (0-15 min) at or above 1.3%. A single vaporizer dial and FGF setting change from 8 to 1.9% and from 8 L/min (O₂/N₂O 30%/70%) to 400 ml/min O₂ and 600 ml/min N₂O, respectively, immediately after overpressure induction would therefore suffice to attain and maintain Et_{sevo} at 1.3%. Et_{sevo} after 3 min was 4.88 ± 1.12%, and decreased slowly after reduction of FGF to 1.83 ± 0.19%, 1.59 ± 0.18%, and 1.52 ± 0.19% at 10, 20, and 30 min, respectively.

This example illustrates how previously derived pharmacokinetic parameters can be clinically



■ : overpressure induction (0-3 min).
 ↑ : placement of laryngeal mask ; fresh gas flow and vaporizer dial setting decreased to 1 L/min and 1.9% respectively.

Fig. 7. — Sevoflurane end-expired concentrations after a single vaporizer (8 to 1.9%) and fresh gas flow (6 to 1 L/min O₂/N₂O) setting change after overpressure induction.

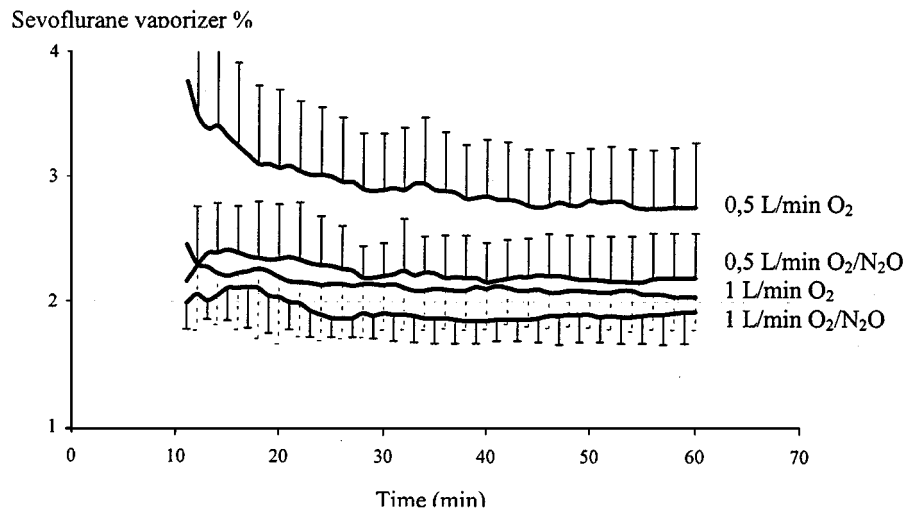


Fig. 8. — Effect of N₂O on vaporizer dial settings required to attain and maintain 0.65 MAC sevoflurane with a total fresh gas flow of 0.5 or 1.0 L/min.

applied to simplify low-flow anesthesia techniques. The number of relatively simple administration schedules that one could develop is almost unlimited. Other authors have been developing such administration schedules on more or less elaborated models based upon previously acquired uptake data (23).

EFFECT OF N₂O ON SEVOFLURANE VAPORIZER DIAL SETTINGS DURING LOW-FLOW AND MINIMAL-FLOW ANESTHESIA (24)

The Et_{sevo} attained after 20 and 30 min using the low-flow technique described in the previous paragraph with O₂ and N₂O as the carrier gas was 1.59 ± 0.18% and 1.52 ± 0.19%, respectively, which is higher than the 1.3% predicted by the previously derived GAEq for sevoflurane in O₂ (3). This finding was unexpected. One important factor had been overlooked : the GAEq as described in figure 4 was obtained using O₂ as the carrier gas. Because uptake of a second gas of a delivered gas mixture might decrease the amount of carrier gas and potent inhaled anesthetic leaving the circle system through the pop-off valve, we hypothesized that the vaporizer settings required to maintain a constant end-expired sevoflurane concentration (Et_{sevo}) during minimal- (MFA, FGF of 0.5 L/min) or low-flow anesthesia (LFA, FGF of 1 L/min) would be lower when sevoflurane is administered in O₂/N₂O than in O₂.

To explore this issue, fifty-six patients receiving general anesthesia were randomly assigned to 1 of 4 groups (n = 14 each), depending on the carrier gas and FGF used : group Ox.5L (O₂, MFA) ;

group NOx.5L (O₂/N₂O, MFA after 10 min high FGF) ; group Ox1L (O₂, LFA) ; and group NOx1L (O₂/N₂O, LFA after 10 min high FGF). The vaporizer dial settings required to maintain Et_{sevo} at 1.3% were compared between groups. Vaporizer settings were higher in group Ox.5L than in groups NOx.5L, Ox1L, and NOx1L ; vaporizer settings were higher in group NOx.5L than in group NOx1L between 23 and 47 min ; and vaporizer settings did not differ between groups Ox1L and NOx1L (Fig. 8).

Two factors affecting the pharmacokinetics of gases and vapors in a circle system may explain these findings. First, when N₂O is used, more carrier gas is taken up by the patient and less gas and vapor will leave the circle system through the pop-off valve. As a result, the vaporizer dial setting required to maintain a constant Et_{sevo} is lower when N₂O is used (compare group Ox.5L vs. NOx.5L). Second, because there is more rebreathing with lower FGF, more exhaled gas (with the lower expired concentration due to uptake by the patient) will dilute the fresh gas concentration to produce a reduced concentration of the vapor in the inspired gas. Consequently, the vaporizer dial setting will have to be higher to maintain the same inspired and alveolar (end-expired) concentrations. This phenomenon explains the differences between groups Ox.5L and Ox1L and between groups NOx.5L and NOx1L. The effect of both phenomena on the vaporizer dial setting required to maintain Et_{sevo} constant apparently becomes insignificant with higher FGF (in this study 1 L/min) : when the amount of gas and vapor lost through the pop-off valve relative to the amount taken up by the patient increases, the effect of N₂O and sevoflurane uptake on vaporizer

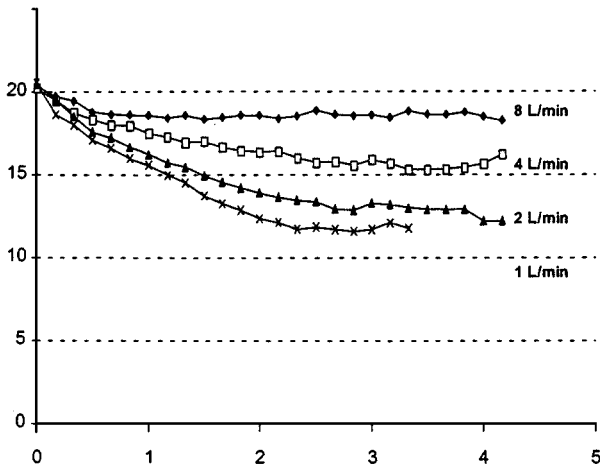


Fig. 9. — Course of $F_I O_2$ when breathing air in a circle system.

dial setting decreases. Above a certain FGF, vaporizer dial settings required to maintain a constant Et_{sevo} remain virtually the same. This phenomenon explains the absence of a difference between groups Ox1L and NOx1L.

AIR/O₂ MIXTURES IN A CIRCLE SYSTEM (25-28)

The carrier gas has a significant effect on the vaporizer dial settings required to attain a certain end-expired concentration of a potent inhaled anesthetic. While the kinetics of N₂O in a circle system have been described, less is known about the kinetics of air/O₂ mixtures at reduced FGF, even though air is commonly used as a component of gas mixtures during anesthesia. Previously published mixing charts for O₂/air were intended for use with non-rebreathing systems (commonly used in intensive care unit ventilators) (25).

The problem of using air in a circle system can be best understood by considering what happens if one breaths from a circle system while running a total FGF of 1 L/min air. This FGF would provide 210 ml/min O₂ and 790 ml/min N₂. A hypoxic inspiratory mixture rapidly ensues because O₂ consumption is 200-250 ml/min – due to rebreathing, the inspired O₂ concentration will progressively decrease while N₂ accumulates.

We studied the course of the inspired O₂ concentration ($F_I O_2$) in a circle system when using air with different FGF in adult volunteers. While the volunteers were breathing air from a circle system through a tightly fitting face mask, the FGF of air was progressively reduced 26 from 8 to 4, 2, and 1 L/min. (26). In all volunteers breathing only air, a hypoxic mixture ($F_I O_2 < 21\%$) developed (Fig. 9). At 8 and 4 L/min, $F_I O_2$ plateaued at 18.6 ± 0.8 and $15.9 \pm 1.3\%$ after 3 min, and SPO₂ did not change from baseline in any subject. At 2 and 1 L/min, $F_I O_2$ dropped precipitously to 13.4 ± 1.4 and $11.8 \pm 0.8\%$ within 2.5 min, and all volunteers were instructed to discontinue breathing from the circle system because the S_pO₂ decreased below 95% and were administered 100% O₂.

Next, we determined which O₂/air mixtures ensured an $F_I O_2$ of 30% with each of the 27 following total FGF : 8, 4, 2, 1, 0.8 and finally 0.5 L/min. (27). The composition of the O₂/air mixture to maintain $F_I O_2$ at 30% in all volunteers depended on the total FGF. The relative proportion of O₂ flow over total FGF of 8, 4, 2, 1, 0.8 and 0.5 L/min was 15 ± 1 , 18 ± 2 , 25 ± 3 , 43 ± 5 , 48 ± 6 , and $71 \pm 6\%$, respectively (Fig. 10).

In an ensuing clinical study in patients undergoing cardiac surgery, we examined the course of the inspired O₂ concentration when administering

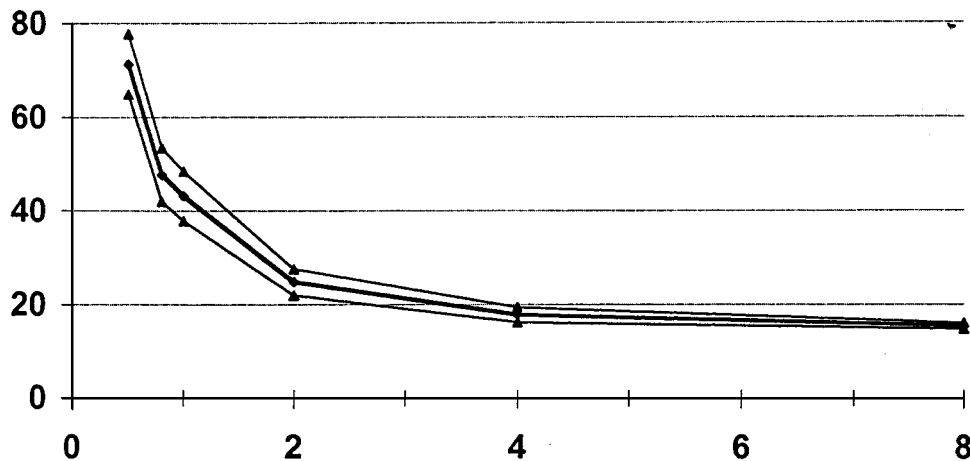


Fig. 10. — Ratio (%) of O₂ FGF/air FGF needed to maintain the inspired O₂ concentration at 30% with FGF ranging from 0.5 to 8 L/min in volunteers breathing in a circle system.

various combinations of air and O₂. During minimal-flow anesthesia (total FGF = 500 ml/min), a combination of O₂ (L/min) with air (L/min) of 0.2/0.3, 0.3/0.2, and 0.4/0.1 led to an F_IO₂ of 32.6 ± 4.2, 50.8 ± 3.6, and 71.7 ± 1.6% (28). The study limb examining the combination of 0.1 L/min O₂ with 0.4 L/min air was aborted because it led to hypoxic mixtures. This study points out that minimal-flow anesthesia with O₂/air mixtures can be easily practiced given appropriate equipment, monitoring, and knowledge.

It is intriguing that an *inspired* hypoxic mixture can form with apparently "safe" (non-hypoxic) mixtures being delivered *at the common gas outlet* with the use of air in a circle system, especially with low FGF. Under these conditions N₂ accumulates, leading to hypoxic gas mixtures due to O₂ uptake by the patient and rebreathing of O₂-depleted exhaled gases. Similarly, O₂/N₂O proportioning devices purport to deliver (= common gas outlet) at least 25% of O₂. If the proportioning device would deliver 200 ml/min O₂ and 600 ml/min N₂O (or even 400 ml/min), it is likely that an inspiratory hypoxic mixture would develop because N₂O uptake at an end-expired concentration of 60-65% is approximately 250-300 ml/min after approximately 15 min. When reducing FGF, it is important to start thinking in terms of *amounts* of agent (O₂, N₂O, air, potent inhaled anesthetic) to be administered *to maintain a certain partial pressure* rather than focusing on the partial pressure or concentration in the delivered gas (common gas outlet) only.

CONCLUSION

A circle breathing system is frequently used to administer potent inhaled anesthetics to adult patients because it has the potential to reduce anesthetic waste and consequently costs and environmental pollution by enabling the anesthesiologist to use lower FGF. Agent analysis is ubiquitous in many modern operating rooms and has the potential to reduce large part of the uncertainty that may exist with regard to the concentration of anesthetic agents that exist in the circle system, which many perceive as a dangerous "black box" when used with reduced FGF. Because O₂ consumption, N₂O uptake (during maintenance at 0.65 MAC), and gas sampling rate by the analyzer are all in the order of magnitude of 200 ml/min, FGF of 400-600 ml/min can be easily used if no major circuit leaks exist. When sampled gases are redirected and when N₂O is not part of the anesthetic, even lower FGF can be

used. Yet, despite all this technology, it is almost paradoxical that many anesthesiologists seem reluctant to reduce FGF below an ill-defined (personal preference) lower limit/threshold. While part of the explanation may be historical (see Lucien Morris), a gap in knowledge and appropriate training as well as lack of good, easy to apply administration schedules may have deterred many clinicians from embracing low-flow techniques more enthusiastically. In this review article, we have tried to "demystify" the kinetics of potent inhaled anesthetics in a circle breathing system with reduced FGF. After reevaluating existing uptake patterns, the concept of the general anesthetic equation is invoked to explain why and when reduced FGF increase the discrepancy between the vaporizer dial setting and the end-expired concentration. A combination of a better understanding of the factors that govern the kinetics in a circle system and the use of anesthetic gas monitoring bring the use of potent inhaled anesthetics with FGFG ranging from closed-circuit to high-flow within the realm of every clinician.

How to waste the least amount of gas when using a circle system? When lowering FGF, the relationship between the dialed vaporizer setting and the end-expired concentration changes: a higher vaporizer dial setting is needed to maintain the same inspired and consequently end-expired concentration because of rebreathing. The same applies to the concentrations of the carrier gases that are administered: the composition of the inhaled mixture no longer matches that of the delivered (common gas outlet) concentration. An analysis of this relationship requires consideration not only of the delivered concentration, but also of the amount of gas or vapor needed (1). Rather than adhering to administration schedules, a thorough understanding of some of the quantitative concepts outlined in this review will help the clinician understand what happens in the circle system when FGF is reduced.

References

1. Morris L. E., *Closed carbon dioxide filtration revisited*, ANAESTH. INTENSIVE CARE, 1994, 22, 345-58.
2. Lowe H. J., Ernst E. A., *The quantitative practice of anesthesia - Use of closed circuit*, Baltimore, Williams & Wilkins, 1981.
3. Hendrickx J. F. A., Van Zundert A. J., De Wolf A. M., *Clinical evaluation of the general anesthetic equation for sevoflurane*, ANESTHESIOLOGY, 1998, 89, A518 (abstract).
4. Eger E. I. II, *Anesthetic uptake and action*. Baltimore, Williams & Wilkins, 1974, 77-96.

5. Eger E. I. II, *Uptake and Distribution*. In : Miller R. D., ed. *Anesthesia*. 5th edition. New York, Edinburgh, London, Madrid, Melbourne, Milan, Tokyo, Churchill Livingstone, 2000, 74-95.
6. Andrews J. J., *Anesthesia systems*. In : Barash P. G., Cullen B. F., Stoeling R. K., ed. *Clinical Anesthesia*. Third ed. Philadelphia, JB Lipincott, 1997, 535-572.
7. Kofke W. A., Latta W. B., *Closed Circuit Anesthesia*. In : Firestone L., ed. *Clinical Anesthesia Procedures of the Massachusetts General Hospital*. Boston/Toronto, Little, Brown and Company, 1988, 226-44.
8. Hendrickx J. F. A., De Wolf A. M., *Costs of administering desflurane or isoflurane via a closed circuit*, ANESTHESIOLOGY, 1994, 80, 240-242 (letter).
9. Carpenter R. L., Eger E. I. 2nd, Johnson B. H., Unadkat J. D., Sheiner L. B., *Pharmacokinetics of inhaled anesthetics in humans : measurements during and after the simultaneous administration of enflurane, halothane, isoflurane, methoxyflurane, and nitrous oxide*, ANESTH. ANALG., 1986, 65575-82.
10. Hendrickx J. F. A., Soetens M., Van der Donck A., Meeuwis H., Smolders F., De Wolf A. M., *Uptake of desflurane and isoflurane during closed-circuit anesthesia with spontaneous and controlled ventilation*, ANESTH. ANALG., 1997, 84, 413-8.
11. Hendrickx J. F. A., Van Zundert A. J., De Wolf A. M., *Sevoflurane pharmacokinetics : influence of cardiac output*, BR. J. ANAESTH., 1998, 81, 495-501.
12. Frietman P., Hendrickx J. F. A., Grouls R., Van Zundert A. A. J., De Wolf A. M., *Fick-derived, sevoflurane uptake*, ANESTHESIOLOGY, 2001, 95, A478 (abstract).
13. Hendrickx J. F. A., Grouls R., Van Zundert A. A. J., De Wolf A. M., *The correlation between the isoflurane uptake pattern and vaporizer dial settings at different fresh gas flows*, ANESTHESIOLOGY, 2001, 95, A479 (abstract).
14. Hendrickx J. F. A., Van Zundert J. A. A., Grouls R., Frietman P., De Wolf A. M., *Fick-derived Halothane Uptake*. Abstract accepted for presentation at the ASA annual meeting, 2002.
15. Hendrickx J. F. A., Van Zundert A. J., De Wolf A. M., *Clinical evaluation of the general anesthetic equation for isoflurane*, ANESTH. ANALG., 1998, 86, S461 (abstract).
16. Hendrickx J. F. A., De Ridder K., De Geyndt A., Vandepuut D., Deloof T., De Wolf A. M., *Clinical evaluation of the general anesthetic equation for desflurane*, ANESTH. ANALG., 1999, 88, S341 (abstract).
17. Hendrickx J. F. A., Schaut L., Van Zundert A. A. J., Deloof T., De Wolf A. M., *Clinical evaluation of the general anesthetic equation for halothane*. Abstract accepted for presentation at the ASA annual meeting 2002.
18. Hendrickx J. F. A., De Cooman S., Deloof T., Vandepuut D. M., Coddens J., De Wolf A. M., *The ADU vaporizing unit : a new vaporizer*, ANESTH. ANALG., 2001, 93, 391-5.
19. Hendrickx J. F. A., Van Zundert A. J., De Wolf A. M., *Influence of the reference gas of paramagnetic oxygen analysis on nitrogen concentrations during closed-circuit anesthesia*, J. CLIN. MONIT. COMP., 14, 381-384, 1998.
20. Hendrickx J. F. A., Van Zundert A. J., De Wolf A. M., *Vaporizer setting variability increases with lower fresh gas flows*, ANESTH. ANALG., 1999, 88, S344 (abstract).
21. Hendrickx J. F. A., Vandepuut D., Van Zundert A. A. J., Deloof T., De Wolf A. M., *The log (flow)-vaporizer to end-tidal ratio (VEER) plot for potent inhaled anesthetics*, BR. J. ANAESTH., 1999, 82 (Suppl. 1) : A410 (abstract).
22. Hendrickx J. F. A., Vandepuut D. M., De Geyndt A. M., De Ridder K. P., Haenen J. S., Deloof T., De Wolf A. M., *Maintaining sevoflurane anesthesia during low-flow anesthesia using a single vaporizer setting change after over-pressure induction*, JOURNAL OF CLINICAL ANESTHESIA, 2000, 12, 4, 303-7.
23. Lerou J. G., Booij L. H., *Model-based administration of inhalation anaesthesia. 1. Developing a system model*, BR. J. ANAESTH., 2001, 86, 12-28.
24. Hendrickx J. F. A., Coddens J., Callebaut F., Vandepuut D. M., Deloof T., De Wolf A. M., *Effect of N₂O on sevoflurane pharmacokinetics during minimal and low flow anesthesia*, ANESTHESIOLOGY, 2002, 96 (8), in press.
25. Richardson F. J., Nunn J. F., *Performance and application of the Quantiflex air/oxygen mixer*, BR. J. ANAESTH., 1976, 48, 1057-64,
26. Schoenmakers B., Hendrickx J. F. A., Deloof T., Coddens J., De Wolf A. M., *Air and the circle system*, ANESTH. ANALG., 2000, 90, S230 (abstract).