

The Effects of Ventilation and Anesthetic Solubility on Recovery from Anesthesia:

An *In Vivo* and Analog Analysis before and after Equilibrium

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Recovery from inhalational anesthesia can be defined as the rate at which the alveolar anesthetic concentration decreases with time. The effects of alveolar ventilation and anesthetic solubility on recovery have not been fully evaluated, although their effects on induction are well known. Our results show that the interaction of ventilation and solubility on recovery is as on induction; i.e., the greater the ventilation the more rapid the fall in alveolar concentration, and the greater the solubility the slower the recovery. After equilibration, increased ventilation hastens recovery from nitrous oxide, but the effect is brief (2-3 min). Recovery from halothane is augmented most by changes in ventilation during the immediate postanesthetic period (10-30 min), while the maximum effect of ventilation on recovery from methoxyflurane is delayed.

An arterial-alveolar methoxyflurane gradient during recovery was demonstrated.

RECOVERY from inhalational anesthesia may be defined as the rate at which alveolar anesthetic concentration decreases with time. This definition provides a basis for studying the effect of alveolar ventilation and anesthetic solubility on recovery. The effects of ventilation and solubility on the rate of rise in alveolar concentration with induction have been studied,¹⁻³ but there is little information concerning their roles in the excretion, and subsequent fall in alveolar concentration, of inhalational agents. Mapleson studied recovery before and after equilibration and predicted that recovery would be the inverse of induction (the same

alveolar curves turned upside down) if total body equilibrium with the anesthetic agent were achieved.⁴ Salanitre *et al.* found close agreement between induction and recovery curves for nitrous oxide.⁵ If recovery is the inverse of induction, one would expect alterations in ventilation and changes in solubility to affect recovery to the same degree but in an opposite direction.

In this study we sought to obtain data *in vivo* concerning recovery from inhalational anesthesia following whole-body equilibration with three inhalational agents with widely different blood/gas solubilities (λ)⁶ at three different alveolar ventilations. We used these data to test the prediction that recovery is the inverse of induction. An electrical analog,⁷ previously shown to be suitable for prediction of the rate of alveolar concentration rise during induction, was used to obtain recovery curves for comparison with data *in vivo*. This same analog was utilized to describe alveolar recovery curves prior to equilibration following anesthesia at a constant alveolar concentration for 15, 30, 60, 120 and 240 minutes.

Methods

Unpremedicated mongrel dogs (15-20 kg) serving as their own controls, were anesthetized on separate occasions with nitrous oxide, halothane (Fluothane®) or methoxyflurane (Penthrane®). Nitrous oxide anesthesia was supplemented with intermittent doses of thiopental (Pentothal®). All dogs received 40 mg of gallamine (Flaxedil®) prior to each determination of recovery. The trachea of each dog was intubated. Total-body equilibration was evidenced by an alveolar anesthetic tension equal to inspired. This was achieved by a prolonged prior period of anes-

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thetia at a higher alveolar concentration. After equilibration had been maintained for at least 30 minutes the endotracheal tube was attached to a nonbreathing system (Fink valve) and the inspired anesthetic concentration was reduced to zero. The rate of recovery was then measured over 30 minutes at minute ventilations previously determined to maintain alveolar P_{CO_2} values at 20, 40 and 80 mm Hg. Alveolar anesthetic gas samples were drawn into glycerinized glass syringes at end-expiration via a narrow-bore nylon tube placed through the endotracheal tube near the carina. All gas samples were analyzed by gas chromatography. Nitrous oxide was analyzed with a thermoconductivity detector and a 24-inch silica gel column at 37 C; halothane with a flame ionization detector and a 6-inch silica gel column at 150 C; methoxyflurane with a flame ionization detector and a 4-inch hexadecane column on Chromosorb-P® at 37 C. The alveolar gas tensions at various times in recovery (F_E) starting at one minute were divided by the alveolar tension at the start of recovery (F_{E0}) (when equilibrium was present and inspired concentration equalled F_E). The resulting ratios (F_E/F_{E0}) were plotted against duration of recovery to obtain the alveolar recovery curves. Ventilation was controlled and PA_{CO_2} monitored continuously by an infrared analyzer. Esophageal temperature was monitored and maintained at 37 ± 1 C.

An electrical analog as described by Severinghaus⁶ and Mapleson⁷ was constructed for each agent. Curves obtained from the analog at ventilations of 2, 4 and 8 l/min were compared with the corresponding equilibrium curves derived from the data *in vivo*. We assumed these ventilations to equal PA_{CO_2} values of 80, 40, and 20 mm Hg, respectively, used in the experiments *in vivo*. The analog was also used to simulate recovery after 15, 30, 60, 120 and 240 minutes at constant alveolar anesthetic partial pressures.

Because of a previous report of an alveolar-arterial methoxyflurane gradient⁹ we determined arterial methoxyflurane levels and compared the recovery curves obtained with those from the corresponding alveolar gas analyses drawn at the same time. Three-ml samples

of arterial blood were drawn into calibrated heparinized 10-ml glass syringes. The barrel of each syringe was then filled to the 10-ml mark with room air and sealed with an airtight metal three-way stopcock. After 30 minutes of tonometry at 37 C the gas portion was analyzed for methoxyflurane by gas chromatography.

Results

Table 1 shows the average alveolar gas ratios and standard deviations for each anesthetic agent studied at three different alveolar ventilations at each time interval following equilibration. The average arterial ratios and standard deviations for methoxyflurane are shown. The corresponding ratios from the computer are also given.

In Figure 1 the average ratios *in vivo* and analog ratios following equilibration are plotted against recovery time for each agent. The close correlation between alveolar recovery curves and those curves derived from the analog allowed us to predict the effects of ventilation and solubility on recovery before equilibration using the analog curves. Nitrous oxide and halothane curves were constructed from alveolar gas values, while arterial blood concentrations were used for methoxyflurane. The most soluble agent studied, methoxyflurane, had the slowest, and the least soluble agent, nitrous oxide, the most rapid, decrease in alveolar concentration. Halothane with an intermediate blood/gas solubility, decreased at an intermediate rate. Regardless of solubility, the greatest decrease in alveolar concentration was always at the lowest PA_{CO_2} (*i.e.*, the greatest alveolar ventilation). The spread between alveolar curves at different ventilations was initially greatest with nitrous oxide, but after three to five minutes the spread was little affected by the volume of ventilation. The spread between methoxyflurane arterial concentrations was also little influenced by the alveolar ventilation during the period of recovery shown. Halothane spread was most affected by the volume of ventilation during the 30 minutes of recovery.

Figure 2 shows the effect of ventilation on the spread of alveolar anesthetic concentrations prior to equilibration.

TABLE 1. Average *in Vivo* Recovery Ratios and Standard Deviations for Each Agent at Various Times in Recovery*

	P_{ACO_2}	Minutes	Analog F_E/F_{E_0}	<i>In Vivo</i> F_E/F_{E_0}	SD	<i>In Vivo</i> F_A/F_{A_0}	SD
Nitrous oxide (6 dogs)	20 mm Hg	1	0.280	0.184	0.063	—	—
		3	0.132	0.115	0.037	—	—
		5	0.094	0.080	0.023	—	—
		10	0.064	0.071	0.038	—	—
		20	0.054	0.052	0.020	—	—
		30	0.044	0.035	0.006	—	—
	40 mm Hg	1	0.468	0.312	0.091	—	—
		3	0.252	0.186	0.053	—	—
		5	0.182	0.152	0.045	—	—
		10	0.124	0.108	0.034	—	—
		20	0.096	0.071	0.026	—	—
		30	0.082	0.067	0.024	—	—
	80 mm Hg	1	0.668	0.569	0.097	—	—
		3	0.440	0.420	0.117	—	—
		5	0.344	0.338	0.093	—	—
		10	0.238	0.272	0.098	—	—
		20	0.180	0.197	0.090	—	—
		30	0.154	0.128	0.042	—	—
Halothane (6 dogs)	20 mm Hg	1	0.596	0.507	0.051	—	—
		3	0.508	0.450	0.054	—	—
		5	0.452	0.412	0.047	—	—
		10	0.360	0.328	0.049	—	—
		20	0.284	0.243	0.051	—	—
		30	0.258	0.208	0.052	—	—
	40 mm Hg	1	0.734	0.664	0.078	—	—
		3	0.668	0.607	0.057	—	—
		5	0.620	0.547	0.066	—	—
		10	0.528	0.501	0.063	—	—
		20	0.440	0.427	0.058	—	—
		30	0.404	0.366	0.026	—	—
	80 mm Hg	1	0.858	0.872	0.083	—	—
		3	0.816	0.797	0.064	—	—
		5	0.780	0.762	0.066	—	—
		10	0.716	0.689	0.060	—	—
		20	0.640	0.609	0.066	—	—
		30	0.604	0.575	0.051	—	—

* The corresponding analog ratios are also shown. F_E/F_{E_0} is the alveolar gas tension at each time in recovery divided by the alveolar gas tension at the start of recovery. F_A/F_{A_0} is the corresponding ratio derived from arterial methoxyflurane concentrations. P_{ACO_2} is the alveolar carbon dioxide tension at each ventilation studied.

Figure 3 illustrates the impact of exposure time (15, 30, 60, 120, 240 minutes of anesthesia and total-body equilibration) on the rate at which the alveolar concentration falls.

At a constant ventilation (4 l/min) the impact of exposure time decreased as the solubility decreased.

In figure 4 methoxyflurane alveolar recovery

TABLE 1.—Continued

	PACO ₂	Minutes	Analog F _E /F _{E0}	In Vivo F _E /F _{E0}	SD	In Vivo F _A /F _{A0}	SD	
Methoxyflurane (5 dogs)	20 mm Hg	1	0.868	0.707	0.080	0.886	0.038	
		2	0.854	0.660	0.106	0.869	0.039	
		4	0.830	0.578	0.047	0.827	0.055	
		6	0.804	0.589	0.069	0.795	0.071	
		10	0.768	0.558	0.071	0.764	0.022	
		20	0.704	0.486	0.075	0.676	0.023	
	40 mm Hg	30	0.664	0.459	0.046	0.623	0.017	
		1	0.924	0.738	0.043	0.926	0.031	
		2	0.918	0.726	0.087	0.917	0.030	
		4	0.898	0.692	0.061	0.881	0.058	
		6	0.886	0.718	0.043	0.877	0.043	
		10	0.860	0.671	0.036	0.859	0.063	
	80 mm Hg	20	0.820	0.621	0.067	0.792	0.058	
		30	0.796	0.580	0.048	0.761	0.087	
		1	0.964	0.827	0.030	0.930	0.028	
		2	0.958	0.804	0.041	0.918	0.016	
		4	0.948	0.793	0.023	0.902	0.030	
		6	0.940	0.771	0.055	0.874	0.030	
			10	0.928	0.776	0.045	0.889	0.050
			20	0.888	0.719	0.076	0.858	0.047
			30	0.864	0.717	0.050	0.837	0.052

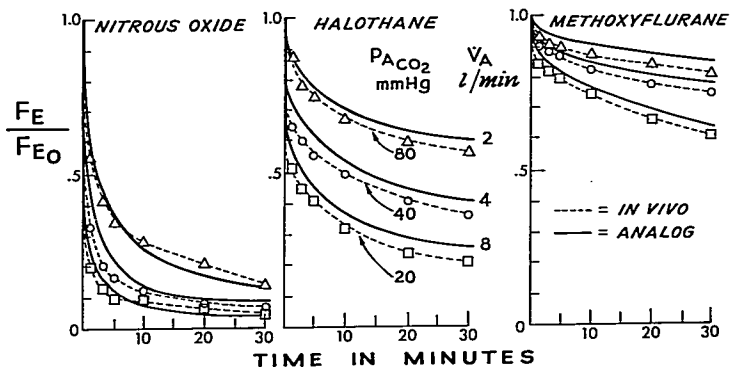


FIG. 1. *In vivo* alveolar recovery curves (dashed lines) following equilibrium at ventilations controlled to maintain alveolar P_{CO₂} values at 20, 40 and 80 mm Hg, are plotted during 30 minutes of recovery. The solid lines represent the corresponding analog recovery curves at alveolar ventilations of 2, 4 and 8 l/min. The *in vivo* F_E/F_{E0} ratios for nitrous oxide and halothane were derived from alveolar gas values, while arterial concentrations were used for methoxyflurane ratios. F_E/F_{E0} is the ratio of alveolar gas tension at each time in recovery divided by the alveolar gas tension at the start of recovery.

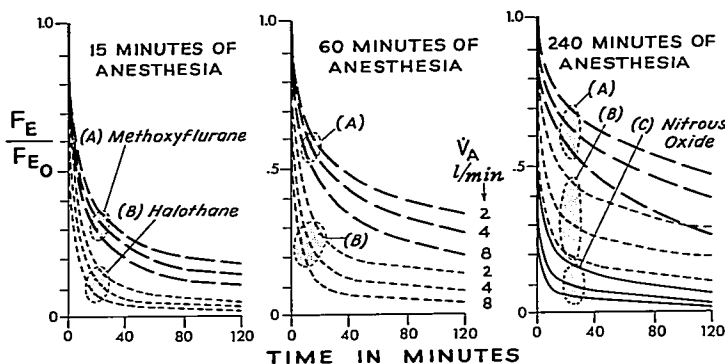


FIG. 2. Simulated F_E/F_{E_0} curves, showing the effects on recovery of alveolar ventilation (2, 4 and 8 l/min) after 15, 60 and 240 minutes of anesthesia.

curves derived from alveolar gas and arterial samples are compared. At each ventilation, the curves derived from the alveolar gas samples fell more rapidly than the arterial recovery curves. As illustrated in figure 1, the arterial curves followed the analog curves closely.

Discussion

Our data show that the alveolar anesthetic concentration on recovery is the inverse of that found during induction, and that the same factors which affect alveolar concentration on induction also affect recovery. During recovery alveolar concentration decreases in proportion to the volume of ventilation. As solubility of the inhalational agent increases, the rate of decrease in alveolar concentration is delayed.

The effects of changes in ventilation and solubility on recovery depend in part on the duration of anesthetic administration. Let us first examine the effects of different ventilations after total-body equilibration (a long anesthetic). An increase in ventilation quickens the rate at which the alveolar concentration falls. The extent to which this produces a separation between the curves for the same one anesthetic is a function of time and anesthetic solubility (fig. 1). With a poorly soluble anesthetic (nitrous oxide) the greatest separation

or spread occurs early in recovery (1-3 minutes). With a moderately soluble agent (halothane) the spread reaches a maximum between 10 and 30 minutes, while with a very soluble agent (methoxyflurane) the maximum spread is not reached for several hours. We note that the maximum spreads, 30-40 per cent, were similar for all three anesthetics [a 30 per cent spread for methoxyflurane is predicted from the analog data (curves were not determined *in vivo* over a long enough period to reach this point)]. The separation is slightly greater with lower solubility. The duration of maximum or near-maximum separation due to differences in ventilation also varies with anesthetic solubility (fig. 1). With nitrous oxide it is brief, lasting but two to three minutes; with halothane it lasts two to three hours; with methoxyflurane, several hours.

The clinical implications of these observations are that in the immediate postanesthetic period (60 minutes), a noticeable acceleration in the fall of alveolar anesthetic concentration by augmentation of ventilation is obtainable with halothane but not with nitrous oxide or methoxyflurane. In general, the effect of augmentation is too brief with a poorly soluble agent, too delayed with a very soluble agent, but "just right" with an agent of inter-

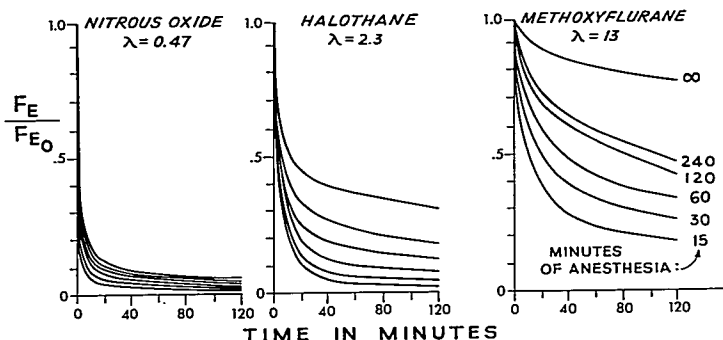


FIG. 3. Analog alveolar recovery curves illustrating the effects of the duration of anesthesia (equilibrium, 15, 30, 60, 120 and 240 minutes) and solubility on the rate of recovery at a constant alveolar ventilation (4 l/min).

mediate solubility. This is in contrast to induction, when augmentation of ventilation has the greatest effect on the rise in the alveolar concentration of the most soluble agent.¹ These observations ignore the effects of varying P_{aCO_2} values on cerebral blood flow.¹⁰ With increased ventilation, and hence lower P_{aCO_2} , cerebral blood flow is reduced and the reduction in alveolar anesthetic concentration achieved by the augmented ventilation is not as quickly reflected in a reduced cerebral concentration. However, the effect is relatively brief, producing but a few minutes delay in any case.

Let us now examine the effect of augmentation of ventilation on recovery when total-body equilibration is not present (fig. 2). The results are similar to those found after equilibration, but the maximum or near-maximum separations of the alveolar concentrations occur sooner and are smaller and briefer. Except for the reduction in size of the separation, the qualitative effect is the same as that resulting from a reduction in solubility of the anesthetic. For example, after 15 minutes of anesthesia the reduction of alveolar concentration by two-thirds requires less than three minutes with nitrous oxide at 2 l/min ventilation. With halothane at a ventilation of 4 l/min, a two-thirds reduction

takes only six minutes; when ventilation is 8 l/min it takes three minutes. With methoxyflurane at 4 l/min ventilation a two-thirds reduction takes 19 minutes; when ventilation is 8 l/min it takes 14 minutes. Note that the values for halothane obtained after 15 minutes of anesthesia are similar to those found after total-body equilibration with nitrous oxide. Similarly, the methoxyflurane recovery times at different ventilations are within the range of those following equilibration with halothane. However, the time separations for methoxyflurane recovery are not nearly as great (in the above examples, 14 and 19 minutes after 15 minutes of methoxyflurane vs. 12 and 90 minutes after equilibration with halothane). In summary, as the duration of anesthesia is shortened, the impact of variations in ventilation on recovery is decreased. As noted above, the decrease is in terms of both the effect (*i.e.*, the maximum separation of the alveolar curves) and the duration of the effect.

As noted by Mapleson, an increase in duration of anesthesia produces a delay in recovery for any one anesthetic and type of ventilation* (fig. 3). This effect varies with the solubility of the anesthetic. With a poorly soluble anesthetic the delay is small, but with increasing solubility duration of anesthesia is of progressively greater moment. For exam-

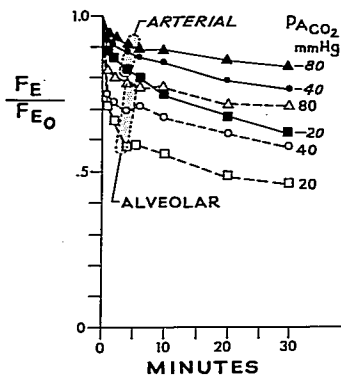


FIG. 4. *In vivo* alveolar (dashed lines) and arterial methoxyflurane (solid lines) recovery curves obtained from samples drawn concomitantly.

ple, suppose we wish to know how long it takes to achieve a two-thirds reduction of the alveolar concentration at an alveolar ventilation of 4 l/min. After 15 minutes of nitrous oxide anesthesia, a two-thirds reduction takes two minutes and is extended to just less than three minutes by a nitrous oxide anesthetic of infinite duration. After 15 minutes of halothane anesthesia, a two-thirds reduction takes six minutes, but after a two-hour anesthetic, 12 minutes. With methoxyflurane the spread is still greater. After a 15-minute anesthetic a two-thirds reduction takes 19 minutes, but after two hours of anesthesia it takes more than 120 minutes. In summary, rapidity of recovery is not greatly influenced by solubility after a short anesthetic but is affected considerably after a long anesthetic. The greater the solubility, the more the duration of anesthesia affects the rate of recovery.

Our data regarding the persistent difference between arterial and alveolar partial pressures of methoxyflurane on recovery (fig. 4) parallel the results of Holaday *et al.*, who observed similar differences on induction. These data underline the inadequacy of alveolar samples as a reflection of arterial partial pressure when a large inspired-to-end-tidal

partial pressure difference exists.¹¹ They also suggest that halothane data *in vivo* and the nitrous oxide data obtained early may be lower than the true arterial partial pressures of these anesthetics. Raising these values would bring them closer to the values predicted by the analog.

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