

## The Effect of Age on the Rate of Increase of Alveolar Anesthetic Concentration

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Using a mathematical model, the authors have confirmed the finding of Salanitre and Rackow that the rate of rise of alveolar halothane *in vivo* is more rapid in children and infants than in adults. The reasons advanced by Salanitre and Rackow for the more rapid approach to equilibrium include greater perfusion and ventilation and diversion of a greater fraction of cardiac output to highly perfused tissues. These partially explain the more rapid increase in the young. Additional explanations relating to differences between the experiments in children and adults are necessary to reconcile findings *in vivo* with simulation findings. Subanesthetic halothane concentrations were used in adults, while anesthetic levels were used in children. The depression of cardiac output and consequent reduction of uptake produced by anesthetic levels contributed to the more rapid increase in children. In addition, metabolism of halothane at subanesthetic levels probably caused a greater fraction of the inspired halothane to be degraded in the adults, thereby slowing the increase in alveolar concentration. (Key words: Uptake; Age; Halothane; Nitrous oxide; Methoxyflurane.)

Work of Salanitre and Rackow<sup>1</sup> suggested that the rates of increase of alveolar anesthetic concentrations in babies and children are substantially different from the rates in adults. For example, after 30 minutes end-tidal halo-

thane in children 1 to 5 years old reached 76 per cent of the concentration inspired. After an hour this value increased to 82 per cent. In contrast, studies in adults by Salanitre<sup>2</sup> and by Sechzer *et al.*<sup>3</sup> gave considerably lower values; at 30 minutes the adult alveolar concentration had risen to only 60-65 per cent of the concentration inspired, and by an hour it had increased further to only 63-68 per cent. Salanitre and Rackow suggested several reasons for these differences between adults and young children. Two explanations were selected as most likely: 1) both ventilation and cardiac output are relatively greater in relation to body mass in the young—this should produce a more rapid approach to tissue equilibration, a consequent decrease in uptake, and hence a higher alveolar concentration; 2) the young divert a higher proportion of cardiac output to well-perfused tissues such as brain, heart, liver and kidney. Since these tissues normally equilibrate rapidly, diversion of a greater fraction of blood flow to them raises the anesthetic partial pressure in mixed venous blood. The consequent reduction in the difference between venous blood and alveolar anesthetic partial pressures leads to the higher alveolar anesthetic concentrations seen in the young.

We sought to test these hypotheses by simulating the changes in ventilation and perfusion and in distribution of flow that might occur in the young. We then examined whether such changes mimicked the above-cited experimental differences found by Salanitre and Rackow. Our results qualitatively support their hypotheses. However, our results also suggest that these hypotheses are insufficient to explain all the differences between curves obtained in the adult and those obtained in the young.

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TABLE 1. Tissue Volumes and Perfusion

| Age Group   | Per Cent of Total Body Volume |              |           | Perfusion per Kg Relative to Adult              |  |
|-------------|-------------------------------|--------------|-----------|---|--|
|             | Vessel-rich Group             | Muscle Group | Fat Group | Proportional Changes in Tissue Group Blood Flow | Nonproportional Changes in Tissue Group Blood Flow |
| Adult       | 10.2                          | 50.0         | 22.4      | 100   | 100  |
| 8 years old | 13.2                          | 44.8         | 21.4      | 133   | 160  |
| 4 years old | 16.6                          | 40.7         | 23.4      | 155   | 222  |
| 1 year old  | 17.3                          | 38.7         | 25.4      | 189   | 281  |
| Newborn     | 22.0                          | 38.7         | 13.2      | 241   | 438  |

### Methods

Calculations of rate of increase of alveolar concentration were based on models described previously.<sup>4</sup> We modified the relative sizes of body compartments, their perfusion, and total perfusion to mimic the conditions found at different ages. As before, we divided the body into four compartments: vessel-rich group (VRG), including heart, liver, kidney, and brain; muscle group (MG), including muscle and skin; fat group (FG); and vessel-poor group (VPG) including bones, cartilage, ligaments and tendons. The percentage of the total body that each group comprises in adult man is known. Somewhat scantier data are available for the young.<sup>5,6</sup> The values we accepted are listed in table 1 and accord with the suggestion of Salanitro and Rackow.

From here our work took three successively more complex paths, each of which depended on an assumption regarding blood flow and relative tissue volume.<sup>5</sup> In the first path (proportional flow changes, tissue volumes constant) we tested the effects of proportional increases in ventilation and circulation without alteration of relative tissue volumes. Flow to each tissue group was increased proportionately (that is, if flow to the VRG were

doubled, then flows to all other groups were also doubled). We assumed a resting adult cardiac output of 5.4 l/min with 4 l/min to the VRG, 1.0 l/min to the MG, and 0.4 l/min to the FG. We assumed adult alveolar ventilation to be 4.5 l/min with a functional residual capacity of 2.5 l. These assumptions regarding ventilation applied to all paths. For this path we successively doubled both ventilation and circulation.

For the second path (proportional flow changes, tissue volumes varied) we related the flow changes to the known changes in cardiac output for specific age groups but altered the relative volumes of the tissue groups as indicated in table 1. These changes increased the volume of the VRG at the expense of the MG and, in the neonate, at the expense of the FG. Total cardiac output, which has been determined for most age groups, relates to surface area<sup>7</sup> or to a fractional exponent of body weight.<sup>8</sup> Metabolism and hence perfusion per surface area is fairly constant for all sizes of mammals, applying equally to adult and neonate, to elephant and mouse.<sup>7</sup> The constancy of perfusion per square meter means that with decreasing size there is an increase in perfusion per kg. We again assumed a resting adult cardiac output of 5.4 l/min. The values of perfusion per kilogram at various ages relative to adult perfusion per kilogram are listed in table 1. No flow was given to the VPG, which explains its absence from table 1. We again assumed that the increased perfusion per kilogram in the young resulted from a proportional increase in blood flow to each tissue group. For example, in the 1-year-old infant the cardiac output per unit mass is about twice that in the adult; thus,

§A note concerning the construction of the models is in order here. We did not reduce the total body size in computing the capacity of the tissue groups in children and neonates. Instead, we increased the perfusion and ventilation relative to those in the adult to agree with the relative flow increases seen in the young. The effect is the same as reducing tissue capacity to the appropriate size with concomitant scaling of perfusion. Of fundamental importance is that the time constants for individual groups and their weighting in their contribution to the drain on the alveolar anesthetic partial pressure are the same regardless of the scaling procedure.

for the 1-year-old we assumed doubling of flows to the VRC, MC and FG relative to the adult flows.

The difficulty with the above approach is that it leads to unreasonable figures for individual tissue groups. For example, neonatal flow to the VRC is 240 per cent of the relative adult flow to this group. This does not mean a neonatal VRC flow 2.4 times that in the adult but a relative value: if VRC flow were 4 l/min in a 70-kg adult, then in an imaginary 3.5-kg neonate, VRC flow would be  $(3.5/70)2.4 \times 4.0$ , or 0.48 l/min. However, since the relative size of this group concomitantly has increased 220 per cent, the flow per kilogram actually does not change. This is in conflict with somewhat scanty data which suggest that blood flow per kilogram of VRC is greater in the young in roughly the same proportion as suggested for total cardiac output.<sup>9-11</sup> That is, flow *per kilogram* of neonatal VRC is 240 per cent of VRC flow in the adult.

This led us to our third path (nonproportional flow changes; tissue volumes varied), in which we assumed an increase in flow per kilogram of a particular tissue group in proportion to the known total increase in cardiac output per kilogram for the whole body. For example, if cardiac output per kilogram doubled, then we doubled flow per kilogram to VRC, MC and FG. The third path would not differ from the previous ones if the relative tissue volumes remained constant. However, they do not. For example, neonatal flow per kilogram is 240 per cent of adult flow. The VRC receives 4 l/min. If the neonate and his VRC were the same size as the adult, then the neonatal VRC would be given  $2.4 \times 4$  or 9.6 l/min (see footnote). However, we know that the neonatal VRC comprises a larger fraction of the whole body, which in our gargantuan example would equal 2.2 times the adult volume. Thus, the flow to the neonatal VRC would be further increased by a factor of 2.2, giving a total VRC flow of  $9.6 \times 2.2$ , or 21.1 l/min! Since the total adult cardiac output equals only 5.4 l/min, this means that blood flow to the neonatal VRC alone would have increased the relative neonatal cardiac output by  $21.1/5.4$ , or 390 per cent. Perfusions per kilogram relative to adult values

TABLE 2. Partition Coefficients

|                       | Nitrous Oxide | Halothane | Methoxyflurane |
|-----------------------|---------------|-----------|----------------|
| Blood/gas             | 0.47          | 2.3       | 13.0           |
| Vessel-rich group/gas | 0.47          | 5.75      | 26.0           |
| Muscle group/gas      | 0.47          | 8.05      | 17.4           |
| Fat group/gas         | 1.05          | 138       | 518            |

(adult = 100 per cent) derived with this technique are listed in the last column of table 1. Although the individual tissue flows now agree with reported data, the relative cardiac output to the whole body of the neonate is well above published values. We have no way of resolving this conflict, and presume that either the "proportional" or the "nonproportional" paths (tissue volumes varied) may be right, or that the truth may fall between the two possibilities.

Finally, we assumed that any change in blood flow occurred in response to a metabolic change. That is, when flow doubled this was due to a doubling of metabolism. Accordingly, to keep arterial  $P_{CO_2}$  constant, we changed ventilation in proportion to the change in blood flow: a doubling of cardiac output doubled ventilation.

Using the above three models, we examined the rate of alveolar concentration increase towards a constant inspired concentration for three anesthetics: nitrous oxide, halothane and methoxyflurane. The blood/gas and tissue/gas values are given in table 2.<sup>12</sup> Calculations of uptake and distribution were made with equations found in previous publications.<sup>12</sup> Computations were performed with a Burroughs 5500 digital computer and the alveolar curves printed on a Cal-Comp plotter.

## Results

Figure 1 illustrates the effects of successive doublings of circulation and ventilation without change in relative tissue volumes (proportional flow changes; tissue volumes constant). Superimposed on the simulated curves for this and figures 2 and 3 are the data given by Salanitro and Rackow for the rates of increase of alveolar halothane in adults and in children 1 to 5 years old. Eightfold increases in cardiac output and ventilation are necessary to

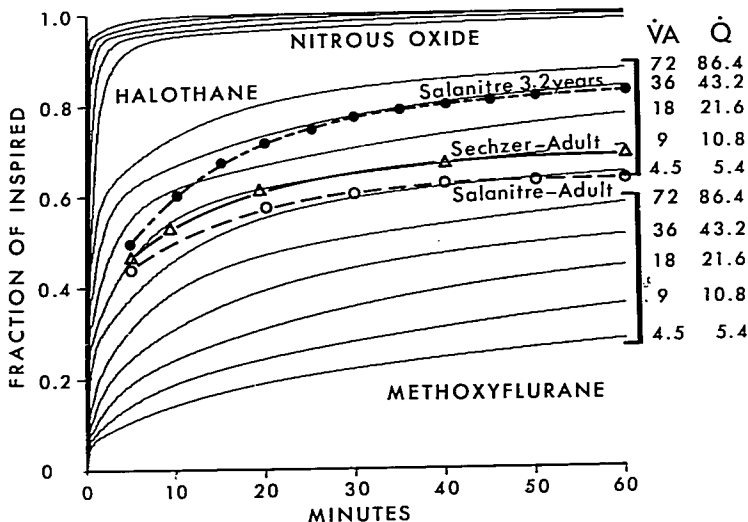


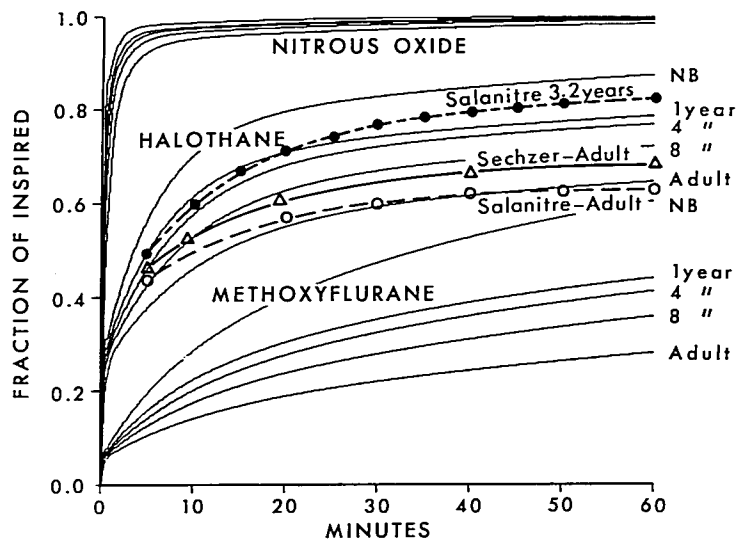
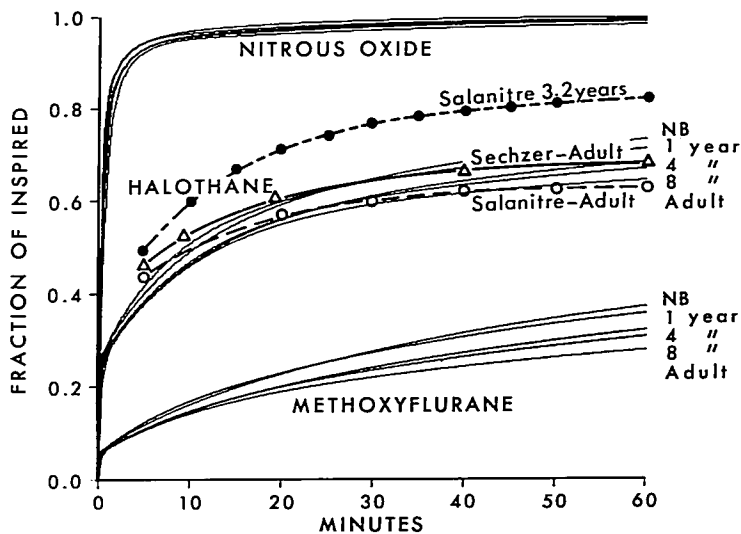
FIG. 1. Proportional flow changes, tissue volumes constant. The rates of alveolar anesthetic concentration increase toward the inspired anesthetic concentration are given for 60 per cent inspired nitrous oxide (top five continuous curves), 1 per cent halothane (middle five continuous curves) and 1 per cent methoxyflurane (lower five continuous curves). For this simulation we progressively doubled alveolar ventilation ( $\dot{V}_A$ ) and cardiac output ( $\dot{Q}$ ) without altering the distribution of blood flow or the size of tissue groups. Superimposed on these and each subsequent figure are the data from the studies of Salanitro and Rackow.

FIG. 2 (above, right). Proportional flow changes, tissue volumes varied. As in figure 1, we compared the rates of alveolar concentration increase for 60 per cent inspired nitrous oxide, 1 per cent halothane, and 1 per cent methoxyflurane. The assumed tissue group volumes and tissue group blood flows (proportional changes) for the various age groups are listed in table 1. In general, the VRG increases in volume at the expense of the MG and, in the newborn (NB) also at the expense of the FG. Total cardiac output increased in proportion to the increase in the surface area-to-weight ratio. The increase was distributed proportionally to all tissue groups.

FIG. 3 (below, right). Non-proportional flow changes, tissue volumes varied. With one exception, these graphs are based on the same assumptions as used for figure 2. They differ in that we assumed, for figure 3, an increase in flow per kilogram of a particular tissue group in proportion to the increase in average flow per kilogram assumed in figure 2. This actually resulted in the young having a greater increase in cardiac output than in figure 2. The explanation for this is indicated in the text.

approach the Salanitro-Rackow finding for children with an average age of 3.2 years. Figure 2 shows the effect of more limited (but realistic) proportional increases in blood flow and ventilation with concomitant alterations to relative tissue volumes (proportional flow

changes; tissue volumes varied). These data do not approach the separation achieved with the Salanitro-Rackow data. Figure 3 gives the result when the tissue group flow is affected by both age and relative tissue size (nonproportional flow changes; tissue volumes



varied). These data do approach the separation found by Salanitre and Rackow. In all cases, as predicted by Salanitre and Rackow, the greater ventilation and cardiac output given to the young allow a more rapid increase in alveolar anesthetic concentration.

### Discussion

All three simulations qualitatively support the Salanitre-Rackow finding of and rationale for more rapid increases of alveolar anesthetic concentration with decreases in age (figs. 1, 2 and 3). However, no simulation produces a result which satisfactorily accounts for all of the experimental differences between children and adults. In the case of the proportional flow changes with or without varied tissue volumes, the discrepancy is large (figs. 1 and 2). For example, in figure 2 at 30 to 60 minutes the observed differences in alveolar halothane concentrations in adults and children 1 to 5 years old are 15 and 17 per cent, respectively, whereas the simulated differences for these ages are about 5 per cent. This discrepancy diminishes with the nonproportional flow change simulation, where the differences at 30 and 60 minutes are 13 to 14 per cent. Remember, however, that this simulation produces a relative increase in cardiac output in the 1- to 4-year-old which is 40 to 50 per cent greater than measured values for these ages.

There appears to be a real difference between the experimental and simulated rates of alveolar concentration increase. The simulations support Salanitre's and Rackow's rationale for the differences between the young and the adult values (*i.e.*, relatively increased ventilation and total perfusion and relatively larger highly perfused tissue group in the young), but suggest that these factors do not provide the whole explanation. We agree that some of the other factors discarded by Salanitre and Rackow (*i.e.*, reflexes from surgical manipulations, changes in body temperature, infusion of intravenous fluids, functional residual capacity-to-tidal volume ratio) are unlikely to have caused the differences found. One of the explanations discarded by Salanitre and Rackow, differences in solubility, may explain a small portion of the difference. The hematocrit tends to be lower in the young, thereby giving a slightly lower blood solu-

bility.<sup>14</sup> This would increase the rate of alveolar concentration increase relative to the adult group. A further difference favoring a more rapid alveolar concentration increase in the young is the tendency toward a higher muscle fat content with age.<sup>15</sup>

Differences between the conditions of the experiments on the adults and children may provide still other explanations. We agree with Salanitre and Rackow that the second-gas effect should cause a more rapid rate of alveolar concentration increase in the young, but that this factor should be significant only during the first 5 to 10 minutes of anesthesia.<sup>16</sup> Three other factors may have contributed to the separation of adults' and children's curves 30 to 60 minutes after introduction of halothane. The adults were awake and breathed subanesthetic concentrations of anesthetic. Furthermore, ventilation was either spontaneous or controlled with a cuirass. The young were anesthetized with cyclopropane (in the case of the halothane determinations) and then exposed to anesthetizing concentrations of halothane (0.75 per cent inspired) and nitrous oxide (60 per cent). The young were also subjected to intermittent positive-pressure breathing sufficient to maintain end-tidal CO<sub>2</sub> at 5 per cent. We suggest that conversion of a cyclopropane to a halothane-nitrous oxide anesthetic in the presence of positive-pressure controlled ventilation may produce a decrease in cardiac output in excess of the decreases in metabolism and CO<sub>2</sub> production.<sup>17</sup> This decrease in cardiac output would not occur in the adults, who were neither anesthetized nor subjected to positive airway pressure (though the cuirass mimics the effects of positive airway pressure when applied to the whole body). The decrease in output would not occur immediately, but would develop as the heart, brain and other tissues equilibrated with the rising halothane and nitrous oxide partial pressures.<sup>18</sup> This would explain why the experimental differences between adults' and children's curves are reasonably described by the simulations for the first 5 to 10 minutes but diverge thereafter as uptake in the young decreases relatively more than that in the adult. Another effect of anesthesia would be to increase ventilation/perfusion abnormalities.<sup>19</sup> This, too,

would cause the end-tidal curves obtained in the young to rise more rapidly than the adult curves.<sup>20</sup>

Finally, Sawyer *et al.* have shown that the fraction of halothane removed by the liver from the hepatic blood flow is concentration-dependent.<sup>21</sup> Increasing the halothane partial pressure decreases the fraction extracted. Sawyer found a 10 to 15 per cent extraction of halothane passing through swine liver at an alveolar concentration of 0.1 per cent (the concentration obtained in the adult experiments) but no measureable extraction at 0.5 per cent (the concentration obtained in the infant experiments). Using another model, we have simulated the effect of metabolism on alveolar concentration (unpublished data): liver extraction of 10 to 15 per cent of halothane lowers the alveolar halothane concentration by 6 to 8 per cent at 60 minutes. Thus, metabolism might account for a third to half of the 15 to 18 per cent difference in alveolar curves observed *in vivo*.

To test these additional hypotheses would necessitate one of two experiments: 1) measure the rate of alveolar concentration increase of subanesthetic halothane concentrations in the young (hard to do); or 2) measure the rate of increase of anesthetizing concentrations in adults (easier).

The simulated results for the three anesthetics are qualitatively similar, but differ in quality and clinical import. With all three and with any of the simulation pathways, the young have a more rapid increase in alveolar concentration. The increased rate partially compensates for the increase in MAC in the young.<sup>22</sup> Thus, the same inspired concentration will tend to produce the same depth of anesthesia in adults and in children. However, the effect of age on the alveolar nitrous oxide concentration is negligible. The effect increases with increasing solubility of the agent in blood and tissues. The rate of alveolar concentration increase is most influenced by age in the case of methoxyflurane, while the effect on halothane lies midway between nitrous oxide and methoxyflurane. Compensation for the increase in MAC with decrease in age, therefore, will be negligible with nitrous oxide, partial with halothane, and roughly complete with methoxyflurane. This

presumes that the age-related changes in anesthetic requirement for nitrous oxide and methoxyflurane parallel those demonstrated for halothane. This assumption awaits testing.

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### Drugs

**L-DOPA IN PARKINSONISM** L-dopa (L-desoxyphenylalanine) is being used with increasing frequency for the treatment of parkinsonism. The present study attempted to define some of the cardiovascular effects of this drug in animals and man. It appears that the effects of L-dopa are in fact similar to those of dopamine, the decarboxylated L-dopa. These effects include alpha- and beta-adrenergic stimulation, which result in improved myocardial contraction, arterial hypertension, tachycardia, and sometimes ventricular arrhythmias.

Most of the undesirable side-effects of L-dopa can be treated or prevented with alpha- and beta-adrenergic blocking agents, *e.g.*, propranolol and phentolamine. Because of the risk of inducing arrhythmias in patients with myocardial irritability or ischemia, it is suggested that L-dopa be administered under electrocardiographic control. Since an increased tolerance to L-dopa is known to occur, the authors suggest that in the presence of myocardial disease therapy be started with a small dose, which is gradually increased over a long period of time. The occasional orthostatic hypotension seen after administration of L-dopa is secondary to its vasodilating effect on the renal and mesenteric vascular beds. (*Goldberg, L. I., and others: Cardiovascular Effects of Levodopa, Clin. Pharmacol. Ther.* 12: 376-382, 1971.)