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Effect of Age on the Solubility of Volatile Anesthetics in Human Tissues

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To determine the effect of age on the solubility of volatile anesthetics in human tissues, the authors measured the solubilities of isoflurane, enflurane, halothane, and methoxyflurane *in vitro* at 37° C in 35 postmortem human tissue specimens. Specimens were taken from neonates, and young (20–50 yr), middle-aged (50–70 yr), and elderly adults (>70 yr). Brain/gas, heart/gas, and liver/gas partition coefficients for all four anesthetics increased significantly ($P < 0.05$) between birth and adulthood, although brain/gas partition coefficients in young adults tended to be higher than those in middle-aged and elderly adults. Heart/gas and liver/gas partition coefficients tended to increase with aging. Muscle/gas partition coefficients for the four anesthetics increased linearly with age. Fat/gas partition coefficients did not change significantly with age. Tissue/blood solubilities for the four anesthetics were of the same order of magnitude for a given tissue and age group. Tissue/blood solubilities for enflurane were 30% lower than those for isoflurane in the same tissue and age group. In summary: 1) the solubility of volatile anesthetics in human tissues increases with age; 2) the lower solubility of anesthetics in neonates partially explains the more rapid increase of alveolar and tissue anesthetic partial pressures in neonates; 3) despite the higher blood solubility of enflurane, its lower tissue solubility may explain a rate of recovery comparable with that of isoflurane. (Key words: Age factors: adults; elderly; neonate. Anesthetics, volatile: enflurane; halothane; isoflurane; methoxyflurane. Solubility: partition coefficients; tissue.)

THE RATE OF INCREASE in alveolar anesthetic partial pressure in infants and children is more rapid than in adults.[1,2] This can be attributed to several factors. Infants have: 1) a greater ratio of alveolar ventilation to functional residual capacity;[1,3] 2) a greater fraction of cardiac output perfusing the vessel-rich group;[3,4] 3) a greater ratio of alveolar ventilation to cardiac output per kilogram body mass; and 4) significantly lower blood/gas partition coefficients than adults.[5] The lower solubility of volatile anesthetics in the tissues of neonates (*i.e.*, the tissue/blood partition coefficient) may also be a factor.

Data concerning the relationship between aging and the solubility of volatile anesthetics in tissues are limited, and much of the data have been obtained from studies in animals. The solubility of halothane in the brain of the newborn rat is less than that in the adult rat.[6] This difference may be attributable to a greater water content in the brain of the newborn rat. Similarly, the solubilities of isoflurane, enflurane, halothane, and methoxyflurane in brain, heart, muscle, and kidney of newborn lambs are 28% less than those found in postpartum ewes.[7] However, the solubilities of volatile anesthetics in human tissues differ as much as three-fold from those in other species.[8,**] As a result, the effect of age on the solubility of anesthetics in rat and sheep tissues may not be applicable to human tissues.

In human brain specimens, the solubilities of halothane and methoxyflurane increase with age.[9] This may result from a decrease in the water content and increase in cholesterol concentration in brain with increasing age.[10,11] Age-related changes also occur in water, protein, and lipid concentrations in other human tissues.[12] Because data on the solubility of volatile anesthetics in human tissues are limited, and because the effect of age on anesthetic solubility in human tissues may differ from that in animal tissues, we determined the effect of aging on the solubilities of isoflurane, enflurane, halothane, and methoxyflurane in human brain, heart, liver, muscle, and fat.

Methods

Tissue specimens of brain (grey and white matter), heart (left ventricle), liver, muscle (rectus abdominis), and fat were obtained from 35 autopsies of humans ranging from neonates to the elderly. Specimens were not taken from tissues affected by the cause of death. Tissue specimens were obtained from comparable areas within each

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** Pearson MRB, Weaver BMQ, Staddon GE: The influence of tissue solubility on the perfusion distribution of inhaled anaesthetics (Abstract). Proceedings of the 2nd International Congress on Veterinary Anesthesia 101, October 1985.

TABLE 1. Anesthetic Solubility in Human Blood and Tissues

	Isoflurane	Enflurane	Halothane	Methoxyflurane
Neonates (mean age 1 mo)				
Blood/gas	1.19	1.78	2.14	13.3
Tissue/blood				
Brain	1.31 ± .03 (5)	0.92 ± .01 (5)	1.54 ± .06 (6)	1.13 ± .08 (6)
Heart	1.74 ± .08 (4)	1.23 ± .06 (4)	2.06 ± .06 (4)	1.35 ± .08 (4)
Liver	2.01 ± .04 (8)	1.48 ± .04 (7)	2.12 ± .06 (8)	1.59 ± .06 (10)
Muscle	1.10 ± .06 (9)	0.81 ± .05 (10)	1.25 ± .07 (10)	0.73 ± .08 (8)
Young adults (20–50 yr; mean age 35 yr)				
Blood/gas	1.46	2.07	2.65	16.0
Tissue/blood				
Brain	1.74 ± .05 (9)	1.30 ± .03 (9)	2.03 ± .04 (7)	1.26 ± .03 (7)
Heart	1.62 ± .07 (8)	1.15 ± .06 (8)	1.42 ± .07 (5)	1.07 ± .09 (5)
Liver	2.00 ± .10 (6)	1.45 ± .08 (6)	2.15 ± .15 (5)	1.53 ± .13 (5)
Muscle	1.52 ± .11 (9)	1.09 ± .10 (9)	1.44 ± .17 (8)	1.54 ± .12 (7)
Fat	53.10 ± 3.07 (7)	40.97 ± 2.19 (7)	60.62 ± 2.98 (7)	52.47 ± 2.45 (5)
Middle-aged adults (50–70 yr; mean age 60 yr)				
Blood/gas	1.37	1.91	2.51	15.5
Tissue/blood				
Brain	1.65 ± .06 (8)	1.28 ± .05 (8)	1.92 ± .08 (8)	1.36 ± .06 (7)
Heart	1.93 ± .09 (6)	1.49 ± .08 (6)	2.17 ± .11 (6)	1.63 ± .08 (6)
Liver	2.18 ± .12 (8)	1.71 ± .10 (8)	2.84 ± .19 (9)	2.01 ± .18 (7)
Muscle	2.06 ± .12 (8)	1.60 ± .09 (8)	2.31 ± .20 (8)	1.60 ± .12 (7)
Fat	56.02 ± 1.77 (3)	45.57 ± 1.57 (4)	66.56 ± 2.67 (3)	60.97 ± 0.82 (4)
Elderly (>70 yr; mean age 80 yr)				
Blood/gas	1.29	1.79	2.41	15.0
Tissue/blood				
Brain	1.77 ± .04 (9)	1.37 ± .04 (10)	2.02 ± .08 (10)	1.36 ± .05 (9)
Heart	1.77 ± .03 (5)	1.35 ± .02 (5)	2.06 ± .13 (6)	1.74 ± .27 (5)
Liver	2.44 ± .10 (11)	1.89 ± .07 (11)	2.80 ± .12 (10)	1.95 ± .10 (10)
Muscle	2.83 ± .17 (7)	2.22 ± .11 (7)	2.90 ± .12 (7)	1.87 ± .12 (5)
Fat	57.72 ± 2.06 (7)	43.48 ± 1.50 (7)	67.34 ± 2.15 (6)	69.27 (1)

Data are mean ± SE.

Number in parentheses indicates number of specimens.

Blood/gas[5] and tissue/blood partition coefficients for isoflurane, enflurane, halothane, and methoxyflurane are given for human blood, brain, heart, liver, and muscle for four age groups and for fat for three age groups. The tissue/blood partition coefficients are of the same order of magnitude for a given tissue and age group, whereas the blood/gas partition coefficients have an eleven-fold variation.[5] The solubility of enflurane in tissues was approximately 30% less than that for isoflurane in the same tissue and age group. The fat/blood partition coefficients did not change significantly with age, but did agree with published data.[18]

organ to minimize variability between patients. The capsule and fascia were removed from each, and the volume measured by displacement immediately after collection. The specimen was then frozen (−80° C) in the normal saline (0.9% sodium chloride) used to determine the specimen volume, and remained frozen until the solubility determination (usually 24–48 h). Immediately before determining the solubility, each specimen was homogenized in normal saline using a mini-cup Waring® blender (20,000 rpm). The homogenate was filtered through a $^1/_{16}$-in^2 aluminum mesh screen to remove extraneous fascia, which spuriously decreases the tissue/gas partition coefficient by increasing the volume of homogenate and by contributing its extremely low anesthetic solubility. The net volume of tissue present in the homogenate was determined as being the difference between the volume of the tissue specimen and the volume of extraneous fascia (measured by saline volume displacement). These refinements in tissue preparation were performed to minimize variability in the partition coefficient determinations in tissue specimens.

Tissue/gas partition coefficients were determined by equilibrating 2–3 ml of homogenate with 15 ml of a mixture of anesthetic gases (isoflurane, enflurane, halothane, and methoxyflurane) in a silicone-greased glass syringe. The syringe was incubated in a water bath at 37° C for 2 h and shaken vigorously, as described previously.[13]

After 2 h of incubation, we measured the concentrations of anesthetics in the gas phase using gas chromatography. We determined the concentrations of anesthetics in the homogenate phase by aspirating an aliquot of homogenate into an evacuated flask, dissipating the vacuum with air, and equilibrating the contents of the flask at 37° C for 1 h, as described previously.[13] The tissue/gas partition coefficient was derived from a mass balance wherein the anesthetic content of the homogenate is equal to the sum of the anesthetic contents of the tissues and saline.[7]

Statistical significance of the results ($P < 0.05$) was de-

termined using the Bonferonni t test,[14] one-way analysis of variance, the Student-Newman-Keuls multiple range test, the coefficient of determination (r^2), and analysis of linearity.[15]

Results

The mean ages for the four groups of patients were 1 month (neonates); 35 yr (young adults); 60 yr (middle-age adults); and 80 yr (the elderly) (table 1).

Brain/gas partition coefficients in young adults were significantly greater than those found for neonates for all agents; and greater than those for middle-aged and elderly adults for isoflurane, enflurane, and halothane ($P < 0.05$) (fig. 1). Heart/gas partition coefficients determined for middle-aged adults were significantly greater than those for neonates for all agents; greater than those for young adults for enflurane, halothane, and methoxyflurane; and greater than those for the elderly for enflurane ($P < 0.05$) (fig. 2). Liver/gas partition coefficients in neonates were significantly less than those found for young, middle-aged, and elderly adults for isoflurane and halothane, and less than those for middle-aged and elderly adults for enflurane and methoxyflurane ($P < 0.05$) (fig. 3). The fat/gas partition coefficients did not differ significantly among the three age groups of adults. Thus, only the fat/blood partition coefficients were reported (table 1).

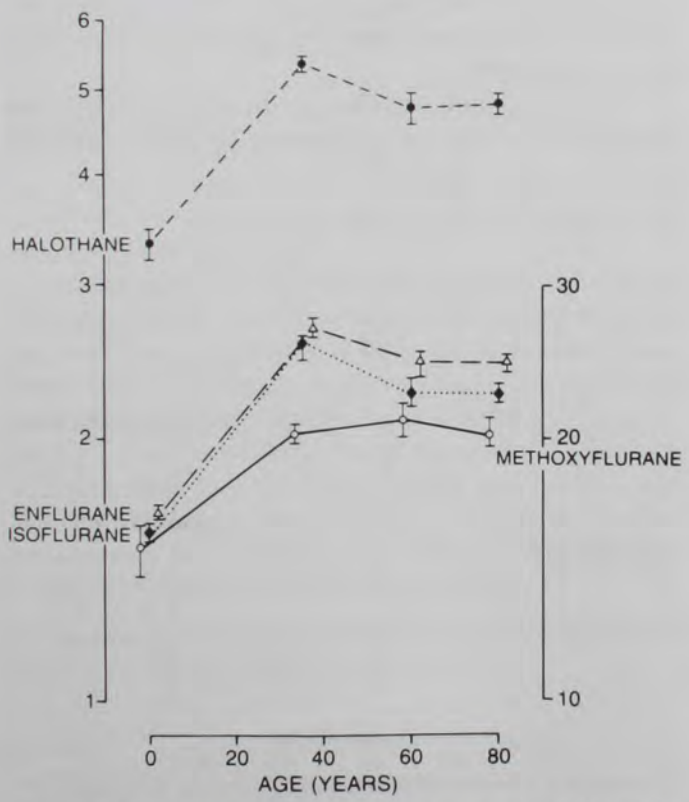

FIG. 1. Aging, particularly between birth and early adulthood, increases the solubility of inhaled anesthetics in human brain tissue. Brain/gas partition coefficients are plotted on a logarithmic scale. Data are mean ± SE.

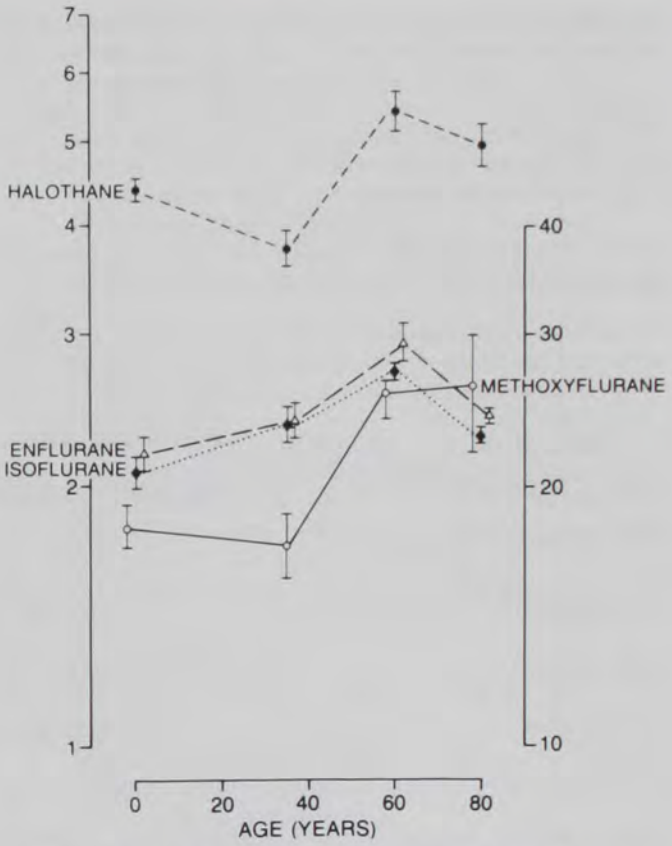

FIG. 2. Aging has less effect on the solubility of inhaled anesthetics in human hearts. Peak values tend to be found in middle-aged adults, but not in the elderly. Heart/gas partition coefficients are plotted on a logarithmic scale. Data are mean ± SE.

On a semilogarithmic scale, muscle/gas partition coefficients for all four volatile anesthetics increased linearly with age (fig. 4). The coefficients of determination, r^2, (the changes in the partition coefficient attributed to the effect of age) were 0.996 for isoflurane, 0.999 for enflurane, 0.994 for halothane, and 0.983 for methoxyflurane. The partition coefficients for each anesthetic differed significantly among the four age groups: neonates < young adults < middle-aged adults < the elderly ($P < 0.05$), except between middle-aged and elderly adults for methoxyflurane (fig. 4). The slopes of the least-squares regression lines for the four anesthetics ranged from 5.39×10^{-3} (for halothane) to 6.00×10^{-3} (for methoxyflurane).

Tissue/blood solubilities were calculated from the ratio of the tissue/gas data from this study and published blood/gas data[5] (table 1). The tissue/blood solubilities (for the four anesthetics) were of the same order of magnitude for a given tissue and age group. The blood solubilities for enflurane were consistently 30% less than those for isoflurane in the corresponding tissue and age

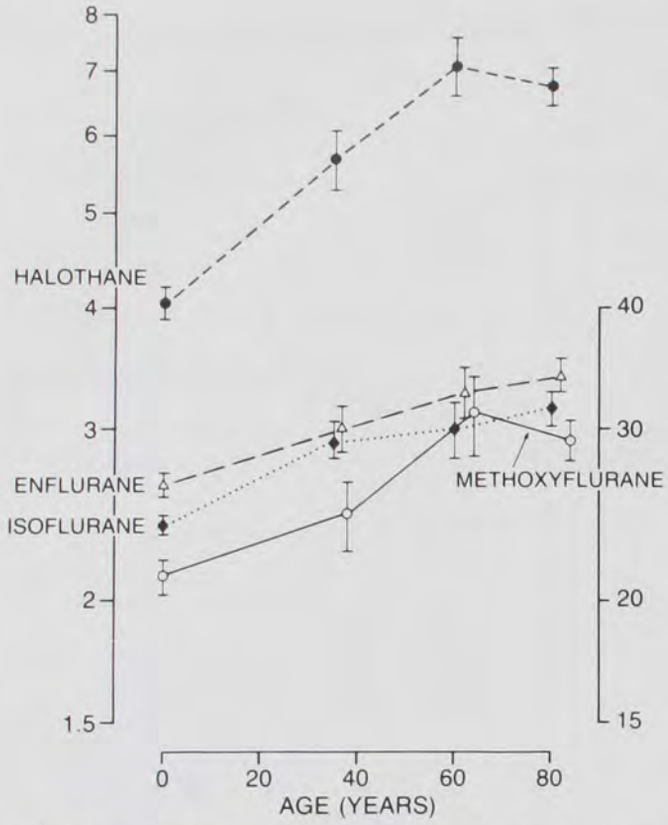

FIG. 3. The liver in neonates has a lower capacity for anesthetics than the liver in adults. Liver/gas partition coefficients are plotted on a logarithmic scale. Data are mean ± SE.

group. The fat/blood partition coefficients did not differ significantly among the three adult groups.

Discussion

Aging significantly affects the solubilities of isoflurane, enflurane, halothane, and methoxyflurane in brain, heart, liver, and muscle of humans. Anesthetic solubilities in brain, heart, and liver increased most between birth and adulthood (approximately 50%). This increase is consistent with changes in the constituents of those tissues, that is, a decrease in water content and an increase in protein and lipid content.[10,11] For muscle, the solubilities of all four anesthetics increased progressively with age (fig. 4). This may be attributed to an increase in the protein concentration in muscle in the first five decades of life, and an increase in the fat content in the subsequent decades.[12,16,17] In summary, aging alters the solubility of anesthetics in brain, heart, liver, and muscle, with the greatest increase occurring between birth and adulthood.

Our results are similar to previous data for solubility and for changes associated with aging.[6–8,18] However, our tissue/blood partition coefficients ([tissue/gas]/[blood/gas]) for the four anesthetics (table 1) were approximately 30% less than those reported previously.[8,18] This difference may be attributed to our efforts to prevent the loss of intracellular water. A loss of water would have increased the partition coefficient because the solubility of volatile anesthetics in water is far less than in protein and fat.[13,18,19]

In adults, the liver/gas partition coefficients are greater than the coefficients for brain and heart tissue. The variability in the liver/gas partition coefficients is also greater than that in brain and heart tissue coefficients (fig. 3). These differences may be attributed to an increasing and variable accumulation of fat within the liver with increasing age. The increase in liver solubility must prolong both the uptake of anesthetic by the liver and the time to equilibration of the anesthetic partial pressure within the liver with that in arterial blood within the liver. This delay in the equilibration of partial pressures in one of the vessel-rich tissues may slow the rate of increase in alveolar anesthetic partial pressure slightly and, thus, the induction of anesthesia, particularly for the more soluble anesthetics.

The rates of induction and emergence from anesthesia with enflurane are thought to be comparable with those for isoflurane,[20–22] despite the greater blood/gas partition coefficient of enflurane. The tissue/blood solubility for enflurane is approximately 30% less than that for isoflurane (table 1). This would suggest that the rate of anesthetic equilibration between the blood and tissues may be more rapid with enflurane than with isoflurane (see equation 1) and thus compensate for the greater blood solubility of enflurane.

The tissue/blood partition coefficient is an important determinant of the rate of increase in tissue anesthetic

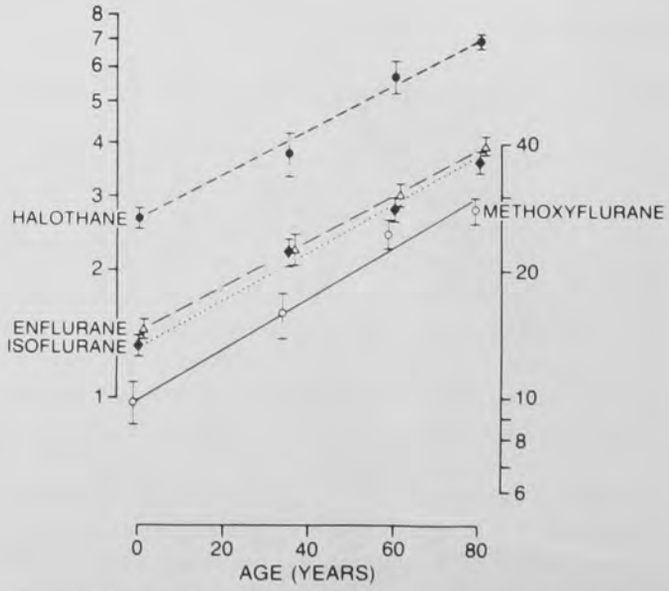

FIG. 4. The muscle/gas partition coefficients increase linearly with age ($r^2 > 0.98$): neonates < young adults < middle-aged adults < elderly ($P < 0.05$). Muscle/gas partition coefficients are plotted on a logarithmic scale. Data are mean ± SE.

partial pressure and, therefore, the rate of induction of anesthesia. The time for equilibration of tissue anesthetic partial pressure in any given organ with a constant delivered partial pressure in arterial blood may be estimated by the time constant (Υ) (min):

$$T = \frac{V_t}{\dot{Q}_t} \times \lambda_{t/b} \quad (1)$$

where

$$\lambda_{t/b} = \frac{\lambda_{t/g}}{\lambda_{b/g}}$$

V_t is the tissue volume (ml), $\dot{Q}_t$ is the tissue blood flow (ml/min), and $\lambda_{t/b}$, $\lambda_{t/g}$, and $\lambda_{b/g}$ are the tissue/blood, tissue/gas, and blood/gas partition coefficients, respectively. $\lambda_{b/g}$ increases 18% between birth and adulthood,[5] whereas $\lambda_{t/g}$ increases approximately 50%. As a result, $\lambda_{t/b}$ (the ratio $\lambda_{t/g}/\lambda_{b/g}$) increases approximately 30% between birth and adulthood (table 1). Because T is proportional to $\lambda_{t/b}$, then T also increases 30% between birth and adulthood. This suggests that the rate of increase in tissue anesthetic partial pressure in neonates is approximately 30% more rapid than in adults. The lower solubility of anesthetics in the tissues of neonates also explains, in part, why the increase in their alveolar anesthetic partial pressure is more rapid than that in adults.[1,2]

The $V_t/\dot{Q}_t$ for any particular organ is greater in adults than in neonates, *i.e.*, blood flow per unit tissue mass is smaller in adults than in neonates.[3,4] As the $V_t/\dot{Q}_t$ increases with age, both T and the time to equilibration of the tissue and blood anesthetic partial pressures also increase. The combined effects of a lower tissue solubility and a lower value for $V_t/\dot{Q}_t$ in neonates produce a more rapid rate of increase in tissue, blood, and alveolar anesthetic partial pressures.[1,2]

The increase in anesthetic solubility in muscle with age will delay the rate of increase in alveolar anesthetic partial pressure for a longer period than will increases in anesthetic solubility in brain, liver, and heart. The uptake of anesthetic by muscle occurs for as long as 200 min following induction of anesthesia.[18] Because the anesthetic solubility in muscle increases directly and linearly with age (fig. 4), aging should prolong the period during maintenance of anesthesia wherein anesthetic must be supplied to counter the removal by muscle.

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