THE PULMONARY EQUILIBRATION OF CYCLOPROPANE IN INFANTS AND CHILDREN

Lack of Functional Brown Adipose Tissue in the Anaesthetized Surgical Infant

H. Rackow and E. Salanitre

SUMMARY

Pulmonary equilibration of a mixture containing 0.5% cyclopropane and 3% nitrous oxide was studied in four infants and four older children who were anaesthetized for surgery using 0.75% halothane, tubocurarine and a constant volume ventilator. Cyclopropane end-tidal concentration approached inspiratory concentration faster in the infants than in the older children. The difference in FE/FI ratios between the cyclopropane and nitrous oxide equilibration curves was smaller in the infants than in the older children. This was interpreted to mean relatively less absorption of cyclopropane into adipose tissue in the infant group. It suggested that brown adipose tissue was not functional in these infants, in spite of a cold stress of 1° to 2.2°C. These results were compared with those of a previous study of pulmonary equilibration of the same gas mixture in awake, spontaneously breathing adults. Both the infants and the older children approached equilibrium with cyclopropane faster and had smaller differences in the FE/FI ratios between the cyclopropane and nitrous oxide curves. This suggested relatively less absorption of cyclopropane into all adipose tissue in the younger age groups.

During the uptake of anaesthetic concentrations of nitrous oxide and halothane, FE/FI ratios (end-tidal to inspiratory concentrations) were found to increase faster in infants and children than in adults (Salanitre and Rackow, 1969). This more rapid approach to equilibrium of end-tidal concentration and inspired concentration was attributed to certain physiological characteristics of infants as compared with adults: greater alveolar ventilation and cardiac output, and a larger fraction of highly perfused tissue. The present study was designed to investigate the pulmonary gas exchange of cyclopropane in infants and children.

A minor modification in our previous method was made in order to study the role of brown adipose tissue on the course of the pulmonary equilibration of cyclopropane. Under a cold stress, the perfusion of this tissue increases (Heim and Hull, 1966), changing it from a slow "sink" to a fast "sink" for fat-soluble anaesthetics such as cyclopropane. This should delay the increase in the alveolar concentration of cyclopropane (and prolong the induction of anaesthesia). On the other hand, nitrous oxide, which has a solubility in oil one-eighth that of cyclopropane, should show less delay in the rise of its alveolar concentration. If cyclopropane and nitrous oxide are administered simultaneously, a separation of their equilibrium curves could be expected if perfusion of brown adipose tissue were increased by a cold stress. Cyclopropane and nitrous oxide are appropriate for this kind of study because they have similar solubilities in blood and lean tissues but widely different solubilities in oil and presumably in fat.

Table I. Oswald solubility coefficients (37°C, 760 mm Hg).

<table>
<thead>
<tr>
<th></th>
<th>Blood/gas</th>
<th>Oil/gas</th>
<th>Tissue/blood</th>
<th>Fat/blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclopropane</td>
<td>0.415†-0.60‡</td>
<td>11.2</td>
<td>0.91 muscle</td>
<td>1.36 liver</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>0.468</td>
<td>1.4</td>
<td>1.13 heart</td>
<td>1.06 brain</td>
</tr>
</tbody>
</table>

*Calculated from blood/gas and oil/gas.
†Larson, Eger and Severinghaus (1962).

MATERIAL AND METHODS

Twenty-two surgical patients, 12 hours to 6 years old, were studied during the course of a surgical...
procedure. None had evidence of cardiopulmonary disease. The three youngest infants were not gaining weight at the time of the study but were in good clinical condition for surgery and anaesthesia. For reasons discussed below, fourteen of the twenty-two studies were discarded, and the data of eight patients are reported.

Premedication and the clinical management of the patient were the responsibility of an anaesthetist who was not a member of the study team. Atropine and quinalbarbitone were given as premedication to the older children and atropine only to the infants; one of the older children received pethidine also. Anaesthesia was induced with halothane in oxygen, given with a face mask. Suxamethonium 1 mg/kg was given intravenously to facilitate orotracheal intubation. Suxamethonium was pumped through the microcuvettes of an infrared nitrous oxide analyser, an infra-red carbon dioxide analyser and a gas chromatograph sample loop of 0.25 ml volume, all arranged in series. The inspiratory tidal volume was adjusted until the end-tidal CO₂ concentration had stabilized at about 5%.

The halothane vaporizer was of the Copper Kettle type, using a separate flow of oxygen which bubbled through liquid halothane. The temperature of the liquid phase in the vaporizer was monitored and reached a steady level before the study began. The output of the vaporizer, at the flow used, was constant for the period required for the study. The output of the vaporizer was added to a diluent gas, which was 100% oxygen up to the beginning of the study. When conditions were stable, as determined by arterial pressure, pulse rate, end-tidal CO₂ concentration and body temperature, the 100% oxygen diluent gas was abruptly changed* to 51% oxygen, 3% nitrous oxide, 0.5% cyclopropane, in nitrogen, delivered from a premixed cylinder.

*The internal volume of the respirator could not be abruptly emptied and refilled at time zero. This created an error with a time-constant calculated to be 0.33 min. (TC=Volume/Flow=200 ml/600 ml per min for the smallest infant). In 2 minutes, the error becomes insignificant.

RESULTS

The sampling, analytical and recording systems have been described previously (Salanitre and Rackow, 1969). Every 10–15 minutes, the inspiratory gas mixture was analysed, and the infra-red nitrous oxide and carbon dioxide analysers were calibrated against known gas mixtures delivered from premixed cylinders. The end-tidal nitrous oxide and cyclopropane concentrations were converted to FE/FI ratios, and plotted against time. At the end of the surgery, an arterialized capillary blood sample from some patients was analysed for pH, Pco₂, bicarbonate, haematocrit, base excess and oxygen saturation. The blood Pco₂ measurement was compared to end-tidal Pco₂ to check that we were obtaining a true end-tidal sample.

The eight cases reported in this study were divided into an infant group (4 days to 9 months of age), and an older child group (3 to 6 1/2 years of age). For each group, equilibrium curves for both test gases were constructed from the averaged FE/FI values. These curves were used for comparing the paediatric groups with each other and with previous curves for adults (Rackow et al., 1965).

Body temperature was monitored by means of rectal or oesophageal electrodes. Maintenance of the patient’s normal temperature was attempted with the help of a water mattress on the operating-room table and by keeping the operating-room temperature in the range 21–29°C. In spite of these measures there was a fall in body temperature of between 1° and 2.2°C in each subject in the infant group.

Four of the twenty-two studies were discarded because of hypotension occurring at some time during or immediately preceding the study. Five studies were discarded because the patients were not maintained consistently on controlled ventilation, and end-tidal samples showed contamination with inspiratory air. Two cases were discarded because of excessive drift in the measuring instruments. One child was underventilated and one child was hyperventilated. Both studies were discarded but the hyperventilated child will be discussed separately. One child developed pulmonary secretions, and there was a large discrepancy between end-tidal Pco₂ and arterialized capillary blood Pco₂; this case was discarded. Seven of the discarded studies were in infants between 12 hours and 10 weeks of life.

RESULTS

Table II lists the age, weight and surgical diagnosis for the eight subjects whose pulmonary equilibration curves for the two anaesthetics were used in this study. Figure 1 shows the equilibration curves of
TABLE II. Description of subjects.

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight (kg)</th>
<th>Haemoglobin (g%)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4 days</td>
<td>2.3</td>
<td>22.8</td>
</tr>
<tr>
<td>2</td>
<td>12 days</td>
<td>2.8</td>
<td>14.7</td>
</tr>
<tr>
<td>3</td>
<td>5 weeks</td>
<td>2.4</td>
<td>12.6</td>
</tr>
<tr>
<td>4</td>
<td>9 months</td>
<td>10.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 years</td>
<td>18.5</td>
<td>11.4</td>
</tr>
<tr>
<td>2</td>
<td>3 years</td>
<td>16.5</td>
<td>11.2</td>
</tr>
<tr>
<td>3</td>
<td>6 years</td>
<td>17.5</td>
<td>12.5</td>
</tr>
<tr>
<td>4</td>
<td>6 years</td>
<td>20.0</td>
<td>12.6</td>
</tr>
</tbody>
</table>

simultaneously administered nitrous oxide and cyclopropane in a 12-day-old, 2.8-kg infant (subject 2). The body temperature range was 34.7–35.3°C; at the end of the procedure the arterialized capillary blood Pco₂ was 42 mm Hg and the PAO₂ was 43 mm Hg. Figure 2 shows the averaged equilibration curves for cyclopropane for the infant group and the child group. It also shows an averaged adult cyclopropane equilibration curve from a previously reported study (Rackow et al., 1965). At 10 minutes, the infant curve reached an FE/Fi ratio of 0.9; the child curve was below this and the adult curve still lower. The same relative positions were maintained until the end of the study (60 min).

Figure 3 shows the averaged equilibration curves in each of the three age groups, for the two test gases, cyclopropane and nitrous oxide. The difference in

![Figure 1](https://academic.oup.com/bja/article-abstract/46/1/35/294299)

**Fig. 1.** Lung uptake curves for 3% nitrous oxide (Δ) and 0.5% cyclopropane (○) expressed as a ratio of expired (Fe) to inspired concentration (Fi) in a 12-day-old 2.8-kg infant. Body temperature range 34.7–35.3°C. The breaks in the curves occur at times when inspiratory mixture was analysed. At the end of the procedure, arterialized capillary blood Pco₂ was 42 mm Hg and PAO₂ was 43 mm Hg.

![Figure 2](https://academic.oup.com/bja/article-abstract/46/1/35/294299)

**Fig. 2.** Averaged equilibration curves of 0.75% cyclopropane in infants, children and adults. The infants and children were anaesthetized and then ventilation was controlled. The adults were awake and breathed spontaneously. The adult data is taken from Rackow et al. (1965). PAO₂ was similar in all three groups.
Fe/Fi ratios between the two test gases amounts to 0.019–0.026 for the infants, 0.042–0.047 for the children and 0.050–0.066 for the adults.

Figure 4 shows the nitrous oxide and cyclopropane equilibration curves of a 19-month-old child who was inadvertently hyperventilated and consequently had a $PA_{O_2}$ of 30 mm Hg. Both curves approach inspiratory concentrations more rapidly than in subjects who were normally ventilated and had a $PA_{O_2}$ of about 40 mm Hg. However, the difference in Fe/Fi ratios between the nitrous oxide and cyclopropane equilibration curves was about the same as in the subjects who were normally ventilated.

**DISCUSSION**

*Cyclopropane equilibration.*

In a theoretical analysis of inert gas exchange in the lung, Kety (1951) predicted the effects of variations in ventilation, cardiac output and, in the solubility of the anaesthetic in blood on the pulmonary equilibration of anaesthetics. This analysis was based upon a simplified model with a single tissue compartment and a blood/tissue partition coefficient of 1.0. Assuming normal physiological parameters for his simplified model, Kety obtained a spectrum of equilibration curves of anaesthetics with a wide variety of blood solubilities. When Kety’s predicted equilibration curves were compared with curves measured in normal adults (Salanitre, Wolf and Rackow, 1967), there was good qualitative agreement. Salanitre and Rackow (1969), in a study of pulmonary equilibration of nitrous oxide and halothane, found that infants equilibrated more rapidly than adults, older children being intermediate, and suggested that these findings could be explained by physiological differences which are most pronounced in infancy: an increased cardiac output and alveolar ventilation, and a proportionately larger compartment of well-perfused tissues relative to body mass. The present study shows a similar pattern in the pulmonary equilibration of another anaesthetic, cyclopropane (fig. 2).

![Figure 3](https://example.com/fig3.png)

**Fig. 3.** Averaged equilibration curves of simultaneously administered 3% nitrous oxide ($\Delta$) and 0.5% cyclopropane (○) in infants, children and adults. Same conditions as fig. 2.

![Figure 4](https://example.com/fig4.png)

**Fig. 4.** Effect of hyperventilation on simultaneous equilibration of 3% nitrous oxide ($\Delta$) and 0.5% cyclopropane (○) in a 19-month-old child. (For further explanation see text.)
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The conditions under which the infants and the older children were studied were the same, and direct comparisons between these two groups may be made. However, the adults were studied under different conditions. The infants and children were both anesthetized with 0.75% halothane in oxygen, paralyzed with tubocurarine and artificially ventilated, the $P_{A_{CO_2}}$ being maintained at about 40 mm Hg with a volume-limited respirator. The adults were awake, breathed spontaneously and adjusted their own ventilation to maintain a stable end-tidal $P_{A_{CO_2}}$ of about 40 mm Hg.

The use of halothane anaesthesia and controlled respiration could have introduced circulatory and pulmonary changes in the infants and children. For example, halothane has been shown to depress cardiac output (McGregor et al., 1958; Severinghaus and Cullen, 1958; Deutsch, Linde and Price, 1962; Eger et al., 1970), and to alter tissue perfusion in brain (Wollman et al., 1964; Christensen, Hoedt-Rasmussen and Lassen, 1967), in skin and muscle (Eger et al., 1970) and in splanchic and renal areas (Epstein et al., 1966; Deutsch et al., 1966). Cardiac output was not measured because of the risk involved. However, all the studies reported above used high anaesthetic concentrations which were associated with hypotension. In our study, a low halothane concentration was used (together with only a trace of nitrous oxide and cyclopropane) and, in each patient, the pulse and arterial pressure were normal before and during the entire study. Finally, pulmonary nitrogen washout curves were the same in subjects who were anaesthetized and ventilated artificially as they were when the subjects were awake and breathed spontaneously (Bergman, 1963). For these reasons, we feel that comparisons of cyclopropane equilibration in the three groups which we have considered, are valid.

The uptake of cyclopropane should be slowed by certain conditions normally found in the infant: a relatively large blood volume, a high haemoglobin concentration which should increase the cyclopropane blood/gas partition coefficient (Possati and Paulconer, 1958), and the large surface-to-mass ratio which favours percutaneous loss. The effect of foetal haemoglobin on cyclopropane solubility is unknown and is being studied at present. Any metabolic degradation of cyclopropane should reduce end-tidal concentrations as would the presence of a stressed brown fat adipose tissue compartment. Those conditions favouring a more rapid increase in alveolar concentration in the infant and child compared to the adult, are the smaller percentage of muscle mass and total body fat, and the larger percentage of total body water.

Effect of brown adipose tissue: the difference in $Fe/Fe$ ratio between the cyclopropane and nitrous oxide equilibration curves.

Previous consideration of the uptake and distribution of anaesthetics has recognized three major body compartments (Price et al., 1960):

1. a well-perfused, aqueous compartment containing brain, heart, the viscera, etc.;
2. a poorly perfused aqueous compartment containing muscle and skin;
3. a poorly perfused compartment containing white adipose tissue.

Those tissues which have a very poor perfusion have little effect on clinical uptake and are not considered. In infants, a fourth compartment consisting of well-perfused brown adipose tissue should be considered.

Brown adipose tissue is found in the newborn of many mammals including man (Smalley and Dryer, 1963). In the human at birth, the mass of fat in brown adipose tissue is variable, depending upon the conditions in utero and foetal maturity. After birth, the fat content in brown adipose tissue falls progressively for the first few days, then increases to reach a maximum by about the fifth week (Aherne and Hull, 1966) and falls again during the first year (Pawlikowski, 1955). In response to a cold stress, brown adipose tissue produces significant amounts of heat by a mechanism called "non-shivering thermogenesis", in which fat is oxidized, generating heat without production of either mechanical work or high energy chemical bonds (Dawkins and Hull, 1963).

In order to predict whether brown adipose tissue should have a significant effect on uptake of fat soluble anaesthetics, one must know both its mass and its perfusion. Neither of these has been determined in the human infant. In animal species, the mass of brown adipose tissue in the newborn varies between 1% and 5% of body mass (Smith and Horowitz, 1969) and the perfusion (when stressed) between 108 and 304 ml/100 g tissue/min (Evonuk and Hannon, 1963; Bullard and Funkhouser, 1962; Heim and Hull, 1966). In the cold-stressed newborn rabbit, brown adipose tissue, with a mass of only 6% of body weight, can have a blood flow of 25% of cardiac output (Heim and Hull, 1966) and its metabolic activity can more than double the total...
viscera. In the human neonate, cold-stressed brown heat production by 100% (Brück, 1961) and oxygen adipose tissue has similar capabilities; it can increase metabolism of this magnitude are characteristic of the uptake 50-100% of the basal value (Dawkins and Scopes, 1965). It is not unreasonable to speculate that in the cold-stressed human neonate, brown adipose tissue also has a perfusion in the order of magnitude of human viscera, 75-85 ml/100 g tissue/min (Price et al., 1960), in which case it should have a significant effect on uptake of fat-soluble anaesthetics.

It is important to estimate the kinetics of this effect on uptake in order to predict when the effect should be seen. In the time for two "half-equilibration times", a tissue will absorb 75% of its final capacity for any given gas. The "half-equilibration time" for a gas in adipose tissue can be estimated as follows:

\[
\text{"Half-equilibration time"} = \frac{0.693 \times \text{tissue/blood partition coefficient}}{\text{perfusion (ml blood/ml tissue/min)}}
\]

The calculated tissue/blood partition coefficient for cyclopropane in fat is between 19/1 and 27/1 (table I). If cold-stressed brown adipose tissue is estimated to have a perfusion of 75 ml/100 ml tissue/min and white adipose tissue a perfusion of 3 ml/100 ml tissue/min (Price et al., 1960) (and presumably the same applies to inactive brown adipose tissue), their respective "half-equilibration times" are between 18 and 25 min, and 440 and 625 min.

Cold-stressed brown adipose tissue should show most of its effect on the pulmonary equilibration curve of cyclopropane in two "half-equilibration times", 36 to 50 min (75% equilibrium), while white adipose tissue and inactive brown adipose tissue should have this effect spread out over 15 to 21 hr (75% equilibrium). Thus, the 1-hour period of our equilibration study should include most of the effect of cold-stressed brown adipose tissue on the pulmonary cyclopropane equilibration curve. On the other hand, the lower solubility of nitrous oxide in fat should make the effect of cold-stressed brown adipose tissue on nitrous oxide equilibration of shorter duration and lesser magnitude. Nitrous oxide with a calculated tissue/blood partition coefficient of 3/1, should have a "half-equilibration time" of 3 min in cold-stressed brown adipose tissue and 75 min in white adipose tissue or inactive brown adipose tissue.

Figure 1 shows the equilibration curves of cyclopropane and nitrous oxide given simultaneously to a 12-day-old infant. The difference between the two curves is small; note the expanded scale of \( \text{Fe}/\text{Fi} \). Because the uptake commences at the same time for both agents, all physiological variables such as cardiac output, ventilation, tissue perfusion and tissue masses have an identical influence on the equilibration of both gases; therefore, the difference between the curves must be the result of solubility differences between the two gases only. If the solubilities of the two gases were identical except for solubility in fat, then the entire difference between the curves would be the result of the different uptakes into adipose tissue. Table I shows that the blood/air and tissue/blood partition coefficients are indeed fairly similar except for the calculated fat/ blood partition coefficients. This suggests that the difference between the two curves is predominantly a reflection of the difference in the affinity of fat for the two gases. Furthermore, between subjects, this difference in the \( \text{Fe}/\text{Fi} \) ratios of the two equilibration curves is insensitive to variations in physiological parameters such as ventilation and cardiac output except that they may affect perfusion of brown adipose tissue. This is so because the adipose tissue time-constant is essentially a function of adipose tissue perfusion, mass and solubility. Therefore, although changes in ventilation and cardiac output do have an effect on the individual equilibration curves (Kety, 1951), such changes affect the relationship between the two curves much less because the effect on each curve is similar. For example, in figure 4, a 19-month-old infant was inadvertently hyperventilated and the \( \text{PACO}_2 \) was 30 mm Hg. By 35 min, end-tidal cyclopropane concentration reached and then exceeded inspiratory concentration.

*In subjects who reach apparent equilibrium, it is often observed that end-tidal concentrations eventually exceed inspiratory concentration. This is seen for both cyclopropane and nitrous oxide in figure 4. This phenomenon is due to the concentrating effect on alveolar gases whenever there is a net absorption of gas from alveolus to pulmonary capillary blood. It becomes apparent when inspiratory and end-tidal concentrations are close. This effect has
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considerably faster than that found in the infant group (fig. 2) in which, by 50 min, the end-tidal concentrations reached only 97.7% of inspiratory concentration. However, hyperventilation also made equilibration of nitrous oxide faster by about the same proportion. Consequently, the difference in Fe/Fi ratios between the two curves is about the same as that found in children ventilated normally, although each of the two individual curves approached equilibrium more rapidly than the individual curves of children ventilated normally.

Figure 3 shows the averaged equilibration curves of both nitrous oxide and cyclopropane in infants, children and adults. The difference in Fe/Fi ratios between the curves is smallest in the infant group (0.019–0.026). The difference between the curves for the children aged 3 to 6 years (0.042–0.047) resembles more closely the difference in the adult curves (0.050–0.066) than that of the infants. We had predicted that, in the presence of a cold stress, the brown adipose tissue compartment in infants would have contributed to a larger difference between the two curves than that found in older children and adults. The relatively small difference found between the cyclopropane and nitrous oxide equilibration curves in the infant suggests that there is little functional brown adipose tissue because of either small mass or low perfusion, or both.

There are several possible explanations for our inability to show an effect of active brown fat in our surgical patients. Partition coefficients of nitrous oxide and cyclopropane in infants may not be the same as those in older children and adults. Another possibility is that halothane anaesthesia may have blocked non-shivering thermogenesis. Information is not available on these points.

There is some evidence that small quantities of cyclopropane are metabolized in the rat, although quantification is difficult (Chenoweth, 1964). Whether or not metabolism occurs in man is unknown. However, if our infants metabolized cyclopropane to a lesser extent than the older child and the adult, it could influence interpretation of our results.

Percutaneous loss of nitrous oxide and cyclopropane in the adult at constant alveolar concentrations have been reported to amount to 0.051 and 0.015 ml/min/m²/1% alveolar concentration respectively (Stoelting and Eger, 1969). This difference in percutaneous loss should tend to slow the nitrous oxide equilibration curve more than the cyclopropane curve. However, these losses cannot be evaluated accurately in our infants because of the effect of the cold stress on cutaneous perfusion and because of the presence of surgical drapes, including an adhesive plastic layer next to the skin.

Our infants may have had little or no functional fat in their brown adipose tissue because of prematurity (fat is laid down in the last few weeks of full-term uterine life), or because the original fat depots were exhausted as a result of disease or poor nutrition. None of the infants was premature. However, the three smallest infants had not been gaining weight prior to surgery. The finding that the experimentally measured difference between the two equilibration curves in the infant group was smaller than that of the child and adult groups suggests that not only was there little or no fat in the brown adipose tissue of the infant but also that the infant had less white adipose tissue or a reduced perfusion of white adipose tissue compared with the children or adults. There is some evidence for the first of these possibilities since the neonate does have proportionately less total fat than the adult: 12% of body mass compared with 18% in the adult (Friis-Hansen, 1971).

REFERENCES


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Further information: R. Saenz Pena, 1110, 2nd floor, Buenos Aires, Argentina.