The Effect of Ketamine on the Functional Residual Capacity in Young Children

D. Shulman, M.D.,* C. S. Beardsmore, Ph.D.,† H. B. Aronson, F.F.A.R.C.S.(1),‡ S. Godfrey, M.D.§

The effect of ketamine on the functional residual capacity (FRC) was measured in nine ASA class I children prior to elective surgery. FRC was determined by the closed-circuit helium dilution method on the day prior to surgery in the awake state and also following induction of anesthesia on the day of the operation. Anesthesia consisted of ketamine by continuous intravenous infusion following preanesthetic sedation with atropine and triclofos or flunitrazepam. There were no significant differences in FRC between the measurements in the awake state and anesthetized (392 ± 43 SEM mL, and 411 ± 53 SEM mL, respectively), and the authors conclude that ketamine does not affect resting lung volume in young children. (Key words: Anesthesia: pediatric. Anesthetics, intravenous: ketamine. Lung: functional residual capacity.)

A decrease in functional residual capacity (FRC) has been reported widely following induction of anesthesia. In a review by Don¹ of studies that reported on a wide variety of anesthetic agents, the average decrease in FRC in anesthetized spontaneously breathing adults was 18.5% and in unanesthetized and paralyzed ventilated adult patients was 14%. In children aged 5–11 yr, the decrease in FRC following induction of general anesthesia with paralyzed and ventilation averaged 44%.² Because FRC is an important determinant of oxygenation during anesthesia, avoiding or minimizing the decrease in FRC may help to prevent intraoperative hypoxemia.

Ketamine is an established anesthetic that is especially useful for diagnostic and minor surgical procedures in children.³ It does not seem to affect gas exchange in the lung and often is used without supplemental oxygen.⁴ We conjectured therefore that the effect of ketamine on FRC might be different than that of other general anesthetics and investigated this hypothesis in a group of young children.

Materials and Methods

Subjects

This study was approved by the Human Experimentation (Helsinki) Committee of this hospital. Nine ASA class I children between the ages of 10 and 83 months (mean age 53.6 ± 7.7 months) were studied following informed parental consent. All patients were awaiting elective surgery. Physical characteristics and type of surgery are listed in table 1.

FRC Determination

FRC was measured by the closed-circuit helium dilution method (fig. 1). The subject breathed through a face mask sealed around the nose and mouth with sterile putty to prevent leaks. Connected to the mask was an apparatus incorporating a pneumotachograph and a T-piece with two pneumatically operated conical valves controlled by a bellows, so that the child could be switched rapidly from breathing room air to breathing from the circuit. The flow signal from the pneumotachograph was measured with a differential pressure transducer (Validyne MP45®) connected to a pressure amplifier (Hewlett Packard 8805C®). The flow signal also was integrated (Hewlett Packard 8815A®), and the flow and volume signals were displayed continuously on a time-base oscilloscope (Tektronix T9535A®).
TABLE 1. Clinical Details of Subjects

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (months)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Operation</th>
<th>Inhilation Ketamine (mg·kg⁻¹)</th>
<th>Maintenance Ketamine (mg·kg⁻¹·min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>10</td>
<td>66</td>
<td>6.8</td>
<td>Synacthy repair</td>
<td>3.7 im</td>
<td>0.200</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>41</td>
<td>96</td>
<td>15.4</td>
<td>Hydrocele repair</td>
<td>2.0 im</td>
<td>0.053</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>40</td>
<td>98</td>
<td>14.5</td>
<td>Strabismus repair</td>
<td>1.7 iv</td>
<td>0.045</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>47</td>
<td>95</td>
<td>13.5</td>
<td>Laparotomy</td>
<td>2.0 im</td>
<td>0.080</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>46</td>
<td>99</td>
<td>15.1</td>
<td>Strabismus repair</td>
<td>1.7 iv</td>
<td>0.160</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>71</td>
<td>108</td>
<td>18.2</td>
<td>Umbilical herniorrhaphy</td>
<td>2.0 im</td>
<td>0.053</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>64</td>
<td>112</td>
<td>21.5</td>
<td>Orchipexy</td>
<td>1.9 iv</td>
<td>0.050</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>83</td>
<td>113</td>
<td>22.2</td>
<td>Strabismus repair</td>
<td>2.3 im</td>
<td>0.053</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>80</td>
<td>110</td>
<td>16.9</td>
<td>Salter procedure</td>
<td>1.3 iv</td>
<td>0.059</td>
</tr>
</tbody>
</table>

Two Plexiglass® water-level spirometers, both incorporating a volume scale, were constructed with volumes appropriate for infants and children. According to the size of the child, one of these was connected in a closed circuit via small-diameter corrugated rubber tubing to a CO₂ absorber, helium analyzer (Morgan Mo/2 FRC), pump, and T-piece. In addition to the pump within the helium analyzer, a second pump was added in parallel to it to provide a total flow of 66 ml/s. This flow ensured rapid mixing and eliminated rebreathing by the child.

Accuracy of the system was assessed by duplicate measurements by helium dilution of the volume in a graduated syringe set at 300 ml, 400 ml, and 500 ml. The frequency response of the circuit was determined using a sinusoidal pump at increasing frequencies, and the volume oscillations of the spirometer were noted.

The helium analyzer was calibrated before each session, using room air and a gas mixture containing a known helium concentration. For the test, the gas introduced into the closed circuit was 9–14% helium (the linear range of the helium analyzer), 21% oxygen, and the balance nitrogen. Before starting the test, the child lay supine and breathed room air quietly through the apparatus. According to the display of tidal volume on the oscilloscope, the subject rapidly was switched into the circuit at end-expiration. The child continued to breathe quietly from the gas mixture, and oxygen was added continuously to ensure a constant end-expiratory circuit volume. The helium concentration was measured continuously and recorded until a stable plateau of at least 2 min duration was obtained. In two measurements on two restless children, a slightly shorter plateau was accepted.

**CALCULATION**

Following completion of the testing, initial circuit volume (V1) was calculated by the method described by Cotes. Briefly, the system was set up as for FRC measurement with the usual gas mixture and spirometer starting volume. Four increments of 100 ml of air then were added in a stepwise fashion, and the new stable helium concentration was recorded after each addition. The linearity of the circuit was examined by plotting the reciprocal of the helium concentration against the added volume. The intercept on the volume axis represented V1.

FRC then was calculated from the following equation:

\[ \text{FRC} = (C1/C2 \times V1) - V1 - DS \]

where C1 = initial helium concentration, C2 = final helium concentration, and DS = dead space of mask, pneumotachograph, and T-piece. The results were corrected to BTPS.

FRC was measured at least three times at each of two sessions, the first while the patient was awake on the day prior to surgery and the second following induction of anesthesia but before the start of surgery. The final result for FRC was the mean of all measurements within

![Fig. 1. Circuit diagram of the closed circuit helium dilution apparatus for measuring functional residual capacity.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931411/ on 06/01/2017)
10% of each other with a minimum of two satisfactory tests. The child breathed room air for at least 4 min between consecutive tests to clear the helium from the lungs.

The mean FRC in the awake state was compared with the mean FRC during anesthesia using Student's paired t test.

**Measurement of Respiratory Cycle Parameters**

Following the FRC determinations in four subjects (subjects 1, 7, 8, 9) during anesthesia but before commencement of surgery, flow and volume during spontaneous breathing were recorded for later analysis. The circuit and valves were removed from the T-piece, leaving the mask connected to a simple pneumotachograph. Via the flow transducer and integrator, and pressure amplifier as described previously, the flow and volume signals were relayed to the oscilloscope and also were recorded (Hewlett Packard Instrumentation Recorder 3964A®) on magnetic tape. Calibration signals from two known flows and a known volume from a plastic syringe were recorded on tape immediately after the testing was completed.

The signals later were played back onto a paper recorder (Hewlett Packard Recorder 7758A®) and analyzed manually. Frequency (f) was determined by counting breaths for a 30-s period of quiet breathing, and tidal volume (Vt) was the mean of the volumes of each breath during this interval. Inspiratory and expiratory times (Ti and Te) were calculated from the time interval between points of zero flow before and after inspiration and expiration. Ti and Te were derived from the mean of the values for each breath during 30 s.

**Anesthetics and Procedure**

Each child was studied on two occasions, once awake and once under anesthesia. On the day before surgery, each child had his FRC measured while awake and lying supine in the presence of a parent. On the morning of surgery, following an 8-h fast, the subjects received preanesthetic sedation with atropine 5–18 µg/kg and either oral flunitrazepam 24–33 µg/kg or oral triclofos 70–100 mg/kg. The doses were determined for each child individually to achieve good sedation. The youngest child received no premedication. Anesthesia was induced in the induction room with ketamine intramuscularly 2.0–3.7 mg/kg or intravenously 1.3–1.9 mg/kg if the patient had an intravenous line in place (table 1). Maintenance ketamine was given as an iv drip at 45–200 µg·kg⁻¹·min⁻¹ according to weight and response (table 1). ECG routinely was monitored throughout. The FRC measurement then was repeated, and flow and volume were recorded from four subjects during an interval of at least 30 s of quiet breathing prior to the commencement of surgery.

**Results**

The correlation coefficients for the reciprocal of helium concentration versus added volume were not less than 0.9999 for all the measurements, demonstrating linearity of the system. Helium dilution estimates of the volumes of the syringe set at 300 ml, 400 ml, and 500 ml were accurate within 2%. The frequency response of the circuit was linear to 2.2 Hz.

The ratio of FRC to V1 was calculated individually, and the mean for all patients was 0.15.

The awake FRC values correlated with height according to the following equations:

\[ \text{FRC (ml)} = 7.98 \times \text{height (cm)} - 404 \quad r = 0.89 \]

\[ \text{FRC (ml)} = 0.0047 \times \text{height}^{2.46} \quad r = 0.96 \]

The results of all FRC measurements in the nine subjects are shown in table 2. In four of the children, the measured value of FRC increased following induction of anesthesia, and in the remaining five it decreased, with a range of +40% to −18%. There was no significant difference between the mean FRC measured awake and anesthetized (P > 0.5).

Values of FRC measured during anesthesia plotted against awake values are shown in figure 2. The regression line for the points has a correlation coefficient of 0.83 and a slope of 1.01.

Results of the analysis of the respiratory cycle are shown in table 3. The mean Ti/Te was 0.82.

**Discussion**

We have shown that FRC does not change significantly following induction of anesthesia with ketamine in healthy children.
children. This is in marked contrast to the studies of Dobbinson et al., who demonstrated a 44% reduction in FRC in healthy children aged 6–11 yr following induction of anesthesia with thiopental, maintenance with methoxyflurane and oxygen in nitrogen, and muscle paralysis with succinylcholine and curare. The presence of muscle paralysis should not in itself be responsible for this change, since succinylcholine did not decrease FRC in adults and caused an increase in FRC in children. The difference between the inspired oxygen concentration (FIO2 during the awake (21%) and the anesthetized (50–100%) states in the study by Dobbinson et al. could have affected the FRC if there was significant gas trapping and subsequent absorption atelectasis. However, there was no significant difference in FRC during anesthesia between the children receiving 50 or 100% O2 (fig. 3 in Dobbinson et al.). Also, Don et al. measured the volume of trapped gas (VTG) in healthy adults during anesthesia and found a VTG of only 3.03% of the total lung capacity, and no difference in VTG was noted between those with an FIO2 of 30 or 100%. Thus ketamine seems to have a different effect on FRC than the thiopental and methoxyflurane anesthesia used by Dobbinson et al.

Although the mean change in FRC following ketamine administration was not significant, the range (+40% to −18%) indicates large individual variation of the response to this anesthetic. Dobbinson et al. found an even greater range of change in FRC following induction of anesthesia (+10% to −58%). They found that the decrease in FRC following induction as related inversely to age of the subjects but was unrelated to body build and postulated that this was due to age-related structural differences in the lungs. We found no size-related effect of ketamine on FRC (fig. 2) and no correlation between change in FRC and age, height, height cubed, or weight. We also compared the change in FRC of individual subjects with their weight/height ratio as an index of body build and found no correlation.

Because of the difficulties in studying lung function in awake preschool children, few data are available for comparison with our results. In two earlier studies, FRC was measured in awake supine children. Gaultier et al. reported FRC in children ages 3 years and less, and Dobbinson et al. measured FRC of children ages 6 years and more. In those of our children whose ages fell within these ranges, our values for FRC were within two standard deviations of the means quoted in these studies. Similarly, our regression line for height against awake FRC was very similar to that of Tausig et al. for boys 3 years of age and younger lying supine with a slight head-up tilt. In other studies of FRC in children, the subjects were older and were sitting or standing, and in these positions FRC is significantly greater than when supine.

For measurement of FRC, a large FRC/V1 ratio best ensures reproducibility of the measurement. This is difficult to achieve in small children due to their small lung volumes, and our mean FRC/V1 of 0.15 is less than that achieved in measurements of FRC in adults. This represents a limitation to the accuracy of this method. However, estimates of the volume of a syringe

<table>
<thead>
<tr>
<th>Patient</th>
<th>VT (ml)</th>
<th>VT (ml)/kg</th>
<th>f (l/min)</th>
<th>Vc (l/min)</th>
<th>Ti (s)</th>
<th>Te (s)</th>
<th>Ti/Te</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>138</td>
<td>8.2</td>
<td>28</td>
<td>3.84</td>
<td>0.94</td>
<td>1.18</td>
<td>0.82</td>
</tr>
<tr>
<td>2</td>
<td>157</td>
<td>7.1</td>
<td>28</td>
<td>4.35</td>
<td>0.90</td>
<td>1.15</td>
<td>0.78</td>
</tr>
<tr>
<td>3</td>
<td>145</td>
<td>8.6</td>
<td>30</td>
<td>4.35</td>
<td>0.91</td>
<td>1.17</td>
<td>0.98</td>
</tr>
<tr>
<td>4</td>
<td>157</td>
<td>7.1</td>
<td>28</td>
<td>4.39</td>
<td>1.15</td>
<td>1.17</td>
<td>0.98</td>
</tr>
<tr>
<td>5</td>
<td>145</td>
<td>8.6</td>
<td>30</td>
<td>4.35</td>
<td>0.91</td>
<td>1.17</td>
<td>0.98</td>
</tr>
<tr>
<td>Mean</td>
<td>138</td>
<td>8.2</td>
<td>28</td>
<td>3.84</td>
<td>0.94</td>
<td>1.18</td>
<td>0.82</td>
</tr>
<tr>
<td>SD</td>
<td>59</td>
<td>0.8</td>
<td>2</td>
<td>2.52</td>
<td>0.15</td>
<td>0.12</td>
<td>0.13</td>
</tr>
</tbody>
</table>
with a measured volume/V1 ratio as low as 0.10 showed a mean error of less than 2%, and thus we feel this did not have an important effect on our results.

We have used dosage schedules for the premedicants and for ketamine that are clinically relevant. There is evidence that a small initial bolus of ketamine followed by a continuous 0.1% iv drip provides good anesthesia with a total dose requirement that is significantly smaller than is necessary with the intermittent bolus technique. In children, Legout et al. showed that the rate of ketamine infusion that was necessary to maintain surgical anesthesia was dependent on the size of the patient. Children less than 10 kg required doses in excess of 0.1 mg·kg⁻¹·min⁻¹ and those weighing more than 10 kg were well anesthetized with 0.06–0.1 mg·kg⁻¹·min⁻¹. Our subjects received infusion rates that corresponded to these values, except for subject 5, who unaccountably required a higher dose (table I). In all cases our subjects had uneventful surgery following the FRC measurements with no anesthesia-related morbidity.

The cause of the decrease in FRC in conjunction with most of the commonly used anesthetic agents is still unknown. The many theories attempting to explain this phenomenon have been summarized elsewhere. One theory is based on the importance of the “braking” effect of the inspiratory muscle tone during expiration, which maintains FRC above the resting volume of the respiratory system. This has been demonstrated in adults and in healthy newborns. During halothane anesthesia, direct measurements demonstrate inhibition and rapid decay of this inspiratory muscle tone during expiration, and this then results in a decrease in FRC. This is further supported by evidence that the chest wall pressure–volume curve is shifted to the right following anesthesia with or without paralysis and following partial curarization without anesthesia. Muscle tone generally is preserved during ketamine anesthesia, and this also may apply to inspiratory muscle tone.

Glottic narrowing also serves a “braking” role during expiration. During anesthesia with ketamine, the upper airway muscles maintain their tonus, and laryngeal reflexes may be intact or hyperactive. Thus, we may conjecture that the tone of the inspiratory and laryngeal muscles during expiration is preserved with ketamine similarly to the awake state and thus the FRC is not affected.

Inspiratory muscle tone during expiration may be particularly important for the maintenance of FRC in young children in whom the chest wall is relatively compliant. Thus they may rely to a greater extent than adults on the inspiratory muscle tone to support the chest wall against the pull of the elastic recoil of the lungs. This may account for the observation that the magnitude of the decrease in FRC in children anesthetized with methoxyflurane varies inversely with age.

Dynamic mechanisms also may contribute to the maintenance of FRC at a volume higher than the relaxed end-expiratory lung volume. The respiratory rate, VT, Ti/Te, and the time constant of expiration determine the volume at which the subject interrupts expiration and begins an inspiration. These factors have been shown to be important in determining FRC in mice and in infants. In adult volunteers, a continuous ketamine infusion caused an increase in f, VT, and Ti/Te, with an associated increase in the end-expiratory chest wall position, as measured by bellows pneumographs, and this was interpreted as an increase in the thoracic gas volume. Ketamine administration results in a marked prolongation of Ti and “apneustic” breathing in cats. We have found a mean respiratory rate of 28/min, mean VT of 8.2 ml/kg body weight, and a mean Ti/Te of 0.82. This suggests that, in young children, the pattern of breathing is not affected greatly by ketamine and expiration is not prolonged, as has been noted in patients receiving inhalational agents or other intravenous anesthetics. Thus, the relative lack of effect of ketamine on the pattern of breathing and the maintenance of preanesthetic FRC may be related. However, this cannot be confirmed without measuring other important parameters, such as the expiratory time constant.

Fluid shifts may play a role in the change in FRC during induction of anesthesia, but the relative contribution of this mechanism and the effect of various anesthetic agents have yet to be elucidated.

The consequences of the decrease in FRC following induction of anesthesia are well documented. Static lung compliance decreases, and FRC may approach or become less than closing capacity (CC), resulting in gas trapping and increased intrapulmonary shunt with hypoxemia. There is an inverse correlation between the magnitude of the change in FRC and the alveolar–arterial oxygen difference. Ketamine does not cause a decrease in arterial blood oxygenation in children breathing room air spontaneously, a finding consistent with no significant change in FRC.

Resistance to airflow is increased at low lung volumes, and thus anesthetics that do not affect bronchomotor tone but that cause a decrease in FRC cause increased pulmonary resistance. Huber et al. have shown that ketamine does not affect airway resistance in healthy adults, although lung volumes were not measured in their study. Our finding of maintenance of baseline FRC during ketamine anesthesia is consistent with and may help to explain the preservation of preanesthetic airway resistance.

The finding of lack of deleterious effect of ketamine
on FRC in children, in contrast to the consistent and marked decrease following induction with all other commonly used anesthetics, emphasizes the unique properties of this agent. This may be a practical consideration for the practicing anesthesiologist in choosing an anesthetic technique for children with spontaneous breathing that will best preserve normal pulmonary physiology.

References