総 説 (Review)

The Effect of Anesthetic Agents on Cardiovascular Function in Infants and Children

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I. Introduction

The induction of anesthesia in an infant or young child can be an stressful time for the anesthesiologist and for the child. Physiologic changes occur quickly and the incidence of critical events in children is high. These critical events, which may include hypotension or bradycardia can all contribute to the anesthesia-related cardiac arrests that occur more frequently in infants than in adults.[1-3] Although there are many ways to induce anesthesia in young children, the technique that is chosen should be safe, rapid, and uncomplicated.

Techniques for the induction of anesthesia in pediatric patients have developed in an empiric manner because accurate, non-invasive methods of evaluating the cardiovascular responses to induction of anesthesia in children had not been available. Frequently the effect of anesthetic agents on adults have, perhaps inappropriately, been extrapolated to the pediatric patient and because of this lack of specific information, we have focused much of our research interest on the period or induction of anesthesia using two-dimentional and pulsed Doppler echocardiography to evaluate the changes in cardiovascular function that occur during the induction of anesthesia in neonates, infants and young children.

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II. Inhalation Induction

Inhalation induction of anesthesia with halothane or isoflurane is a very common technique used to put a young child to sleep for surgery. Numerous studies have provided comparative data evaluating the cardiovascular effects of inhalation anesthetic agents in adults but few studies exist evaluating their use in pediatric patients. Those studies that have been done in children have either not been comparative studies; have used indirect methods of determining cardiac output; or have been limited to changes in blood pressure and heart rate. In 1978 Barash et al[4] used M-mode echocardiography to demonstrate that halothane caused significant depression of myocardial function in healthy children aged 19 months to twelve years. He reported that the mean blood pressure, cardiac output and ejection fraction all decreased significantly as the concentration of halothane was increased. Friesen and Lichtor,[5,6] studied healthy patients less than six months of age and found that inhalation induction of anesthesia with both halothane[5] and isoflurane[6] in combination with nitrous oxide was associated with marked decreases in heart rate and blood pressure. In these studies,

however, no evaluation of cardiac output, ventricular volumes or ejection fraction was made, so the specific cause of the hypotension could not be identified.

Wolf et al[7] compared the hemodynamic effects of isoflurane and halothane in fifteen healthy children (mean age 5.7 years) and concluded that halothane causes a significant, dose-dependant decrease in myocardial function. In contrast to other investigators,[6,8,9] Wolf stated that myocardial function was preserved in children receiving isoflurane. In her study, however, only a single dimension of the myocardium was measured and it was assumed that all other determinants of cardiac function, including preload, afterload, heart rate and conduction, were unchanged. As a result, the effect of halothane and isoflurane on all the determinants of cardiovascular function could not be effectively evaluated from this M-mode echocardiographic data. In our studies we have used two-dimensional imaging of the heart to more accurately assess ventricular volumes than is possible using M-mode echocardiography. In addition, pulsed Doppler echocardiography, which uses a directed Doppler signal to provide a measure of blood flow velocity, was used to determine cardiac output. Combined two-dimensional and Doppler echocardiography permits the simultaneous measurement of ventricular volumes and aortic or pulmonary blood flow velocity. This provides an accurate, non-invasive method of determining ventricular volumes, ejection fraction, stroke volume and cardiac output and the values obtained in children correlate closely with invasive, angiographic techniqus.

A. Comparison of Halothane and Isoflurane

In the first study[10] 20 children aged 9 days～32 months were studied during induction of anesthesia with halothane or isoflurane. Heart rate, blood pressure and echocardiographic measurements were completed 10-30 minutes prior to induction of anesthesia and served as the control data. From the echo studies pulmonary artery diameter and blood flow velocity were measured, as were left ventricular area and length in diastole and systole. From these measurements cardiac output, stroke volume and ejection fraction were determined.

In the operating room anesthesia was then induced by mask with either halothane or isoflurane. Once the child was asleep ventilation was controlled and an intravenous catheter was placed. The anesthetic concentration was then reduced and maintained at an end-tidal concentration of 0.75 MAC (adjusted for age) and the cardiovascular and echocardiographic data were collected again. The end-tidal concentraion was then raised to 1.0 MAC; then 1.25 MAC and all measurements were repeated at each anesthetic level.

The awake and the first three measurements under anesthesia at 0.75, 1.0 and 1.25 MAC were used to assess the effect of equipotent concentrations of halothane and isoflurane on cardiac function (Table 1). Isoflurane anesthesia increased heart rate significantly from awake levels at all anesthetic concentrations while halothane significantly decreased heart rate at 1.25 MAC. The mean blood pressure decreased in both groups at 1.0 and 1.25 MAC. There was a decrease in cardiac index from awake values with both halothane and isoflurane that was significant at 1.25 MAC and the stroke volume index was also decreased at 1.0 and 1.25 MAC with both drugs.

Systolic and diastolic left ventricular volumes, determined from two-dimensional imaging, were increased significantly from control levels with both isoflurane and halothane. This was associated with a decrease in ejection fraction at all anesthetic levels.

The changes in blood pressure and pulse seen in this study were similar to those observed in prior studies of infants and children.[4-7,11] The

Table 1 Hemodynamic Data

	Awake	0.75 MAC	1.0 MAC	1.25 MAC
Heart rate (beats·min^{-1})				
Halothane	124.6 ±4.6	124.8 ±5.0†	124.4± 4.5†	119.4 ±3.5*†
Isoflurane	128.7 ±4.2	142.5 ±6.0*	143.3 ±8.1*	142.7 ±6.7*
Mean blood pressure (mmHg)				
Halothane	72.2 ±3.9	67.8 ±2.4	59.9 ±3.1*	58.9 ±2.9*
Isoflurane	76.4 ±2.3	71.9 ±4.4	64.9 ±3.0*	60.6 ±3.1*
CI (l·min^{-1}·m^{-2})				
Halothane	3.99±0.3	3.35±0.31	3.42±0.24	3.43±0.29*
Isoflurane	4.7 ±0.5	4.91±0.55	4.47±0.59	4.32±0.54*
SVI (ml·m^{-2})				
Halothane	32.7 ±2.5	26.8 ±2.0	27.8 ±2.0*	28.9 ±2.5*
Isoflurane	36.9 ±3.8	34.2 ±3.4	30.9 ±3.5*	30.2 ±3.5*
LVEDV (ml)				
Halothane	15.1 ±2.2	15.9 ±1.9	16.4 ±2.0*	16.9 ±2.0*
Isoflurane	16.7 ±2.6	17.3 ±2.7	17.8 ±2.7*	18.5 ±2.7*
LVESV (ml)				
Halothane	7.7 ±1.0	8.4±1.0*	8.8 ±1.1*	9.9 ±1.2*
Isoflurane	8.1 ±1.4	8.7 ±1.4*	9.0 ±1.5*	9.4 ±1.4*

Values are expressed as mean±SEM.

* $p<0.05$ from awake.

† $p<0.05$ from isoflurane.

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decrease in cardiac index with 1.25 MAC halothane corresponds to previously reported values in older children.[4,7] The effect of isoflurane to decrease the cardiac index, despite an increase in heart rate, differs from other studies in children which have reported that contractility (PEP, LVET, STI) and cardiac output was unchanged or increased in children during isoflurane anesthesia.[7]

The effects of halothane and isoflurane on blood pressure, ventricular volumes, stroke volume and ejection fraction in the study by Murray et al[10] suggest that these two agents produce similar, clinically significant, impairment of myocardial function. This agrees with animal studies,[8,9] which also found that similar decreases in myocardial contractility occur with both isoflurane and halothane.

B. Effect of Fluid Loading

It has been suggested that hypotension during the induction of anesthesia in children due, at least in part, to the dehydration that occurs during pre-operative fasting and that volume loading at the time of induction may attenuate the cardiac depression that is seen. To test this hypothesis, each child in the study described above received a fluid bolus of 15 ml·kg^{-1} of lactated Ringer's administered over two minutes while maintaining anesthesia at the 1.25 MAC level. A final set of hemodynamic measurements were then made. Althogh volume loading resulted in an increase in left ventricular end diastolic volume (LVEDV), or preload, in both groups of patients, it did not correct the hypotension (Table 2). In fact, in the children receiving halothane there was a further significant decrease in stroke volume and ejection fraction following the fluid bolus. In

Table 2 Hemodynamic Data Before and Following Fluid 15 ml/kg Lactated Ringers at 1.25 MAC

	Before Fluid	Following Fluid
HR (beats·min^{-1})		
Halothane	119.4 ±3.5†	123.0 ±2.7†
Isoflurane	142.7 ±6.7	135.0 ±7.5
MBP (mmHg)		
Halothane	58.9 ±2.9	57.9 ±2.5†
Isoflurane	60.6 ±3.0	49.5 ±3.1*
LVEDV (ml)		
Halothane	16.9 ±2.0	18.8 ±2.2*
Isoflurane	18.5 ±2.7	19.7 ±2.8*
LVESV (ml)		
Halothane	9.9 ±1.2	10.6 ±1.2*
Isoflurane	9.4 ±1.4	10.0 ±1.6*
CI (l·min^{-1}·m^{-2})		
Halothane	3.43±0.29	3.32±0.39
Isoflurane	4.32±0.54	4.72±0.73
SVI (ml·m^{-2})		
Halothane	28.9 ±2.5	27.1 ±3.0*†
Isoflurane	30.2 ±3.5	34.7 ±4.2*

Values are expressed as mean±SEM.

* $p<0.05$ from before fluid.

† $p<0.05$ from Isoflurane.

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contrast, in the patients receiving isoflurane administration of a fluid bolus was followed by an increase in stroke volume and ejection fraction. This difference in the myocardial response to a fluid load, when the isoflurane group was compared to the halothane group, seems to be an important clinical difference between these two agents. It may indicate that subtle differences do exist in their cardiovascular effects and might be evidence for increased cardiovascular reserve during isoflurane anesthesia.

In addition to administering a fluid bolus in an effort to overcome the cardiovascular depression or hypotension associated with the induction of anesthesia using halothane or isoflurane, it has been suggested that the addition of nitrous oxide to halothane or isoflurane will lessen the cardiovascular depression that occurs when halothane or isoflurane are used alone. Others believe the use of intravenous atropine can attenuate the cardiovascular depression produced by the volatile anesthetics. We have evaluated both these factors in an effort to determine their influence on the cardiovascular changes associated with the use of halothane and isoflurane.

C. Effect of Nitrous Oxide

The first question asked was whether the combination of nitrous oxide with either halothane or isoflurane was less of a cardiovascular depressant than equianesthetic concentrations of halothane or isoflurane alone.[12] To determine this the effects of halothane or isoflurane with and without nitrous oxide were compared, again using two-dimensional and pulsed Doppler echocardiography to determine ventricular volumes, cardiac output, stroke volume and ejection fraction in the same way as described in the previous study. Thirty-one children were studied. Fifteen received halothane and sixteen received isoflurane anesthesia after awake, control echocardiographic studies were completed. Anesthesia was then induced using 60% nitrous oxide, which was assumed to equal 0.6 MAC, and the concentration of the halothane or isoflurane was gradually increased to achieve an end-tidal concentration of 0.9 MAC, resulting in a total additive MAC of 1.5. The two-dimensional and pulsed Doppler echocardiographic studies were then repeated. Following this, the nitrous oxide was discontinued and the halothane or isoflurane concentration was increased to maintain the end-tidal anesthetic concentration at 1.5 MAC. A third set of cardiovascular data was collected following the washout of the nitrous oxide.

Heart rate and mean blood pressure decreased below control awake values during anesthesia with 0.6 MAC nitrous oxide and 0.9

Table 3 Cardiovascular Data

	Awake	0.9 MAC+60% N_2O	1.5 MAC
Heart rate (beats·min^{-1})			
Halothane	127±5.5	116±6.2*	115±6.0*†
Isoflurane	141±5.0	130±4.6*	140±4.5
Mean blood pressure (mmHg)			
Halothane	74.3±1.9	59.1±2.1*	55.4±1.5*
Isoflurane	73.5±2.4	59.2±2.5*	57.8±2.6*
Left ventricular end-diastolic volume (m*l*)			
Halothane	11.9±1.2	13.8±1.1*†	14.0±1.1*†
Isoflurane	9.5±0.6	9.7±0.7	10.2±0.8*
Left ventricular end-systolic volume (m*l*)			
Halothane	5.6±0.5	7.7±0.6*†	7.4±0.6*†
Isoflurane	4.8±0.4	5.2±0.4	5.2±0.5

* $p<0.05$ from awake.

† $p<0.05$ from isoflurane.

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MAC halothane or isoflurane (Table 3) and the magnitude of the decrease was similar in the two groups. After discontinuing nitrous oxide and increasing the concentration of the volatile agent, heart rate and blood pressure in the halothane group were unchanged. In the isoflurane group, although mean blood pressure was unchanged, the heart rate increased significantly above the rate measured during nitrous oxide and isoflurane anesthesia.

During anesthesia with halothane and isoflurane, with or without nitrous oxide, the cardiac output decreased from the awake values as did the stroke volume. Decreases in ejection fraction also occurred with both agents, with or without nitrous oxide, but the decrease in ejection fraction was greater in the children that received halothane.

In this study, the combination of 60% nitrous oxide with halothane or isoflurane did not result in any significant alteration in blood pressure, cardiac output, stroke volume or ejection fraction when compared to equianesthetic levels of halothane or isoflurane in oxygen. This suggests that, unlike adults, the use of nitrous oxide in combination with a volatile angent in children dose not attenuate the cardiovascular depression than occurs when halothane or isoflurane are used alone. Perhaps the direct myocardial depression produced by nitrous oxide is more profound in infants than in adults or, alternatively, the increase in sympathetic activity that occurs during nitrous oxide anesthesia in adults may be less pronounced in children.

D. Effect of Atropine

The next study of the cardiovascular effects of inhalation anesthesia again used two-dimensional and pulsed Doppler echocardiography to assess the effect of atropine on the myocardial depression produced by halothane and isoflurane.[13] After obtaining the awake echocardiography measurements, anesthesia was induced with halothane or isoflurane and maintained at an end-tidal concentration of 1.5 MAC. A second set of cardiovascular data was then obtained. Finally, atropine 0.02 mg·kg^{-1} was administered intravenously and two minutes later the last echocardiographic study was completed.

In this study the effects of halothane and

Table 4 Changes in heart rate, mean blood pressure and left ventricular end-diastolic volume (LVEDV)

	Awake	1.5 MAC	1.5 MAC+atropine
Heart rate (beats·min^{-1})			
Halothane	127±5.5	115±6.0*†	151±4.0†
Isoflurane	141±5.0	140±1.5	168±3.0*
Mean blood pressure (mmHg)			
Halothane	74.3±1.9	55.4±1.5*	62.5±2.7*†‡
Isoflurane	73.5±2.4	57.8±2.6*	59.4±3.1*
LVEDV (m*l*)			
Halothane	11.9±1.2	14.0±1.1*†	14.4±1.3*†
Isoflurane	9.5±0.6	10.2±0.8*	9.8±0.8‡

Results are expressed as mean±SEM.

* $p<0.05$ from awake measurement.

† $p<0.05$ from isoflurane.

‡ $p<0.05$ from prior to administration of atropine.

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isoflurane on heart rate and mean blood pressure were the same as those seen in earlier studies of the inhalation agents.[10,12] Cardiac output and stroke volume decreased to a similar degree with both drugs; but, halothane caused a greater increase in left ventricular diastolic volume and a greater decrease in ejection fraction than did an equianesthetic concentration of isoflurane. Following the administration of atropine, the heart rate increased in both groups of patients, but there was no change in stroke volume nor did the ejection fraction or ventricular volumes return toward control levels (Table 4).

From the results of this study it was concluded that the use of atropine diminished the differences in heart rate that exist during halothane or isoflurane ansthesia in pediatric patients. In addition, atropine augmented cardiac output through its effects on heart rate, but it did not influence the depression in myocardial contractility that occurred during inhalation anesthesia with halothane and isoflurane.

III. Rectal Methohexitone

Induction of anesthesia using rectal methohexitone is a safe, pleasant technique to produce anesthesia in young children up to five years of age because it avoids the problems encountered when pediatric patients are faced with separation from their parents, venipuncture, or an inhalation induction of anesthesia just prior to surgery.

Although several doses and concentrations of the drug have been used, most anesthesia textbooks recommend a single dose for all children, that is 25 mg·kg^{-1} of a ten percent methohexital solution. However, with this dose, up to 15% of patients will not fall asleep and this unpredictability probably occurs because of variation in the absorption and systemic availability of the methohexitone.

Although the rectal administration of methohexitone appears to be a safe and effective technique for the induction of anesthesia in children, the bioavailability of the drug is low and therefore relatively large doses of methohexitone must be used to insure that a prompt and

reliable onset of sleep is achieved.[14,15] The hemodynamic response to the intravenous administration of short-acting barbiturates, at least in adults, is complex and usually includes a decrease in mean arterial pressure and cardiac output and increase in heart rate. Both direct myocardial depression and alterations in vascular tone may contribute to the hypotension that is seen. Therefore, the purpose of the next study was to evaluate the hemodynamic changes produced by the induction of anesthesia using rectal methohexitone in children.

A. Hemodynamic Effects of Rectal Methohexitone

Twelve children were studied with two-dimensional and pulsed Doppler echocardiography before and immediately after induction of anesthesia with a two percent solution of rectal methohexitone (25 $mg \cdot kg^{-1}$).[16]

Following the rectal administration of methohexitone, the heart rate increased significantly above awake values (Table 5). Systolic, diastolic and mean blood pressures were unchanged. Cardiac index, left ventricular end-diastolic volume, stroke volume and ejection fractions also did not change significantly from the pre-induction values. No apnea or arterial desaturation occurred following the onset of sleep.

In studies of adults the hemodynamic changes that occurred following intravenously administered barbiturates were affected by both the depth of anesthesia achieved[17] and by the rate of drug administration.[18] Deeper levels of anesthesia and rapid bolus administration of the drug produced more profound hemodynamic effects. Following administration of rectal methohexitone the onset of sleep usually occurs within 15 minutes, co-incident with peak plasma methohexitone concentrations. Although rectal and intravenous administration of methohexitone produce similar peak plasma levels, the relatively slower rise in plasma concentration that follows rectal administration may lessen the hemodynamic effect that are seen. Also, although methohexitone inhibits sympathetic nervous activity, the barostatic reflexes remain active and this too may contribute to the cardiovascular stability seen following rectal methohexitone.

Table 5 Cardiovascular data before and following rectal methohexitone (mean±SEM)

	Pre-induction	Post-induction
Heart rate (beats·min^{-1})	113±6.6	126±4.5*
Mean blood pressure (mmHg)	73±2.4	68±2.0
Cardiac index ($l \cdot min^{-1} \cdot m^{-2}$)	2.86±0.2	3.07±0.18
Left ventricular end-diastolic volume (m*l*)	24.4 ±3.2	24.9 ±3.4
Stroke volume (m*l*)	13.3 ±1.7	13.9 ±1.4
Ejection fraction	0.56	0.57

* $p<0.05$. Pre-induction vs post-induction.

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Baroreceptor stimulation, secondary to vasodilation, has been suggested as a cause of the tachycardia seen following methohexitone, but no change in blood pressure occurred in this study suggesting that methohexitone may have a direct chronotropic effect on the heart. An increase in heart rate may also occur if airway obstruction or respiratory depression resulted in changes in oxygenation or ventilation. Oxygenation by pulse oximetry and ventilation by clinical evaluation appeared to be adequate in these children; however, if $PaCO_2$ did increase, the associated sympathetic stimulation could also have contributed to the increase in heart rate that was observed. From this study it was concluded that rectal administration of methohexitone for induction of anesthesia in healthy pediatric patients has minimal hemodynamic effect.

IV. Conclusion

Providing anesthesia for pediatric patients can

be a time of great stress for everyone involved and much of pediatric anesthetic practice is based upon relatively sparse information, often appropriated from studies originally done in adults. Consequently there is a continuing need to focus research interest upon this very dynamic period of patient care. These studies of the cardiovascular effects of inhalation anesthetic agents in children, have demonstrated that the depression in cardiovascular function produced by both halothane and isoflurane is quantitatively similar; but when a fluid challenge is given a difference does become apparent. In patients who received halothane, administration of a fluid bolus produced a further impairment of cardiac function. In those children receiving isoflurane a fluid bolus increased the stroke volume and the ejection fraction, although there was no change in blood pressure. Also, it was found that combining nitrous oxide with halothane or isoflurane produced the same degree of myocardial depression that occurred during the use of equianesthetic concentrations of halothane or isoflurane alone. This suggests that the cardiovascular effects of nitrous oxide in children may be more profound than the effects seen in adults. These studies also confirm that, although atropine can increase the heart rate during halothane or isoflurane anesthesia, it does not diminish the myocardial depression produced by these two anesthetic agents. Finally it was demonstrated that the induction of anesthesia in children with rectal methohexitone had minimal cardiovascular effect.

Many differences exist in the cardiovascular function of infants or young children when they are compared to adults. Therefore, studies done in adults that evaluate their hemodynamic response to anesthetic agents may not be applicable to pediatric patients. The purpose of these studies has been to use non-invasive techniques to more accurately evaluate the effects of anesthetic agents in young children. By improving our understanding of the effects of these potent anesthetic agents on this fragile group of patients, perhaps the quality of the anesthetic care they receive can be improved.

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