

Epinephrine-Halothane Interactions in Children

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Cutaneous infiltration of dilute solutions of epinephrine for hemostasis during halothane anesthesia can result in ventricular dysrhythmias. Our clinical experience, published reports, and a study comparing piglets with adult swine suggest that children may be less susceptible than adults to dysrhythmias under these conditions. We therefore undertook a prospective survey of heart rate and rhythm in halothane-anesthetized children who received subcutaneous epinephrine for hemostasis. Mass spectrometry was used to quantify end-tidal halothane and to avoid hypercarbia. In 83 children anesthetized with halothane, we continuously recorded ECG, heart rate (HR), end-tidal halothane (ET_{Halo}), and carbon dioxide (ET_{CO_2}). The surgeons injected 0.4–15.7 $\mu\text{g}/\text{kg}$ of epinephrine (in saline or 1% lidocaine) to provide hemostasis at a variety of sites. No child developed a ventricular dysrhythmia. One child had self-limited premature atrial contractions (PAC). Sixty-three children had some increase in heart rate after epinephrine injection, while seven increased their HR 15% or more above pre-injection levels. No relation between any increase in HR and epinephrine dosage, ET_{Halo} , ET_{CO_2} , physical status, or age was found by multiple linear regression; however, HR was increased significantly in patients receiving epinephrine in head and neck sites other than the palate. The authors conclude that children tolerate higher doses of subcutaneous epinephrine than adults during halothane anesthesia. The arrhythmogenic dose of epinephrine in children receiving halothane has yet to be determined, but at least 10 $\mu\text{g}/\text{kg}$ of epinephrine infiltration may be used safely in normocarbic and hypocarbic pediatric patients without congenital heart disease. The presence of PAC and tachycardia emphasize the need for continuous ECG monitoring and caution during halothane anesthesia with epinephrine injection. (Key words: Anesthesia: pediatric. Anesthetics, volatile: halothane. Heart: arrhythmias. Sympathetic nervous system: catecholamines, epinephrine.)

TWENTY YEARS AGO, Katz *et al.* reported that cutaneous infiltration of dilute solutions of epinephrine for surgical hemostasis during halothane anesthesia can result in ventricular dysrhythmias.¹ Subsequent studies have shown that adult patients and animals often have such problems,^{2,3} whereas children and young animals appear less susceptible.⁴⁻⁶

Many factors other than age may influence the incidence of epinephrine-associated dysrhythmias during halothane anesthesia. These include the perfusion of

the site injected,¹ the speed of injection,¹ presence of hypercarbia,¹ presence of lidocaine in the injectate,^{1,2} other concomitant anesthetic drugs,^{3,7-9} as well as heart rate,^{10,11} blood pressure,¹¹ electrolyte imbalance,¹² fasting,¹³ verapamil,¹⁴ and prostaglandins.¹⁵ Subjectively, the senior authors were impressed that they rarely observed such dysrhythmias in children. We then retrospectively reviewed the anesthetic records of 28 children undergoing craniofacial surgery at The Children's Hospital of Philadelphia during 1979 and found no description of any dysrhythmias during halothane anesthesia with epinephrine doses up to 8.8 $\mu\text{g}/\text{kg}$.

The absence of this classical problem in our practice was gratifying, but surprising. To confirm this observation and possibly discover the reason for our low incidence, we undertook a prospective survey of heart rate and rhythm in halothane-anesthetized children who received subcutaneous epinephrine for hemostasis. Mass spectrometry was used to quantify end-tidal halothane and to avoid hypercarbia.

Materials and Methods

After obtaining approval from the Hospital's Committee for the Protection of Human Subjects, we studied 83 children, 3 months to 17 years old, scheduled for elective procedures in which epinephrine is commonly used for hemostasis. Twenty-two patients were less than 1 year old; 25 were 1 to 5 years; 19 were 6 to 10 years; and 17 were over 10 years. Their weights ranged from 5 to 68 kg. The majority were classified ASA Physical Status I(63) and II(13), but seven were judged to be Physical Status III, usually because of severe mental retardation and chronic seizure disorders. Children with congenital heart disease or those receiving hypotensive anesthesia were excluded.

Sixty-seven of the children were premedicated as follows: patients 0–6 months of age received 0.02 mg/kg atropine; those between 6 and 12 months received 4 mg/kg pentobarbital as well as the atropine; and for children over 12 months, 0.1 mg/kg morphine was added to the atropine and pentobarbital. Four older patients received atropine only, two received 0.01 mg/kg glycopyrrolate, and six patients were premedicated but received no anticholinergic. Four children were not premedicated.

Seventy-four patients then underwent inhalation induction with 70% nitrous oxide (N_2O), 30% oxygen (O_2), and halothane delivered through a Mapleson D circuit; nine children received intravenous thiopental

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for induction. Routine measurements of precordial heart tones, ECG (the limb lead which showed the clearest P wave and QRS complex), rectal temperature, and systemic arterial pressure (doppler method) were made. Pancuronium, 0.1 mg/kg, was added to N₂O, O₂, and halothane during maintenance of anesthesia. End-tidal N₂O, halothane, O₂, and CO₂ were sampled immediately proximal to the endotracheal tube with a coaxial airway adapter, and analyzed with a mass spectrometer (Chemtron Medspec II). Ventilation was controlled manually. The anesthetist was allowed to determine the clinically indicated inspired halothane concentration and to adjust ventilation to keep ET_{CO₂} below 5.6% (40 mmHg). ECG, heart rate, and end-tidal concentrations of CO₂ and halothane were recorded continuously on a strip chart recorder.

The surgeon injected a volume and concentration of epinephrine in saline or 1% lidocaine sufficient to provide hemostasis. The most commonly used epinephrine preparation was 10 µg/ml (1:100,000) epinephrine in 1% lidocaine (72 patients). Eleven patients received 1–10 µg/ml epinephrine in saline. Injection sites included the palate, lips, external nares, ears, back, scalp, and several other peripheral regions; all injections were completed within eight minutes. We limited the dose to 10 µg/kg in the first 57 patients, and then, with the concurrence of the Committee for the Protection of Human Subjects, we removed the dose limit.

Correlations between changes in HR and many other variables were made using multiple linear regression or chi-square analysis as appropriate; *P* < 0.05 was considered statistically significant.

Results

No patient developed premature ventricular contractions (PVC) or other ventricular dysrhythmia despite the large number of children (73) receiving doses of epinephrine exceeding the recommended adult dosage (1.7 µg/kg).¹

One patient developed premature atrial contractions (PAC) following injection. This 15-year-old, 50-kg healthy girl, received a nasal submucosal injection of 10 µg/ml (1:100,000) epinephrine in 1% lidocaine. Immediately prior to injection, HR was 140 beats per minute, ET_{CO₂} was 4% (29 mmHg), and ET_{Halothane} was 0.6%. Within 3 minutes of injection of 3 µg/kg epinephrine, HR reached 175 beats per minute and supraventricular ectopic beats with aberrant conduction occurred. No further epinephrine was injected, and the dysrhythmia resolved spontaneously over the next minute.

All but five children had higher heart rates immediately prior to the injection of epinephrine than those

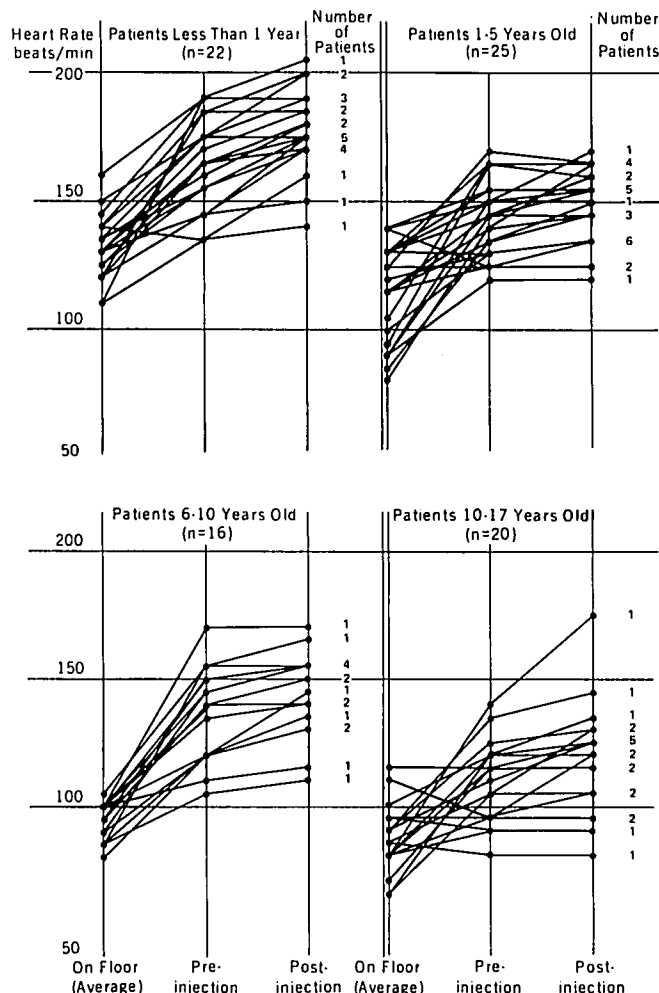


FIG. 1. Individual heart rate data at three different times. Patients are separated into four groups according to age. HR values include: 1) the average of the values recorded by floor nurses prior to administration of pre-anesthetic medication, 2) the average value recorded during the minute prior to injection of epinephrine, and 3) the highest value recorded during the 10-min post-injection period.

recorded before anesthesia induction (fig. 1). Within ten minutes post-injection, sixty-three children had some increase in heart rate, while seven increased HR 15% or more above the pre-injection level. Maximum HR was reached 2 to 7 minutes after the beginning of injection. Of these seven tachycardic patients, two received 2.5 and 15.7 µg/kg epinephrine in saline, and five received 0.8–11.3 µg/kg epinephrine in 1% lidocaine. Techniques of blood pressure measurement varied too much to permit inclusion of this variable.

Figure 2 illustrates the distribution of ET_{Halothane} and total dosage of epinephrine injected in the 83 children studied. The dosage of epinephrine ranged from 0.4 to 15.7 µg/kg with a mean value of 5.4 and standard de-

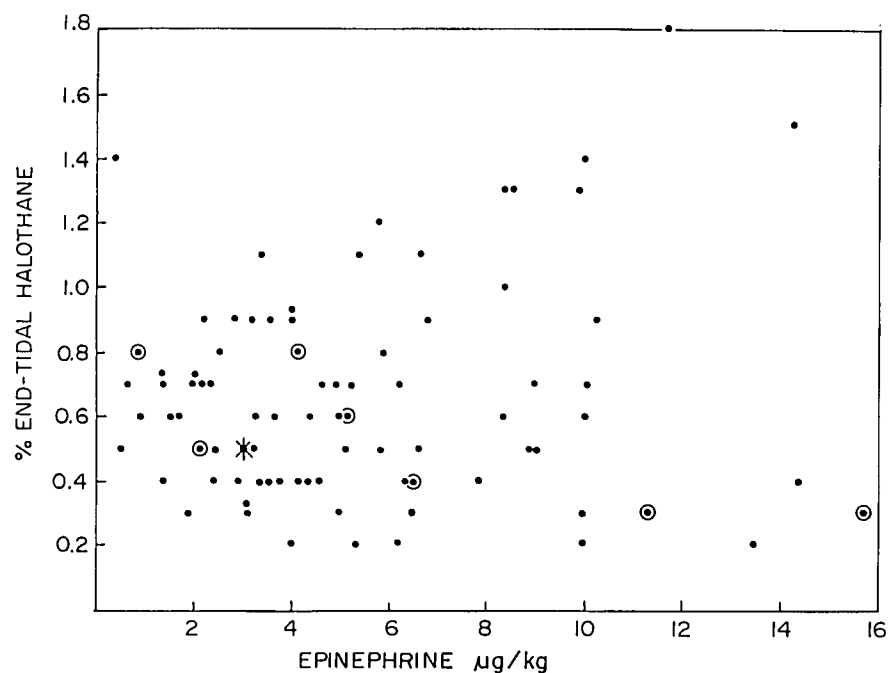


FIG. 2. Clinically significant tachycardia was unrelated to either ET_{halo} or total dose of epinephrine. ● = represents an individual patient whose post-injection HR was unchanged or increased less than 15% above pre-injection level; ○ = represents a patient whose post-injection HR was 15% or more above the pre-injection level; and * = identifies the patient who developed PAC.

viation of 3.5. ET_{halo} concentrations ranged from 0.2 to 1.8% with a mean value of 0.66 and standard deviation of 0.33. ET_{CO_2} values ranged from 2.8 to 5.6% with a mean value of 4.3 and standard deviation of 0.72. No significant relation between any increase in HR and epinephrine dosage, ET_{halo} , ET_{CO_2} , physical status, or age could be found by stepwise multiple linear regression^{16,17}; however, increased HR was significantly higher ($P < 0.05$) in those patients who received epinephrine in head and neck sites other than the palate. Chi-square analysis of a 2×2 contingency table¹⁸ failed to demonstrate that the presence of nonstandard pre-anesthetic medication, thiopental induction, or lidocaine in the injectate influenced the incidence of clinically significant tachycardia (an increase in HR 15% or more above pre-injection level).

Discussion

With maintenance halothane levels and hyperventilation, large subcutaneous and submucosal doses of epinephrine were given safely to children without the development of ventricular dysrhythmias. Our findings and those of Wallbank⁵ differ considerably from those of Johnston *et al.*² who observed ventricular irritability in eight of 15 adult patients undergoing transphenoidal pituitary surgery with halothane-oxygen anesthesia. These patients received 2.0 to 4.1 $\mu\text{g}/\text{kg}$ of epinephrine in saline or 0.5% lidocaine. The dose producing 3 PVC at any time during or immediately following epinephrine injection in 50% of patients (ED_{50}) was lower in

patients given epinephrine in saline (2.11 $\mu\text{g}/\text{kg}$) than the ED_{50} for those receiving epinephrine in 0.5% lidocaine (3.69 $\mu\text{g}/\text{kg}$). If children in our study had an 8/15 chance of developing PVC with halothane and epinephrine as in the report of Johnston *et al.*,² the chances of 83 consecutive patients having no PVC can be calculated as a Benoulli trial¹⁹ and is vanishingly small ($<10^{-28}$). Obviously, our incidence is much lower.

Puerto *et al.* and Atlee and Malkinson⁷ demonstrated a lower threshold for atrial than for ventricular dysrhythmias in adult dogs receiving halothane and epinephrine infusion. Perhaps more frequent atrial and even ventricular dysrhythmias will occur if higher epinephrine doses than we used are injected in children undergoing halothane anesthesia. Wallbank⁵ noted tachycardia in the majority of his patients as well, and took this as "evidence of rapid systemic absorption." The nearly universal occurrence of some tachycardia in our patients confirms this, though there is no quantitative relationship between the dose of epinephrine administered and the change in heart rate.

While our results confirm the clinical impression that children are less susceptible than adults to dysrhythmias when epinephrine is infiltrated during halothane anesthesia, the reasons for this difference remain unclear. Further laboratory and clinical studies are needed to determine whether the absence of significant atherosclerotic cardiovascular disease in pediatric patients, or perhaps their higher heart rates, or the presence of hypocarbia are factors in protecting children from dysrhythmias caused by the halothane-epinephrine com-

ination. Using this anesthetic regimen, at least 10 $\mu\text{g}/\text{kg}$ of epinephrine may be safely used to achieve hemostasis by infiltration in pediatric patients without congenital heart disease.

In conclusion, a wide range of end-tidal halothane concentrations and doses of epinephrine by infiltration as employed in a variety of operative procedures has been shown to be free of dysrhythmias in normocarbic and hypocarbic pediatric patients. The arrhythmogenic dose of subcutaneous or submucosal epinephrine during halothane anesthesia in children remains to be determined. The occasional presence of premature atrial contractions and tachycardia emphasizes the need for continuous ECG monitoring and caution during halothane anesthesia with epinephrine injection.

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