Pitfalls and Problems in Pediatric Anesthesia

Linda J. Mason, M.D. Redlands, California

OBJECTIVES

1. Learn which pediatric patients are at the highest risk for morbidity and mortality during anesthesia.
2. Learn prevention and management of complications that can occur while under anesthesia, e.g. cardiac arrest, laryngospasm, and aspiration.
3. Learn current standards for cardiopulmonary resuscitation in pediatric patients.

CASE PRESENTATION

ANESTHESIA-RELATED CARDIAC ARREST IN THE PEDIATRIC PATIENT

The etiology of cardiac arrest in the pediatric patient has changed over the past 20 years as practice has evolved in the care of these patients. The Pediatric Closed Claims Study in 1993 showed respiratory events were the most common category accounting for 43% of claims with inadequate ventilation seen in half of the respiratory events. The typical profile in this category of inadequate ventilation were healthy, non-obese children breathing halothane spontaneously whose arrest was preceded by hypotension or bradycardia. These children were difficult to resuscitate successfully, 70% died and 30% had permanent central nervous system impairment. Pulse oximetry was used in 7% of the Closed Claim cases and capnometry in 5%.[1] Recently the Pediatric Perioperative Cardiac Arrest (POCA) Registry has provided some new data. Out of 1,089,200 anesthetics, there were 150 cardiac arrests which were deemed anesthesia related (1.4/10,000).[2] Several points are relevant in analysis of this data. First, an increased incidence of cardiovascular causes (32%) have differed from the Pediatric Closed Claims Study in 1993 where only 13% were from cardiovascular causes. This may have some basis in the fact that using chest compression was necessary as entry criteria for the POCA Registry or the fact that the use of pulse oximetry in 98% and capnography in 86% of cases may be more effective in preventing respiratory than cardiovascular incidents before arrests occur. Most of the cardiac arrests (82%) occurred during induction or maintenance of anesthesia. Bradycardia (54%), hypotension (49%), abnormality of SpO_2 (46%) or inability to measure blood pressure (25%) were the most common antecedent events. Twenty-one percent of arrests occurred during emergency surgery.

Second, infants are at increased risk. Infants <1-year accounted for 55% of the anesthesia related cardiac arrests. Several pediatric studies have confirmed that infants <1-year have the highest anesthetic risk[3,4] and that mortality is inversely proportional to age with the highest risk in the <1 month of age group.[5] This may be notably related to a higher ASA Physical Status (PS) Classification with underlying patient disease (particularly congenital heart disease) but also to cardiovascular depression by inhalational agents. In infants <30 days of age the MAC of halothane is .87%[6], as compared with children 1-6 months of age - MAC of 1.08.[7] With isoflurane, the MAC for preterm infants (<32 weeks) is 1.28, 32-37 weeks is 1.41[8], and for term (0-1 month) 1.60, with 1-6 months being 1.87. Only sevoflurane appears to be different with the MAC being constant at 3.2-3.3% for neonates and infants less than one month, decreasing to 3% at 1-6 months, and 2.5-2.8% for 7 months - 12 years.[9]
Recent studies show sevoflurane may be less of a myocardial depressant and have less potential for producing bradycardia than halothane in infants.[10,11] Sevoflurane may also be safer for use in children with congenital heart disease. In comparison with children receiving halothane, the halothane treated patients experienced twice as many episodes of severe hypotension as those who received sevoflurane. Recurrences of hypotension occurred despite increased vasopressor use in the halothane as compared to the sevoflurane treated patients. Risk of hypotension was increased in children less than one year of age compared with older children and patients with preoperative cyanosis had a higher incidence of developing severe desaturation with halothane. Thus sevoflurane may have hemodynamic advantages over halothane in infants and children with congenital heart disease.[12] Another area of concern in relation to inhalational agents is if a patient is intubated without muscle relaxants twice the dose of inhalational agent is needed in 95% of children, which will cause myocardial depression.[13]

Third, 33% of all anesthesia related cardiac arrests occurred in previously healthy ASA PS 1 and 2 patients - mostly medication-related errors (64%). Fifty percent of the arrests caused by halothane cardiovascular depression were seen at inspired concentrations of 2% or less with the median age being 6 months. Controlled ventilation may accelerate the rise in halothane concentration compounded by prolonged exposure due to difficult intravenous access. Four cases of arrest occurred following probable intravascular injection of local anesthetics. These occurred during combined halothane and caudal anesthesia with injection of 0.25% bupivacaine with 1/200,000 epinephrine despite negative test dose and aspiration. They occurred when both needles and catheters were used to deliver the medication. All had ventricular arrhythmias but were successfully resuscitated without injury.

Mortality rate in ASA PS 3-5 patients was 37% compared to 4% in ASA PS 1-2 patients. ASA PS 3-5 was the strongest predictor of mortality followed by emergency status. Overall mortality rate in all arrests was 26%.[2]

CLASSIFICATIONS OF CARDIAC ARRESTS

Cardiac Disease

Although most patients who present with a previously undiagnosed heart murmur do not have significant pathology, some do have anatomic disease. Lesions that are implicated with problems during anesthesia are those that include the diagnosis of pulmonary hypertension, hypoplastic arteries and ventricles and left to right shunts. Murmurs should be characterized prior to surgery - especially in infants. A history of easy fatigability or poor feeding with failure to thrive should alert the anesthesiologist that this may be a pathologic murmur. A call should be placed to the pediatrician to see if the murmur has been characterized - if not, a pediatric cardiology consult possibly with ECHO may be necessary prior to surgery.

Sudden death does occur in pediatric patients and unfortunately can occur during a surgical procedure. In children less than 1 year of age the most common cause is ductus dependent, complex cyanotic congenital heart disease followed by myocarditis and prolonged QT syndrome. From the first year through the third decade the most common cardiac causes are myocarditis, hypertrophic cardiomyopathy, coronary artery disease and congenital anomalies, aortic dissection and conduction system abnormalities. In older children, prodromal symptoms are seen in 50% of patients with the most common symptoms being syncope or chest pain. ECG abnormalities along with symptoms during high risk behavior (strenuous exercise) such as palpitations or chest pain, need prompt cardiac evaluation, especially if this information is discovered in a preoperative interview.[14]

Difficult Airway

Loss of airway in the pediatric patient has been a common cause of acute deterioration and cardiac arrest. In the patient with a difficult airway, mask ventilation or intubation may be impossible. It is important to maintain spontaneous ventilation with an inhalational agent such as sevoflurane in these patients. A variety of airway equipment is necessary to deal with these situations. This may include various size masks, airways, LMAs, Bullard laryngoscope and pediatric fiberoptic bronchoscopes. Also obstructed tubes, esophageal intubation, or dislodged tubes may precede an arrest. In small children sounds of air passage may be transmitted from the esophagus and are misinterpreted as being from the airway. Obstruction or kinking of the tube may cause progressive hypoxemia or hypercarbia - making resuscitation more difficult.

Intravascular Volume

Intravascular fluid loss and current volume status are often underestimated in the pediatric patient especially in newborns. Lack of good vascular access can compound these problems. Assessment of intravascular volume depends more on clinical signs than invasive measures that are used in the adult. By the time the pediatric patient becomes hypotensive they are severely behind in fluid and can be close to an arrest situation.

Inhalational Agents

Anesthetic agent overdose, particularly halothane, in the face of decreased intravascular volume, is one of the most common causes of sudden hypotension, especially in infants. Bradycardia (less than 100 beats per minute) is an ominous sign. In a study of causes of bradycardia in infants < 1 year of age, 1/3 was due to inhalational agent, 1/3 due to hypoxemia and 1/3 due to patient disease or surgical factors.[15] Inhalational agent overdose responded to a discontinuation of the inhalational agent and atropine in most cases but some needed epinephrine and chest compression. Continuous auscultation of heart sounds is a clinically useful tool for the hemodynamic monitoring of anesthetized infants and children. In a recent study during induction of anesthesia with halothane a dramatic dose dependent decrease in amplitude of S_1 and S_2 heart sounds occurred in all 19 patients ages 6 mo - 12 years. Monitoring was accomplished by a precordial stethoscope. These changes were clearly audible, occurred rapidly and were followed by corresponding decreases in heart rate and blood pressure.[16] Thus heart sound changes may be an early warning sign of decreased cardiac function and impending disaster. As far as dysrhythmias, when halothane anesthesia was administered via "nasal masks" for dental surgery a strong association between halothane and ventricular arrhythmias particularly ventricular tachycardia was seen, but all episodes resolved spontaneously. No dysrhythmias were seen with sevoflurane. Unfortunately end tidal CO_2 level was not reported in this study.[17]

Succinylcholine Induced Arrest

In infants who have not been given atropine, especially in the presence of hypoxemia, the potential for bradycardia is significant with succinylcholine. Administration of succinylcholine to a patient with unrecognized myopathy can result in massive potassium release and sudden arrest. This is not malignant hyperthermia (MH) which has a slower onset. Also rhabdomyolysis is likely to have bradycardia or arrest as its presenting sign in contrast to tachycardia, tachypnea, PVC's, hypertension and hyperthermia that are common with MH.

Topical Vasoconstrictor Induced Cardiac Arrest

Application of mucosal topical vasoconstrictors such as phenylephrine have lead to arrests in pediatric patients during general anesthesia. The scenario is the onset of severe hypertension without baroreceptor induced bradycardia because of pretreatment with atropine or glycopyrrolate. In response to these hemodynamic changes, beta blocking agents are sometimes administered. This has lead to pulmonary edema, cardiac arrest and death. It has occurred with both esmolol and labetalol, however only labetalol has been associated with death possibly due to esmolols briefer duration of action. Isoproterenol, epinephrine, and

dopamine did not consistently reverse this myocardial dysfunction but glucagon (which has been effective in reversing the cardiovascular effects of beta blockers) may be beneficial. The dose is 5-10 mg in adult, 1 mg in children (infusion of 1-5 mg/hr). Current recommendations for topical phenylephrine use are limiting the dose to 20 ug/kg in children up to 25 kg and if hypertension ensues waiting 10-15 minutes before antihypertensive meds are given, then using direct vasodilators or alpha receptor antagonists for treatment. Administration of beta blockers, calcium channel blockers and increasing inhalational agents should be avoided while glucagon should be considered to counteract the beta blocker effect if these drugs have been administered. Using a topical vasoconstrictor such as oxymetazoline 0.025-0.05% may be safer than phenylephrine 0.25-1%.[18]

Intravascular Local Anesthetic Injection

In the POCA Registry data intravascular injection of local anesthetic during caudal anesthesia occurred despite negative aspiration and lack of response to a test dose. Incremental rather than bolus injection has been advised for earlier detection of an intravascular injection.[19] Also use of agents with less myocardial toxicity such as ropivacaine or levobupivacaine may be safer.

Allergic Reactions

Allergic reactions may occur in pediatric patients in relationship to drug administration (eg. antibiotics, muscle relaxants) or on repeated exposure to latex. Clinical signs of anaphylaxis include increased vascular permeability (urticaria and laryngeal edema), contraction of smooth muscle, (bronchospasm) vasodilatation (flushing and hypotension), stimulation of sensory nerve endings (pruritus) and cardiac histamine receptor stimulation (tachycardia and arrhythmia). Muscle relaxant allergies have been shown to be responsible for more than 80% of cases of anaphylactic shock during anesthesia[20], but is a less frequent cause in children than adults.[21] Most recently an anaphylactic reaction to cisatracurium has been reported in a child.[22]

Latex allergy has been implicated in 17% of episodes of intraoperative anaphylaxis and is the most frequent etiology noted in children.[21] Although it has been associated in patients with neural tube defects it has also been reported in patients with multiple surgeries[23] and even in children on prolonged mechanical home ventilation.[24] Total avoidance of latex products is essential in these patients. Latex allergy may present up to 1 1/2 hours into the case. It onsets as sudden bronchospasm followed by profound hypotension seemingly unrelated to any other events. Although a delay in onset may be seen once the signs become evident progression to hypotension and arrest may take only a short time.[25] Treatment of suspected intraoperative anaphylaxis should include 100% O_2, discontinuance of anesthetics, blood, antibiotic and muscle relaxant infusions and withdrawal of exposure to latex. Epinephrine should be administered as well as volume resuscitation, H_1 and H_2 blockers and steroids. Albuterol inhaler can be very effective in treating bronchospasm, with sodium bicarbonate being used for persistent acidosis and hypotension. Blood samples should be sent for allergy investigation including IgE antibodies to latex (if suspected), tryptase and histamine levels.

Investigation and Management of Intraoperative Cardiac Arrest

1. Pulse oximetry is an early warning sign of developing hypoxemia or decreased perfusion and precedes clinical signs in anesthetized children.[26] If your pulse oximeter stops working and your noninvasive BP monitor keeps reading something is wrong. Don't ignore the monitors.
2. An absent or poor capnograph tracing is indicative of loss of cardiac output or impaired ventilation. It may be the earliest warning of events with the greatest likelihood for significant morbidity, even prior to the onset of desaturation.[27] The amount of expired CO_2 can correlate well with cardiac output during cardiopulmonary resuscitation.[28] and may also have some prognosticative ability. If the end-tidal CO_2 level is 10 mmHg or less measured 20 minutes after initial resuscitative efforts, death can be predicted with 100% sensitivity and specificity.[29]
3. A stethoscope monitor is invaluable. Changes in intensity of heart sounds may alert you to problems before bradycardia and hypotension become apparent.
4. The airway must be rechecked when the cause of sudden deterioration is unclear. If the patient is not intubated, intubate immediately - if this is not possible (due to a difficult airway) use an LMA or bag and mask ventilation. Children in out of hospital arrests whose airway management was randomized to receive bag and mask ventilation until they reached the hospital had outcomes that were statistically identical to those that were intubated in the field.[30] Look for common problems first - airway, volume status, inhalational agent overdose etc. Discontinue anesthetic agents and administer 100% O_2.
5. Start CPR early - to be effective in maintaining adequate circulation a peripheral pulse should be discernible.
6. Vascular access that is reliable can make the difference as to the success of the resuscitation. A free flowing peripheral intravenous line may be all that is necessary since studies have shown that onset time and peak levels of resuscitation drugs (epinephrine, calcium, sodium bicarbonate, glucose) are similar whether given centrally or peripherally.[31] It is important that peripheral lines are flushed well with 5-10 ml of saline to ensure entry of the resuscitative drugs into the central circulation.
If no intravenous access is present at the time of the arrest the safest and easiest site to cannulate is the femoral vein, whose measured pressures accurately reflect central venous pressure. If no other access can be obtained a styleted intraosseous needle can be inserted into the anterior tibia, distal femur, medial malleolus or anterior iliac spine. Any resuscitation drug that can be given intravenously can be given into the intraosseous space with similar onset times.[31] Drugs that can be administered via the trachea are described by the pneumonic LEAN; Lidocaine, Epinephrine, Atropine, and Naloxone. Onset and peak levels of epinephrine administered by this route is delayed as compared to the intravenous route.[32,33]
7. Epinephrine is the single most useful drug - don't waste time with repeated atropine doses. Although bradycardia is the most frequent rhythm preceding cardiac arrest in children, atropine alone is frequently not sufficient to produce return of circulation.

Atropine is the drug of choice only for vagally mediated bradycardia, 0.02 mg/kg intravenously with a minimum dose of 0.1 mg. After adequate ventilation and oxygenation have been ensured, epinephrine is the drug of choice. The dose recommended by the American Heart Association is 10 ug/kg administered intravenously every 3-5 minutes or 100 ug/kg intratracheally diluted to 5 ml and followed by five manual ventilations.[32] High dose epinephrine (100-200 ug/kg) may cause post arrest myocardial dysfunction and necrosis but may be useful if the diastolic pressure is less than 20 mmHg. There is inadequate pediatric data for routine use of vasopressin during cardiac arrest!

8. For initial fluid resuscitation current recommendations are to avoid glucose-containing solutions in children unless hypoglycemia is suspected or confirmed. Animal studies have reported that when hyperglycemia is produced prior to a cerebral ischemic event neurologic outcome is worse.[34,35] This may be because increased lactic acid production in the brain aggravates neurologic injury. Normal saline or Ringer's lactate are preferred over colloid solutions since studies have suggested that albumin administration may be associated with increased mortality.[36,37]

9. Obtain a blood gas and electrolytes early - this can be helpful in determining the cause of the arrest.

10. Routine calcium does not improve outcomes but is indicated for hyperkalemia, hypermagnesiumia, calcium channel blocker excess and documented hypocalcemia. It is not indicated for electromechanical dissociation or asystole.[38,39]

11. Magnesium should be used for hypomagnesemia and Torsades de pointes (polymorphic ventricular tachycardia) at a dose of 25-50 mg/kg with a maximum dose of 2 grams.

12. Routine administration of sodium bicarbonate doesn't improve outcomes and should be given only for severe metabolic acidosis, hyperkalemia and hypermagnesemia at a dose of 1 mEq/kg.

13. Obtain a chest x-ray to help rule in or out the cause of the arrest. Tension pneumothorax should be on your differential diagnosis list.

14. Have ready access to a defibrillator. Be sure it is working properly and that pediatric paddles are available. Defibrillation with 2-4 joules/kg is the mainstay of therapy for pulseless ventricular fibrillation (VF) and ventricular tachycardia (VT).

15. Amiodarone can be used for "shock resistant" VF and VT. Amiodarone is a competitive inhibitor of both alpha and beta adrenergic receptors[40] causing both vasodilatation and AV node suppression and is an alternative to lidocaine use an antiarrhythmic agent. It inhibits both the outward potassium current resulting in prolongation of the QT interval[41] and the inward sodium channels thereby slowing ventricular conduction and prolonging the QRS duration.[42] The recommended loading dose is 5 mg/kg over several minutes to 1 hour with repeated doses up to 15 mg/kg. In addition, amiodarone is also recommended for use in functional ectopic tachycardia[43] and ectopic atrial tachycardia.[44] Side effects include hypotension, which is due to the antagonism of adrenergic receptors and calcium channels and may require calcium salts and vasopressors. Other acute side effects include heart block, sinus bradycardia and congestive heart failure.

LARYNGOSPASM

Laryngospasm is a frequent occurrence during the administration of anesthesia to pediatric patients. The incidence is 8.7/1000 patients in a total population and 17.4/1000 in patients ages 0-9 years[45], with the age group 1-3 months having the greatest incidence - more than 3 times the rate in any other age group. Although laryngospasm has been seen as a self limiting complication - 5/1000 laryngospasm patients have a cardiac arrest.[45] Other complications include bronchospasm, hypoxia, gastric aspiration, arrhythmias, pulmonary edema and delayed recovery.[46]

Etiology

Laryngospasm occurs as a response to glottic or subglottic mucosal stimulation and continues long after the stimulus is gone. Risk factors include age, NG tube or oral airway placement, endoscopy or esophagoscopy, upper respiratory infections or volatile anesthetics (induction with isoflurane and desflurane).

Two areas have recently come into focus as relative to the risk of development of laryngospasm. First of 15,183 children in a day surgery unit who had general anesthesia, those who developed laryngospasm were 2.05 times more likely to have an active upper respiratory infection (URI). They were also more likely to be younger and be undergoing airway surgery.[47] Bronchospasm has been shown to be higher in intubated patients with a URI.[48,49] LMA use instead of intubation has shown that laryngospasm was equal in both groups but the incidence of mild bronchospasm was higher in the intubated group. Therefore the LMA may be a suitable alternative if the decision is made to proceed with anesthesia in a child with a URI but will not decrease the risk of laryngospasm.[50]

Secondly, children exposed to environmental tobacco smoke (ETS) were studied. Of those exposed to ETS, 9.4% developed laryngospasm whereas those without domestic ETS exposure, only 0.9% developed laryngospasm. All occurred on emergence from general anesthesia.[51,52]

Management

Laryngospasm may present as complete or incomplete airway obstruction. If incomplete airway obstruction is present sounds should be present - eg. grunts, expiratory squeaks. Complete or incomplete airway obstruction should have initial treatment with jaw thrust and chin lift. The middle finger of each hand should be placed in the "laryngospasm" notch. It is behind the lobule of the pinna of each ear and is bounded anteriorly by the ascending ramus of the mandible adjacent to the condyle, posteriorly by

the mastoid process of the temporal bone and cephalad by the base of the skull. Press firmly inward toward the base of the skull with both fingers at the same time lifting the mandible at the right angle to the plane of the body (jaw thrust or forward displacement of the mandible). This will convert laryngospasm within one or two breaths to laryngeal stridor and then to unobstructed respirations.[53] This should include administration of 100% O_2 with gentle positive pressure. It must be remembered that incomplete airway obstruction may rapidly become complete.

Complete airway obstruction shares many of the signs of incomplete airway obstruction - tracheal tug, retractions of the chest wall and marked abdominal respiration, but there is no sound present. Positive pressure will not "break" laryngospasm in the presence of complete airway obstruction.[54] It may worsen it by forcing supraglottic tissues downward into the glottic opening. High pressure generated by the flush valve may dilute anesthetic gases, and lead to a lighter level of anesthesia. It may also force gas down the esophagus into the stomach making ventilation more difficult. If IV access is present succinylcholine 1.5 mg/kg with atropine 0.02 mg/kg can be given. If no IV access is present IM succinylcholine 4 mg/kg is recommended to be given in the deltoid muscle. Intralingual atropine and succinylcholine can cause ventricular arrhythmias in patients anesthetized with halothane.[55] If laryngospasm is sustained and the child is extremely hypoxic it may be necessary to intubate without muscle relaxants. If these measures have not proved successful in securing the airway cricothyrotomy or emergency tracheostomy may be required.

Prevention

Mucosal stimulation and tracheal suctioning should only be done when the patient is deeply anesthetized. The effect of lidocaine is controversial. Intravenous lidocaine 2 mg/kg given one minute before extubation may attenuate or prevent laryngospasm. However Leicht[56] has suggested that IV lidocaine does not prevent laryngospasm if the patient is extubated after they begin to swallow. To benefit from lidocaine, patients must be extubated before swallowing begins.

ASPIRATION

A previous study reported that the incidence of anesthesia related pulmonary aspiration in a university affiliated pediatric hospital has been shown to be 0.10% (twice that reported in adults).[57] In a new report the pediatric groups at risk have been identified in a retrospective review by Warner.[58] The data included 56,138 infants, children and adolescents younger than 18 years of age who underwent 63,180 general anesthetics. Anesthesia for elective procedures comprised 93.5% of all cases. The overall frequency of perioperative pulmonary aspiration was 1:2,632 anesthetics, 24 patients (0.04%). Emergency procedures were associated with a greater frequency of aspiration than were elective procedures (1:373 vs 1:4,544 anesthetics, $p < 0.001$). There was no significant difference in frequency of pulmonary aspiration across different ages or ASA Physical Status Classification. Seven of the 24 patients were ASA PS 1 & 2 children undergoing elective procedures (1 in 8,000 cases); the same ratio as the adult population. None of these aspirations resulted in serious pulmonary complications.

Fifteen of the 24 children did not develop respiratory symptoms within 2 hours. Five of the other nine needed respiratory support with 3 needing mechanical ventilation greater than 48 hours. None died from the pulmonary aspiration. If patients were asymptomatic within 2 hours of the aspiration they were sent home (if they were ambulatory surgery patients) or to a regular nursing unit. If they were symptomatic and had a pO_2 >90% on room air or supplemental oxygen they were sent to a regular nursing unit. All others were admitted to an intensive care area.

The majority of patients with serious aspiration had a bowel obstruction or ileus especially those <3 years of age. Possibly these children have a decreased effectiveness of the lower esophageal sphincter.[59,60,61] Younger children have more air in the stomach due to swallowed air and higher intraabdominal pressure due to crying or gagging. Also the ability to apply effective cricoid pressure may be more difficult in infants and toddlers especially when gagging occurs. These patients who aspirated, gagged or coughed during induction or airway manipulation in which paralysis with muscle relaxants was not present or insufficient to prevent a gag or cough. Unlike adults in which 1/3 of patients aspirated at the end of anesthesia only 1 in 8 aspirations occurred at this time in children, possibly because children are usually awake with good gag reflexes before extubation.

Gastroesophageal Reflux and Other GI Disorders

Studies have shown that patients with gastroesophageal reflux have normal gastric emptying of liquids but delayed gastric emptying of solids[62] not related to the severity of reflux symptoms. It is true particularly in children >3 years of age that gastric emptying may be delayed if reflux is present.[63] In patients presenting for upper endoscopy after a fast of 6 hours (age <6 months) or 8 hours (age >6 months) from solids and liquids, the gastric residual volume was similar to healthy patients for elective surgery. Thus a 6-8 hour fast from solids and liquids is advised in patients with reflux symptoms.[64]

REFERENCES

1. Morray JP, Geiduschek JM, Caplan RA, et al. A comparison of pediatric and adult anesthesia closed malpractice claims. Anesthesiology 1993;78:461-467.
2. Morray JP, Geiduschek JM, Ramamoorthyt C, et al. Anesthesia-related cardiac arrest in children: Initial findings of the pediatric perioperative cardiac arrest (POCA) registry. Anesthesiology 2000;93:6-14.

3. Olsson GL, Hallen B. Cardiac arrest during anesthesia. A computerized study in 250,543 anaesthetics. Acta Anaesthesiol Scand 1988;32:653-64.
4. Tiret L, Nivoche Y, Hatton F, et al. Complications related to anaesthesia in infants and children. Brit J Anaesth 1988;61:263-269.
5. Cohen MM, Cameron CB, Duncan PG. Pediatric anesthesia morbidity and mortality in the perioperative period. Anes Analg 1990;70:160-167.
6. Lerman J, Robinson S, Willis MM, Gregory GA. Anesthetic requirements for halothane in young children 0-1 months and 1-6 months of age. Anesthesiology 1983;59:421-424.
7. Gregory GA, Eger EI, Munson ES. The relationship between age and halothane concentrations in man. Anesthesiology 1969;30:488-491.
8. Le Dez KM, Lerman J. The minimum of alveolar concentration (MAC) of isoflurane in preterm neonates. Anesthesiology 1987;67:301-307.
9. Lerman J, Sikich N, Kleinman S, Yentis S. The pharmacology of sevoflurane in infants and children. Anesthesiology 1994;80:814-824.
10. Holzman RS, van derVelde ME, Kaus SJ, et al. Sevoflurane depresses myocardial contracility less than halothane during induction of anesthesia in children. Anesthesiology 1996;85:1260-1267.
11. Wodey E, Pladys P, Copin C, et al. Comparative hemodynamic depression of sevoflurane versus halothane in infants: An echocardiogrpahic study. Anesthesiology 1997;87:795-800.
12. Russell IA, Hance WCM, Gregory G, et al. The safety and efficacy of sevoflurane anesthesia in infants and children with congenital heart disease. Anes Analg 2001;92:1152-1158.
13. Watcha MF, Forestner JE, Connor MT, et al. Minimum alveolar concentration of halothane for tracheal intubation in children. Anesthesiology 1988;69:412-416.
14. Liberthson RR. Sudden death from cardiac causes in children and young adults. N Engl J Med 1996;334:1039-1044.
15. Keenan RL, Shapiro JH, Kane FR, Simpson PM. Bradycardia during anesthesia in infants. Anesthesiology 1994;80:976-982.
16. Manecke GR, Nemirov MA, Bicker AA, et al. The effect of halothane on the amplitude and frequency characteristics of heart sounds in children. Anesth Analg 1999;88:263-267.
17. Blayney MR, Malins AF, Cooper GM. Cardiac arrhythmias in children during outpatient general anaesthesia for dentistry: a prospective randomised trial. Lancet 1999;354:1864-1866.
18. Groudine SB, Hollinger I, Jones J, DeBouno BA. New York State guidelines on the topical use of phenylephrine in the operating room. The Phenylephrine Advisory Committee. Anesthesiology 2000;92:859-864.
19. Ved SA, Pinosky M, Nicodemus H. Ventricular tachycardia and brief cardiovascular collapse in two infants after caudal anesthesia using a bupivacaine-epinephrine solution. Anesthesiology 1993;79:1121-1123.
20. Laxenaire MC. Epidemiology of anesthetic anaphylactoid reactions. Fourth multicenter survey. Ann Fr Anesth Reanim 1999;18:796-809.
21. Laxenaire MC. Substances responsible for peranesthetic anaphylactic shock. A third French multicenter study. Ann Fr Anesth Reanim 1996;15:1211-18.
22. Legros CB, Orliaguet GA, Mayer MN, et al. Severe anaphylactic reaction to cisatracurium in a child. Anesth Analg 2001;92:648-649.
23. Porri F, Pradal M, Lemiere C, et al. Association between latex sensitization and repeated latex exposure in children. Anesthesiology 1997;86:599-602.
24. Nakamura CT, Ferdman RM, Keens TG, et al. Latex allergy in children on home mechanical ventilation. Chest 2000;118:1000-1003.
25. Holzman RS. Latex allergy: An emerging OR problem. Anesth Analg 1993;76:635-641.
26. Cote CJ, Goldstein EA, Cote MA, et al. A single-blind study of pulse oximetry in children. Anesthesiology 1988;68:184-188.
27. Cote CJ, Rolf N, Liu LM, et al. A single-blind study of combined pulse oximetry and capnography in children. Anesthesiology 1991;74:980-987.
28. Weil MH, Bisera J, Trevino RP, Rackow EC. Cardiac output and end-tidal carbon dioxide. Crit Care Med 1985;13:907-909.
29. Levine RL, Wayne MA, Miller CC. End-tidal carbon dioxide and outcome of out-of-hospital cardiac arrest. N Engl J Med 1997;337:301-306.
30. Gausche M, Lewis RJ, Stratton SJ, et al. Effect of out-of-hospital pediatric endotracheal intubation on survival and neurological outcome: a controlled clinical trial. JAMA 2000;283:783-790.
31. Orlowski JP, Porembka DT, Gallagher JM, et al. Comparison study of intraosseous, central intravenous, and peripheral intravenous infusions of emergency drugs. Am J Dis Child 1990;144:112-117
32. American Heart Association: Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Circulation 2000;102:I1-I384.
33. Quinton DN, O′Byrne G, Aitkenhead AR. Comparison of endotracheal and peripheral intravenous adrenaline in cardiac arrest. Is the endotracheal route reliable? Lancet 1987;1:828-829.
34. Lanier WL, Stangland KJ, Scheithauer BW, et al. The effects of dextrose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: examination of a model. Anesthesiology 1987;66:39-48.

35. Pulsinelli WA, Waldman S, Rawlinson D, Plum F. Moderate hyperglycemia augments ischemic brain damage: a neuropathologic study in the rat. Neurology 1982;32:1239-1246.
36. Cochrane Injuries Group Albumin Reviewers: Human albumin administration in critically ill patients: Systemic review of randomised controlled trials. BMJ 1998;317:235-240.
37. Schierhout G, Roberts I. Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. BMJ 1998;317:235-240.
38. Stueven HA, Thompson B, Aprahamian C, et al. The effectiveness of calcium chloride in refractory electromechanical dissociation. Ann Emerg Med 1985;14:626-629.
39. Stueven HA, Thompson B, Aprahamian C, et al. Lack of effectiveness of calcium chloride in refractory asystole. Ann Emerg Med 1985;14:630-632.
40. Bauthier J, Broekhuysen J, Charlier R, Richard J. Nature of inhibition by amiodarone of isoproterenol-induced tachycardia in the dog. Arch Int Pharmacodyn Ther 1976;219:45-51.
41. Yabek SM, Kato R, Singh BN. Effects of amiodarone and its metabolite, desethylamiodarone, on the electrophysiologic properties of isolated cardiac muscle. J Cardiovasc Pharmacol 1986;8:197-207.
42. Mason JW. Amiodarone. N Engl J Med 1987;316:455-466.
43. Raja P, Hawker RE, Chaikitpinyo A, et al. Amiodarone management of junctional ectopic tachycardia after cardiac surgery in children. Br Heart J 1994;72:261-265.
44. Figa FH, Gow RM, Hamilton RM, Freedom RM. Clinically efficacy and safety of intravenous Amiodarone in infants and children. Am J Cardiol 1994;74:573-577.
45. Olsson GL, Hallen B. Laryngospasm during anaesthesia. A computer aided incidence study in 136,929 patients. Acta Anaesthesiol Scand 1984;28:567-575.
46. Lee KWT, Downes JJ. Pulmonary edema secondary to laryngospasm in children. Anesthesiology 1983;59:347-349.
47. Schreiner MS, O′Hara IO, Markakis DA, Politis GD. Do children who experience laryngospasm have an increased risk of upper respiratory tract infection? Anesthesiology 1996;85:475-480.
48. Rolf N, Cote CJ. Frequency and severity of desaturation events during general anesthesia in children with and without upper respiratory infections. J Clin Anesth 1992;4:200-203.
49. Cohen MM, Cameron CB. Should you cancel the operation when a child has an upper respiratory tract infection? Anesth Analg 1991;72:282-288.
50. Tait AR, Pandit UA, Voepel-Lewis T, et al. Use of the laryngeal mask airway in children with upper respiratory tract infections: a comparison with endotracheal intubation. Anesth Analg 1998;86:706-711.
51. Lakshmipathy N, Bokesch PM, Cowan DE, et al. Environmental tobacco smoke: a risk factor for pediatric laryngospasm. Anesth Analg 1996;82:724-727.
52. Skolnick ET, Vomvolakis MA, Buck KA, et al. Expsure to environmental tobacco smoke and the risk of adverse respiratory events in children receiving general anesthesia. Anesthesiology 1998;88:1144-1153.
53. Larson CP. Laryngospasm - the best treatment. Anesthesiology 1998;89:1293-1294.
54. Berry FA. Anesthesia for the child with a difficult airway. In: Berry FA, ed. Anesthetic Management of Difficult and Routine Pediatric Patients. 2nd ed. New York: Churchill Livingstone, 1990:183.
55. Mazze RI, Dunbar RW. Intralingual succinylcholine administration in children: an alternative to intravenous and intramuscular routes? Anesth Analg 1968;47:605-615.
56. Leicht P, Wisborg T, Chraemmer-Jorgensen B. Does intravenous lidocaine prevent laryngospasm after extubation in children? Anesth Analg 1985;64:1193-1196.
57. Borland LM, Sereika SM, Woelfel SK, et al. Pulmonary aspiration in pediatric patients during general anesthesia: incidence and outcome. J Clin Anesth 1998;10:95-102.
58. Warner MA, Warner ME, Warner DO, et al. Perioperative pulmonary aspiration in infants and children. Anesthesiology 1999;90:66-71.
59. Neuhauser EBD, Berenberg W. Cardioesophageal relaxation as a cause of vomiting in infants. Radiology 1947;48:480-486.
60. Berquist WE. Gastroesophageal reflux in children. A clinical review. Pediatr Ann 1982;11:135-142.
61. Boix-Ochoa J, Canals J. Maturation of the lower esophageal sphincter. J Pediatr Surg 1976;11:749-755.
62. Heyman S. Pediatric nuclear gastroenterology:evaluation of gastroesophageal reflux and gastrointestinal bleeding. In: Freeman LM, Weissmann HS, eds. Nuclear medicine annual 1985; New York: Raven, 1985:133-69.
63. Di Lorenzo C, Piepsz A, Ham H, Cadranel S. Gastric emptying with gastro-oesophageal reflux. Arch Dis Child 1987;62:449-453.
64. Schwartz DA, Connelly NR, Theoroux CA, et al. Gastric contents in children presenting for upper endoscopy. Anesth Analg 1998;87:757-760.