Chapter 47
Thermoregulation: Hypothermia and Hyperthermia

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You are taking care of a 4 kg, 5-month-old infant scheduled for a hernia repair.

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Preoperative Considerations

Questions

1. What are the mechanisms of heat loss in humans? What are the mechanisms of heat generation? Is heat generation different for an infant vs. an older child or adult? What is "thermoneutrality"?

2. What effect does general anesthesia have on thermoregulation? Contrast this with the effect of regional anesthesia on thermoregulation.

Answers

1. Heat loss can occur through several mechanisms:
   (a) Radiation – heat lost between objects that are not in contact. This could occur between the baby and the cool walls (or any other object) in the OR.
   (b) Convection – heat lost from a body to moving molecules such as air or liquid. The amount of heat lost depends on the temperature of the air and the speed of the air moving around the patient.
   (c) Evaporation – heat that is lost through the latent heat of vaporization of water or any other liquid evaporating on the patient. This can occur from the skin, a surgical incision, or from mucosal surfaces (which can be 30 % or more of heat loss if dry air is used for ventilation in an infant).
   (d) Conduction – the heat loss that occurs between objects that are in direct contact. The extent of this loss depends on temperature differences and the area of contact. Heat generation can occur through voluntary muscle activity, non-shivering thermogenesis, shivering (non-voluntary muscle activity), and dietary thermogenesis. Non-shivering thermogenesis occurs from metabolism of brown fat in infants and toddlers (perhaps up to 2 years of age). Brown fat contains an increased number of mitochondria and is therefore very effective at generating metabolic energy/heat. The effect is significantly decreased in children under anesthesia, whether this is with inhaled agents or those that have received fentanyl/propofol. Shivering is of minimal importance in maintaining body temperature in newborns and infants as the musculoskeletal system is immature and the muscle mass is limited. Young infants will shiver between 35 and 35.3 °C, but the effect is generally negligible in maintaining core temperature. Dietary thermogenesis is stimulated by nutrients (proteins and amino acids). An infusion of a small amount of amino acids under anesthesia may increase heat generation by up to fivefold in adult models. Infants have a larger surface area to body mass ratio and a higher thermal conductance (lose heat faster due to less fat and greater surface area.). The combination of faster heat loss and reduced ability to generate heat markedly predisposes the infant to hypothermia.

      Thermoneutrality or thermoneutral environment is the ambient temperature at which the oxygen demand is minimal and temperature regulation is accomplished by non-evaporative physical processes alone. For the adult, the neutral temperature is 28 °C, while for neonates and young infants, it is approximately 32 °C.

2. General anesthesia interferes with thermoregulation. This is due to many factors but includes redistribution of core heat to the periphery, a 30 % reduction in heat generation, inhibition of central thermoregulation, and increased exposure (depending on the procedure).

3. How do you define hypothermia? Where would you measure the temperature? Describe the advantages and disadvantages of each site.

Intraoperative

Questions

1. What would be your strategies for preventing heat loss during this case?

Vasoconstriction and non-shivering thermogenesis are the only thermoregulatory responses that are active under anesthesia. Maximal vasoconstriction is similar in the awake and anesthetized patient, although the threshold for vasoconstriction is reduced under anesthesia. Non-shivering thermogenesis is profoundly inhibited under general anesthesia within 10–15 min of induction. Under regional anesthesia in older children and adults, central temperature regulation is preserved, but areas that are anesthetized cannot sense temperature and therefore have inappropriate redistribution of blood flow by vasodilation. In addition, there is no vasoconstriction in the blocked areas. With major neuraxial blockade, vasoconstriction may be lost in a large portion of dermatomes with the result being a large amount of heat redistribution, which can be as marked (or worse) than general anesthesia. Contrary to this finding is the fact that caudal block in infants does not affect the temperature for vasoconstriction.

3. Hypothermia can be mild (33.9–36 °C), moderate (32.2–33.8 °C), or severe (below 32.2 °C). Temperature may be measured from the tympanic membrane (by placing a probe in the auditory canal and sealing it to the external environment), nasopharynx (convenient but can be associated with nosebleeds or inaccuracy if an uncuffed tube is in place), esophagus (convenient but can be confounded by transmission of respiratory gas temperature if not in the distal third of the esophagus), axillary (very convenient but can be very inaccurate if not placed carefully), rectal (can cause trauma and may be inaccurate if embedded in stool or during laparotomy in an infant), bladder (accurate if urine output is copious, not widely available), and skin (wildly inaccurate depending on body area and vasoconstriction).

Answers

1. I would prevent heat loss by:
   (a) Using a radiant heater during induction
   (b) Covering the skin as much as possible – particularly the head which comprises as much as 20 % of the surface area in an infant. A plastic head wrap in an intubated patient is particularly effective.
   (c) I would use a convective forced-air warmer, which should prevent heat loss and rewarm the patient as needed.
   (d) I would avoid a warming mattress as these are minimally effective after the newborn period.
   (e) I would be cautious with fluid administration and I would rewarm fluid – administering through a short length of tubing.
   (f) I would use a heat/humidity filter to attempt to minimize evaporative losses and maximize ciliary function in the respiratory tract. In addition, I would use low fresh gas flows to assist in maintaining heat and humidification.
   (g) I would warm the operating room prior to bringing this patient into the OR.

2. After 1 h of surgery, the temperature is 34.5 °C. Outline the positive and negative effects of hypothermia on an infant.

3. You institute a series of interventions to warm the patient and 90 min later the temperature is 39 °C. What is your differential diagnosis? What do you do for this situation?

Additional Questions

Questions

Case 1 A 16-year-old Asian male is brought to your ICU after a car accident where he experienced multiple traumas and a head injury. He was intubated in the field with fentanyl and succinylcholine. As he is rolled into your unit, he appears to be rigid in appearance. His temperature is 42 °C. His ECG has peaked T waves.

Diagnosis:

1. What is malignant hyperthermia (MH)? What is happening on a cellular level when this occurs? What is the incidence in the pediatric population? What is the inheritance of MH? Which myopathies are associated with MH?

2. Hypothermia can increase the surgical site infection rate threefold and impair the coagulation cascade. This occurs because of changes in perfusion as well as a decrement in immune function including decreased activity of natural killer cells. Platelet function is significantly inhibited, adding to the coagulopathy. Hypothermia decreases drug metabolism – by as much as twofold for a 10 °C reduction in temperature.

3. Excessive temperature can increase oxygen consumption and CO_2 production. The same anatomical and physiological factors that make heat loss a problem in this age group also make rewarming easier than it is in older children or adults. Iatrogenic warming is the most common problem causing hyperpyrexia. Generally this situation is easily reversed by removing the heat generating/preserving strategies outlined above. The convective blanket may be placed on "ambient." Other causes of hyperpyrexia could include viral or bacterial infection. Some diseases such as arthrogryposis and osteogenesis imperfecta as well as those with autonomic dysfunction (Riley-Day syndrome) are associated with increased temperature under anesthesia. Other possible causes could include thyroid storm, pheochromocytoma, neuroleptic malignant syndrome, and meperidine administration.

Answers

Case 1

Diagnosis

1. MH is an inherited disorder associated with a potentially fatal hypermetabolic response to certain pharmacological agents – notably succinylcholine and inhaled anesthesia agents. On a cellular level, exposure to these agents triggers the release of excessive myoplasmic Ca^{++} that in turn leads to diffuse and sustained muscle contraction associated with a hypermetabolic response. The incidence of MH has been reported extensively and varies greatly with the population studied and the definition of the problem that is used. Widely quoted rates report an incidence of approximately 0.2:10:000 in adults and 1–2:10:000 in children. There are reports of specific populations that set the rate at 0.67:10,000 in adults with a quadrupling of that rate when succinylcholine is combined with inhaled agents. The rate of severe, fulminant MH, which includes evidence of a rapid increase in temperature accompanied by critical changes in metabolism, dysrhythmias, and increases in creative kinase (CK), has been reported to be between 0.04 and 0.05:10,000. MH is inherited as an autosomal dominant disorder with variable penetrance. It is often difficult to follow exact inheritance patterns and

2. What is the typical clinical presentation for MH? What is the relationship between masseter spasm and MH? How would you make the diagnosis of MH? What other problems could present in this same manner?

Treatment:

1. What would be your first interventions for this patient? How would this differ if he were presenting in the OR with the same set of symptoms/signs? How does dantrolene work? What are the advantages of using Ryanodex® rather than standard dantrolene?

not everyone who is susceptible will have an episode on first exposure to triggering agents. As a general rule, anyone with first- or second-degree relatives with a history of MH should be considered at risk. Myopathies associated with MH include central core disease and King-Denborough syndrome, which have a high concordance with MH and have been shown to have similar abnormalities in the RYR1 gene that is associated with MH. Other myopathies such as Duchenne muscular dystrophy and Becker muscular dystrophy have been associated with rhabdomyolysis when exposed to succinylcholine or (less commonly) inhaled agents but have not been convincingly associated with the full MH pathology. It is best to avoid exposure to the "triggering" agents, but these entities are not (strictly speaking) associated with MH.

2. MH presents with hypermetabolism. The earliest clinical sign is that of an elevated end-tidal CO_2 which is not controlled by increasing the minute ventilation. Other nonspecific signs include an increase in heart rate and blood pressure. Sinus tachycardia is the most consistent change associated with this problem. Masseter spasm is considered a highly suspicious sign but not pathognomonic of possible MH. Significant (severe) masseter spasm is associated with tetany of the masseter muscle that prevents mouth opening to the degree that would allow the insertion of a laryngoscope blade regardless of the force applied. Muscle biopsy testing of those with masseter rigidity reveals that 20–50 % are susceptible for MH. Generalized muscle rigidity develops as Ca^{++} accumulates in muscle. This can be the case even in the presence of non-depolarizing muscle blockade. The rigidity is very marked, making a person "boardlike" where lifting the feet results in a fulcrum at the cranium. Hyperthermia is a late sign and will be extreme if not treated. Temperatures up to 44 °C have been reported. Acidosis results from accumulation of CO_2 as well as lactate. Initial findings will appear as a pure respiratory acidosis – with the metabolic component more obvious as time goes on. Oxygen consumption will be high enough to result in hypoxia in spite of supplemental O_2 therapy. Skin mottling will occur accompanied by rhabdomyolysis and severe hyperkalemia. Death usually occurs due to ventricular dysrhythmias, pulmonary edema, cerebral hypoxia/edema, disseminated intravascular coagulation, and renal failure.

   Other pathological entities that present in a somewhat similar manner include hyperthyroidism, fulminant sepsis, pheochromocytoma, metastatic carcinoid, cocaine intoxication, neuroleptic malignant syndrome, serotonergic toxicity, and rhabdomyolysis associated with myopathies such as Duchene muscular dystrophy.

Treatment

1. To treat MH, it is critical that all possible triggering agents be stopped. The patient should be ventilated at a maximal rate with 100 % O_2. A call for help should be made immediately, and the MH cart should be brought to the bedside where dantrolene should be drawn up for immediate administration. Approximately 2.5 mg/kg are needed for initial treatment. The drug is prepared

2. What are the late complications of MH – how would you manage this patient in the hours/days after the episode?

with mannitol – so the two are given simultaneously. Mannitol will force a diuresis of the myoglobin-containing serum, which can significantly damage renal function. Improvement should be extremely rapid. Clinical endpoints would include resolution of hypercapnia and tachycardia, resolution of muscle rigidity, return of consciousness, correction of acidosis, and electrolyte abnormalities. Doses should be repeated until symptoms and signs of MH resolve. It should be appreciated that large doses of dantrolene may cause muscle weakness that requires prolonged ventilation. Cooling measures should be initiated if the body temperature has reached dangerous levels. The administration of cooled IV fluids or the administration of a cool "bath" of fluid externally can help to bring hyperthermia under control. Avoid direct contact with ice on the skin since this can cause vasoconstriction and impair heat dissipation. A urinary catheter should be inserted to allow collection of copious urine that should result from the infusion of diuretics along with dantrolene. An arterial catheter should be inserted for serial blood gas determination as well as CK and electrolyte analysis. Metabolic acidosis can be treated with 1–2 mEq/kg of bicarbonate. Hyperkalemia should be aggressively treated with glucose and insulin infusions as well as exogenous calcium. Release of potassium from cells combined with acidosis makes hyperkalemia one of the most life-threatening aspects of this syndrome. If this scenario were to occur in the OR, it would be critically important to discontinue the anesthetics that could trigger MH and communicate with the surgeon concerning the diagnosis. Efforts to end the surgery and position the patient in a manner that will allow maximal therapy must be accomplished quickly. Dantrolene acts by binding to the ryanodine receptor and thus decreasing the concentration of free calcium in the intracellular milieu. Ryanodex® is a lyophilized powder form of dantrolene sodium. It comes supplied as 250 mg and can be reconstituted in 5 cc of sterile water. Compared to older preparations of dantrolene, this form can be prepared in approximately 1 min and requires only one vial for a patient. Older formulations required multiple vials to be prepared and required 15–20 vials depending on the dose required for weight. In addition, Ryanodex® is much more concentrated and a full dose can be administered from one vial.

2. Late complications of MH could include injury to any of the critical organ systems (neurological, cardiac, hepatic, renal) depending on the nature and duration of the MH episode. The child should remain in the ICU for close monitoring for whatever duration is required to assure recovery in terms of mental status, urine output, muscle tone, temperature regulation, and laboratory findings (including muscle enzymes, electrolytes, and liver functions). A major late complication is recurrence of the symptoms/signs of MH that may take place hours after initial exposure to the triggering agent. For this reason, repeated doses of dantrolene should be available and administered every 6 h until all physical and laboratory signs indicate the MH episode is completed. Weakness from repeated administration of dantrolene should be anticipated and provisions for respiratory support should be made.

Posttreatment:

Questions

1. What kind of testing would you suggest for members of the family? How would you compare muscle contracture testing to genetic testing?

Case 2 A newborn child has experienced an episode of severe hypoxic ischemic injury. Is it appropriate to institute cooling to protect neurological outcome? If so how would you do this? What would be your concerns?

Answers

1. The most sensitive and specific testing for MH is the in vitro contracture test that is performed on a live preparation of muscle prepared in a physiological medium. The muscle (obtained from the vastus lateralis) is attached to a strain gauge and is electrically stimulated at baseline and then after exposure to halothane, caffeine, or both. There are a couple of protocols for this testing, but both are between 97 % and 99 % sensitive for MH susceptibility with slightly lower specificity. The testing is performed at a limited number of centers in the USA. Gene testing for a limited number of RYR1 gene mutations is also available. This testing can be done on blood collected at any location and sent to one of two centers in the USA. This testing can be helpful when positive but does not rule out MH susceptibility when negative. It is most helpful when the gene mutation in a family is known and is one that has been described and is part of the testing procedure. If this is the case, such genetic testing could be used instead of muscle biopsy.

Case 2 I would agree to pursue cooling as an effort to limit the chance of death or severe injury as long as the child had residual brain function. Hypothermia attenuates blood-brain barrier damage, release of excitatory neurotransmitters, and free radical production. Anti-inflammatory cytokines are increased. Hypothermia decreases cerebral metabolic rate for glucose and oxygen and reduces the loss of high-energy phosphates during ischemia. Finally hypothermia appears to decrease apoptosis. In animal models, mild hypothermia reduces damage in the cortex, thalamus, and hippocampus. Cooling may be accomplished by a "cooling cap" which is a cap of coiled tubing filled with cooled fluid wrapped around the head. Cooling can also be accomplished by passively lowering the whole body temperature to 33.5 °C. Hypothermia is associated with physiological changes including decreases in heart rate and blood pressure. The QT interval of the electrocardiogram increases with cooling, and arrhythmia has been observed in adults with these temperatures although studies in infants have failed to indicate there is a significant effect. Hypothermia can alter clotting, however, in the trials that have been undertaken to date; no significant biochemical changes have been noted in the patients that were cooled in this manner.

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