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Case Report

Intraosseous flow Characteristics and Esophageal/Endotracheal Capnometry during Acidotic States in an Animal Model - A Protocol

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Abstract

Introduction and Background: End-tidal pCO_2 monitoring (Capnometry) is used to assist in the confirmation of endotracheal intubation. However, this is unreliable in low flow states, such as during severe shock and also during Cardiopulmonary Resuscitation (CPR). It has been anecdotally noted that during severely hypercapnic and acidotic states, esophageal pCO_2 is abnormally high. This may mislead the resuscitation team into believing that the endotracheal tube is in the trachea, when in fact it is in the esophagus. The purpose of this part of the study is to confirm the existence of this phenomenon and to further investigate its characteristics in an animal model.

Part II: During the CPR of infants, it has been anecdotally noted that the flow resistance encountered during intraosseous infusion increases dramatically during resuscitation. This has not been reported in the literature. This increase in flow resistance could be due to epinephrine or acidosis-induced vasoconstriction, a low flow state, an inherent characteristic of intraosseous infusion or a combination there of. The purpose of this second part of the study is to confirm the existence of this phenomenon and to further investigate its characteristics in an animal model.

Materials and Methods: For Parts I and II, animals will be fully anesthetized using the facilities and expertise of the Cardiovascular Research team responsible for this work. The research team will need to be very experienced in animal research. The facility will consist of a fully-equipped animal surgical suite, research monitoring equipment, and technical support. Following general anesthesia, baseline measurements will be obtained from intraosseous and arterial lines, as well as intraesophageal, and endotracheal monitors. Various resuscitation scenarios will be simulated during different phases of the study, which will include isolated states of hypercapnia, shock, CPR, and metabolic acidosis. The most suitable animal model for this study will be based on animal availability, cost, and input from researchers in the field. At this time, it appears that young pigs will be the optimal choice, given these factors.

Part III (Optional): Chest tube thoracotomy is a life-saving procedure for the critically ill patient suffering an acute tension pneumothorax. This procedure is done infrequently and, even then, is usually performed by critical care specialists in an emergency department or an intensive care facility. The transport of critically ill infants and children from rural hospitals to the tertiary resources of a major medical facility is carried out by a team of nurses specially trained for neonatal and pediatric transport. Such transportations need to occur via fixed wing aircraft, helicopters, and ground ambulances. The risk of developing a pneumothorax during transport is real, and the transport nurses' experience in performing an emergency tube thoracotomy is less than ideal. To improve the potential outcome for patients with this type of emergency during transport, we would propose that these nurses (approximately eight of them) be allowed to perform the tube thoracotomy procedure in these animals after they have died. The animals would sustain no additional suffering, and this would maximize their benefit to medicine without the need to sacrifice further animals.

Keywords: Tracheotomy; Acidosis; Capnometry

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Introduction

End-Tidal Volume of Carbon Dioxide ($ETCO_2$) is a useful parameter for the monitoring of the quality of Cardiopulmonary Resuscitation (CPR) and the status of ventilation in a post-cardiac arrest patient [1-3]. It is also a valuable predictor for in-hospital mortality in post-cardiac arrest patients [4-6]. Generally, $ETCO_2$ correlates well with the arterial partial pressure of carbon dioxide ($PaCO_2$). The gradient between these two entities should be approximately 2 mm Hg to 5 mm Hg [7-9]. That said, this gradient may be increased by respiratory dead space or by low pulmonary circulation and can thus present as a mismatch of the ventilation / perfusion (V/Q) ratio [10-14]. Patients with a V/Q mismatch or an increased $PaCO_2/ETCO_2$ gradient have a high probability of mortality in-house [15]. This can occur in post cardiac arrest patients due to traumatic lung injury secondary to vigorous lung compression, early onset pneumonia due to aspiration, pulmonary interstitial edema secondary to ischemia - perfusion injury, or myocardial stunning, which can lead to deterioration in lung function [16-18].

Materials and Methods

The protocol will first need to be approved by the Institutional Review Board (IRB) of the institution where the work will be performed. The facility will also house the animals and will have a veterinarian on call to care for them and in emergencies.

Animals to be used

Based on the availability and cost, young piglets would be the most appropriate and suitable species that can be used in this work. We propose to use 8-10 animals per group as described below.

Category A: Animals in this group are to experience little or no pain. Anesthetics, analgesics, and/or tranquilizers will not be administered.

Category B: Animals in this group experience some pain or stress. Anesthetics, analgesics, and/or tranquilizers will be administered to alleviate the pain and/or distress.

Category C: These animals shall experience significant, but unavoidable pain and/or stress. Anesthetics, analgesics, and/or tranquilizers will NOT be administered to alleviate the pain and/or distress.

Sedation

Piglets (10 kg to 15 kg) will be sedated with IM Telazol (9 mg/kg; Zoetis, Parisippany, NJ) and Rompun (2 mg/kg; Bayer Healthcare LLC, Shawnee Mission, KS). We would then wait 2-3 minutes for the animal to be fully sedated. At this point, the animal will be washed, shaved and intubated. An Intravenous (IV) line will be established through an ear vein. Following the infiltration of Lidocaine (<1 ml at the site of incision), the groin region will be shaved for vascular access.

Experimental Design

Part I

Venous vascular access will be obtained through a femoral cut down. Diazepam (Valium, 0.8 mg/kg/hour) and Fentanyl (2.7 mg/kg/hour) will be administered Intravenously (IV) as needed to maintain sedation and anesthesia. Arterial access will be obtained through the same cut down. Trachea will be intubated with an endotracheal tube via oral laryngoscopy (direct visualization of the larynx with a laryngoscope). Tracheal intubation will be confirmed with end-tidal CO_2 monitoring. If tracheal intubation through the oral route cannot be achieved, a tracheotomy will be performed. The esophagus will be intubated with an endotracheal tube by passing the tube through the mouth towards the esophagus. It is expected that the tube will enter the esophagus blindly since the trachea will already be intubated. Esophageal intubation will be confirmed by the absence of an end-tidal CO_2 wave form. The esophageal tube will then be capped to prevent any gas exchange through it. The endotracheal tube in the trachea will be attached to a ventilator at standard settings for the animal (50% FiO_2, Tidal Volume of 11 ml/kg, Rate of 12 per minute).

Following intubation, the animal will be given a paralyzing dose of Pancuronium (0.2 mg/kg, Pfizer Limited) IV for pharmacologic paralysis to control the ventilation and the degree of CO_2 retention (hypercapnia) to ensure unconsciousness during paralysis. Without Pancuronium paralysis, the degree of hypercapnia cannot be controlled. The use of Pancuronium for this purpose will need to be discussed and approved by the veterinarian. The degree of hypercapnia will be monitored by serial Arterial Blood Gas sampling (ABG) and end-tidal CO_2 monitoring using a standard end-tidal CO_2 monitor. The degree of oxygenation and metabolic acidosis will be monitored by serial ABG sampling. If we have access to a pulse oximeter, it will be used to monitor changes in oxygen saturation as well. It is our expectation that there will be some discrepancy between end-tidal CO_2 monitoring and pCO_2 measurements by ABG sampling. This discrepancy will be monitored. It is our expectation that the animal should be able to survive a pCO_2 of 60 mm Hg - 80 mm Hg for 30-60 minutes as long as oxygenation is maintained. After maintaining a hypercapnic state for 30 minutes, the end-tidal CO_2 monitor will be attached to the esophageal tube to measure the degree of CO_2 accumulated in the esophagus. A ventilation bag will be used to ventilate the esophagus. These measurements will be repeated every 15 to 20 minutes for no more than 60 minutes, depending on how long the animal can survive this state. Clinical experience from humans suggests that a hypercapnic state with pCO_2 in the 60 mm Hg - 80 mm Hg range can be well-tolerated indefinitely in conscious adults and children, as long as oxygenation is adequate and maintained.

Part II

Intraosseous (IO) access will be obtained in the femur or tibia using Cook 18 or 19 gauge intraosseous needles. An intraosseous infusion with normal saline will be maintained at a constant rate of 100 ml/hour. Pressure monitoring through the IV pump will allow us to calculate resistance through the IO needle (Pressure = Flow Rate × Resistance). IO resistance as a function of time will be monitored in a control animal for one hour. In the experimental group, two animals will receive an IO infusion of Epinephrine (a commonly-used resuscitation drug; 0.01 mg/kg every 5 minutes for 5 doses). IO resistance as a function of time will be monitored for one hour. Two other animals will be phlebotomized 20 ml/kg to 40 ml/kg (*via.* a femoral artery cut down) to induce a state of hypovolemic shock. Since the intention of the study is to produce shock in these animals, more or less blood would be drawn to achieve this goal. Intra-arterial blood pressure monitoring will monitor the degree of hypotension. This will also result in a metabolic acidosis. Other than the control animal, those subjected to Epinephrine and hypovolemic shock will suffer irreversible end organ damage. Resuscitation for full recovery will not be possible. Epinephrine alone will induce substantial renal and gastrointestinal ischemia, which would result in renal failure. The control animal will recover from anesthesia spontaneously. IO resistance as a function of time will be monitored and compared to

the pattern noted for the control animal to determine the degree of resistance due to time versus catecholamine-induced vasoconstriction versus shock and acidosis.

Part III

Once the animal has died, chest tube thoracotomy will be performed on the animal's thorax as a standard procedure. This involves a scalpel incision over an intercostal space in the anterior auxiliary line. A hemostat will be inserted into the incision to bluntly dissect an opening through the intercostal musculature until it enters the pleural cavity. A chest tube is inserted in the superior anterior direction through this hole to a depth, ideally, just below the apex of the lung. The tube is sutured or taped in place to prevent movement, and an occlusive petroleum jelly-type dressing is applied over the site of entry. In an emergency situation, no anesthesia is used. However, electively, local anesthesia is applied to the area.

Post Experimental Procedures or Euthanasia

In case of injury to the animal or if problems arise where the animal(s) may unexpectedly not respond normally, it is the investigator's responsibility to consult the veterinarian on duty or a local veterinarian for emergency treatment or euthanasia.

Post-experimentally, the piglets will be sacrificed since they will have sustained irreversible end organ damage not compatible with life. They will be given Sodium Pentobarbital (60 mg/kg) IV post-experimentally. If approval is granted for Part III, the dead animals will be used for training purposes.

Facilities

Our facility has a long history of housing animals and performing surgeries and is more than adequate in meeting the requirements.

Federal assurances

(a) In lay terms, summarize the rationale for the use of animals as opposed to an in vitro or model system.

We are simulating the human condition in this work, and therefore, it is essential to use live animals. The use of dead animals in the optional Part III is for training purposes only. To our knowledge, a satisfactory in vitro model for these purposes does not exist.

(b) Why have you selected this species?

We have experience in the handling of pigs. They are a lower form of animals which will allow us to study the complex biological processes in which we are interested. They are also cost effective.

(c) Why have you selected this number of animals?

For a preliminary study, we need 8-10 animals. A minimum of 3-4 animals will be necessary to document the phenomenon in Part I of the experiment. A minimum of 5 animals will be necessary to document the phenomenon in Part II. These numbers are less than the numbers needed for statistical validity. However, since this is a pilot study, only a small number of animals will be needed to demonstrate whether the phenomena described exists.

If applicable, list the numbers of animals in the control and each treatment group of the experimental design. Part I will not use any controls. Part II will require at least one control animal receiving an intraosseous infusion with no pharmacologic agents and no shock states. The remaining animals will be subject to either shock (phlebotomy of 20-40 /kg) or epinephrine (0.01 mg/kg every 5 minutes for 5 doses).

Reference Sources for Research

1. Why is this work necessary? State in narrative form, the database sources consulted to determine the deficiency or non-existence of earlier efforts for this research, or the necessity for the duplication of earlier efforts (e.g. Medline, Toxline, AWIC).

2. State, in narrative form the database sources (e.g. Medline, Toxline, AWIC) consulted to determine the necessity to use these procedures that you have described that cause more than momentary pain and / or distress to the animal (Animal Use Categories B and C). Are there alternate procedures or methods in your type of research that can be used or substituted to alleviate pain and / or distress to the animal?

We have consulted Medline. We could find no alternative to the use of animals for the phenomena we are attempting to produce. The animals will be subjected to humane treatment, including anesthesia during the study.

Reference sources for research

Part I: The reliability of capnometry in confirming tracheal intubation is a well-established medical principle [19,20]. It is highly accurate in confirming tube placement for patients who are not in cardiac arrest [21]. Dr. Yamamoto's textbook chapter as well as his review article on emergency anesthesia and airway management has given us considerable input on the use of manometry in emergency intubation [21,22]. A known false negative of this is a low flow state, such as during shock and CPR [23-25]. However, there are a limited number of studies that include false positive capnometry [26,27]. The meta-analysis done by James Li shows a 7% false negative rate, and a 3% false positive rate for emergency capnography use [26]. A review done by a group of researchers on carbon dioxide kinetics and capnography during critical care states several possible causes for false negative capnometry readings; during circulatory arrest, where pulmonary ventilation will result in low and decreasing values of exhaled CO_2. Positive-pressure ventilation by face mask can force pharyngeal gas, containing exhaled carbon dioxide from the previous breath, into the esophagus and stomach resulting in initial cyclic 'exhaled' CO_2. Another cause mentioned in this review is a pathology causing absence of ventilation, including severe bronchospasm, patient apnea, or plugged ETT that can result in the absence of expired CO_2 and a false negative diagnosis that the ETT is not in the trachea [23]. Keller and colleagues in their attempt to find a relationship between colorimetric capnometric readings during esophageal intubation and ingestion of carbonated beverages concluded that under proper circumstances, a significant potential exists for false-positive colorimetric capnometric results in the presence of even small amounts of carbonated beverages [27].

Anecdotal observations suggest that hypercapneic patients may produce enough intra-gastric and/or intraesophageal CO_2 to result in a false positive condition, where CO_2 is detected in the esophagus via capnometry. This would mislead the resuscitation team into believing that the trachea is intubated when in fact it is the esophagus that is intubated. It has also been reported by Yamamoto who experienced this in a patient transferred by air ambulance from Hilo hospital to Honolulu, Hawaii [28]. On arrival, the patient's endotracheal tube was attached to an end-tidal CO_2 monitor. The monitor read 25 mm Hg but with a peak pattern rather than the usual plateau pattern. Other clinical assessment parameters indicated that the patient's esophagus was probably intubated despite the end-tidal CO_2 result. The patient

was re-intubated, resulting in an immediate improvement in all clinical parameters. The patient's end-tidal CO_2 monitoring wave showed the classic plateau pattern with a high reading in the 80's. An arterial blood gas confirmed hypercapnea that was rapidly reversed with hyperventilation. This phenomenon has not been described in the literature. Although the literature has extensively studied the use of capnometry, no study to date has found a clinical situation where a positive capnometry reading is associated with an esophageal intubation. A Medline computerized literature search was conducted *via*. Grateful Med Software through the National Library of Medicine. Using the search parameters Capnometry and Esophagus, only two articles were retrieved. Both articles fail to identify any conditions that show a positive capnometry reading associated with esophageal intubation. Using other search parameters to locate such a study resulted in nothing further.

Part II: There are many reports on intraosseous infusion. First described in 1922 by Drinker and colleagues [29], it is now a well-established route of fluid and drug administration in critically ill children and adults [30-32]. A review conducted by Anson states that 'intraosseous vascular access can be achieved quickly with minimal disruption of chest compressions' [31]. It is discussed in all standard emergency medicine textbooks, and is taught as a skill station in Pediatric Advanced Life Support (PALS) courses. The reliability, ease of use, speed of insertion, and success rate of intraosseous access have been studied by many researchers [30,31,33-36] and is now considered a safe alternate route for fluid and drug administration in the infant or child when intravenous access cannot be achieved rapidly [32,34,37,38]. Medications or blood products that can be administered IV can be safely infused *via*. IO, with rapid delivery to the systemic circulation (300-32, 38). Despite its' favorable profile, IO flow rates vary depending on many factors [30,36]. Physiologic response to stress during circulatory collapse [28], a low flow state [36], and blood pH levels [38] may alter bone marrow blood flow.

Drugs such as Epinephrine and Norepinephrine have vasoconstrictor action on the bone marrow [38-40]. However, no report to date has described the vascular flow resistance characteristics of intraosseous infusions. It has been anecdotally noted that during the resuscitation of patients using an intraosseous infusion, after about 30 minutes, the flow resistance through the intraosseous becomes very high in some instances, making it difficult to use [41]. In his review on intraosseous vascular access, James H. Paxton mentions that anecdotal evidence that IO infusion rates 'slow down automatically as body fluids become replenished [36]. This could be due to afore mentioned factors controlling IO flow rates during CPR, or even inherent characteristic of IO infusion [36,42]. Dubick and Holcomb state that 'the tortuous vascular architecture of bone marrow presents substantial hydraulic resistance to infusions' [42]. Confirmation of the existence of this phenomenon, where the flow resistance of intraosseous infusion increases during resuscitation, is not described in the literature. Using the search parameters Infusions, Intraosseous, and Vascular Resistance, no articles were found.

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