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Critical importance of tracheal tube cuff pressure management

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Abstract

The ideal range for tracheal tube cuff pressures is usually taken to be between 20 to 30 cm H₂O. This is easily measured with a cuff pressure manometer and should be measured in each instance. The importance

of tracheal tube cuff pressures is highlighted by the spectrum of airway complications that can occur with incorrect cuff pressures. High cuff pressures can result in complications ranging from sore throat and hoarseness to tracheal stenosis, necrosis, and even rupture. In such cases, the postulated causative factor is diminished blood flow to tracheal mucosa due to excessive cuff pressure on the tracheal wall. This hypothesized ischemic injury then produces healing fibrosis months or even years later. On the other hand, cuff pressures that are too low place the patient at risk for aspiration of gastric contents and consequently, aspiration pneumonitis and pneumonia. This is why the authors recommend that cuff pressures be measured following all intubations.

Key words: Tracheal tube cuff pressure; Tracheal injury; Tracheal stenosis; Patient safety; Intubation

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Core tip: The ideal range for tracheal tube cuff pressures is typically between 20 to 30 cm H₂O and is easily measured with a cuff pressure manometer. The importance of tracheal tube cuff pressures is highlighted by the spectrum of complications that can occur: high cuff pressures can result in complications ranging from sore throat and hoarseness to tracheal stenosis, necrosis, and even rupture, while cuff pressures that are too low place the patient at risk for aspiration and consequently, aspiration pneumonitis and pneumonia.

Feng TR, Ye Y, Doyle DJ. Critical importance of tracheal tube cuff pressure management. *World J Anesthesiol* 2015; 4(2): 10-12 Available from: URL: <http://www.wjgnet.com/2218-6182/full/v4/i2/10.htm> DOI: <http://dx.doi.org/10.5313/wja.v4.i2.10>

Anesthesiologists who spend the bulk of their clinical time in ear-nose-throat (ENT) and bronchoscopic pro-

cedures (such as the third author) see a surprising number of cases of tracheal stenosis that appear to be related to prior tracheal intubation. In such cases, the postulated causative factor is diminished blood flow to tracheal mucosa due to excessive cuff pressure on the tracheal wall. This hypothesized ischemic injury then produces healing fibrosis months or even years later^[1-4]. However, despite a substantial body of published literature dealing with cuff pressure monitoring^[5-8], routine monitoring of endotracheal tube (ETT) cuff pressure in clinical practice is rarely done and no established guidelines exist to direct its measurement^[9].

The ideal range for ETT cuff pressures is typically between 20 to 30 cm H₂O^[10-13] and is most reliably assessed with direct continuous manometers during the operative period^[14]. One can easily and inexpensively display real-time cuff pressures using an ordinary patient monitor with invasive pressure capability as follows^[5]. An ordinary pressure transducer is first electronically connected to the pressure channel of the monitor and zeroed. Next, the hydraulic end of the transducer is connected to the pilot balloon/cuff inflation line of the ETT using air-filled tubing and a three-way stopcock. A 10 mL syringe inserted in the side arm of the stopcock allows air to be added or removed. Finally, a male plug ("dead end") is placed in the remaining port of the pressure transducer to seal the system (Ordinarily this port is hooked up to a high-pressure fluid source to make a flush system).

Despite this, few anesthesiologists use such methods in daily clinical practice and typically rely on less quantitative methods to estimate the cuff pressure (Table 1), often with poor compliance. Additionally, these commonly used techniques are much less accurate and often poor estimates of ETT cuff pressures^[9,14]. This dilemma is not remedied by clinical experience, as studies have shown that inaccurate cuff pressure assessments can occur in the hands of even the most seasoned anesthesiologists^[11,15]. On the contrary, Wujtewicz *et al.*^[15] concluded that anesthesiologists may be worse at estimating cuff pressure than a decade ago.

The importance of ETT cuff pressures is highlighted by the spectrum of complications that can occur outside the ideal pressure range. High cuff pressures can result in complications ranging from sore throat and hoarseness^[16,17] to tracheal stenosis, necrosis, and even rupture^[18-21]. Conversely, lower cuff pressures place the patient at risk for aspiration and consequently, aspiration pneumonitis and pneumonia^[22,23]. Although certain complications such as tracheal stenosis remain rare entities, the serious morbidity associated with the disease should be balanced against the ease and low expense of intra-operative cuff pressure monitoring.

Despite the large body of literature dealing with cuff pressure monitoring and the relative ease with which accurate intra-operative cuff pressure monitoring can be implemented, there remains a lack of guidelines and recommendations regarding the issue. Given the fact that studies have shown cuff pressures over 30 cm H₂O

Table 1 Common techniques for assessing endotracheal cuff pressures^[5,9,24]

Method	Description
Minimal occlusive volume technique	Determination of volume of air to inject into cuff based on how much is required to eliminate audible end-inspiratory leak with positive pressure ventilation
Minimum leak technique	Determination of volume of air to injection into cuff based on how much is required to auscultate a small end-inspiratory leak
Predetermined volume technique	Injection of pre-determined volume of air to inflate cuff
Palpation technique	Palpation of pilot balloon after inflating endotracheal cuff
Direct intracuff pressure monitoring	Use of a pressure transducer to directly provide a quantitative pressure reading

occur in about 50% of cases where cuff inflation was performed using pilot balloon palpation^[24], it raises the question of why mandatory monitoring is not standard of practice. As a profession, should we not be more vigilant with regards to tracheal tube cuff pressures? We say yes.

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Translating the expression of pain in the face of uncertainty: The importance of human pain experiments for applied and clinical science

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Abstract

This brief commentary attempts to provide a concise synthesis of social psychology experiments that inform an interpretation of clinical pain. From a social perspective the expression of pain is a complex phenomenon that is greater than the patient's physiology. Numerous experiments show that pain is modulated by social and

contextual factors. These experiments point to the role of the listener as a social agent that can modulate the patient's expression. Within the clinical setting the patient's pain experience can be understood as the uncertainty of physical damage and their expression as an attempt to reduce that uncertainty. How successfully this occurs is in part dependent on the empathetic reception of the provider. Chronic pain is a state that is challenging to effectively model in humans but may persist in patients due to an inability to receive effective empathetic reception at the critical time of need (at or near onset). Rather than focusing on pain's alleviation future avenues of pain interventions may do well by turning attention to the most effective ways to impart a message that the patient will be "okay" in a genuinely empathetic manner.

Key words: Pain; Social psychology; Uncertainty; Fear; Catastrophizing; Contextual modulation; Health; Medicine; Pain management

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Core tip: The experience of pain has much to gain from a social psychology perspective where experiments modulate the patient's context and affect their expression. Clinicians and providers should understand that listening sends powerful social cues back to the patient in terms of empathetic feedback. When this feedback is provided in a timely fashion (at or near the time of onset) and in combination with ruling out serious medical pathology a clinician can provide powerful signals that changes patient's experience of pain.

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Pain is difficult to study. Typically, clinical pain originates at a specific time and location that is far removed from the controlled confines of a healthcare setting. Experimental pain studies fill the gap between healthcare settings and real-life conditions. Historically, experimental pain studies have focused on medical treatments to decrease discomfort. More recently, social scientists have begun to explore the social and contextual contingencies that surround the experience and expression of pain. Findings thus far reveal a rich but complicated relationship between pain-evoking stimulus and the context in which it occurs. Here we briefly review a social psychological perspective of pain expression and how that perspective might inform interventional philosophy for clinical practice.

Our understanding of pain has been drastically overhauled during the last 50 years. Before this remaking, the Cartesian model of perception guided medical reasoning as follows: a pain stimulus leads to a pain experience, which leads to pain's expression. Initially, this framework fit nicely with medicine's imperative to reduce signs and symptoms (pain's expression) by eliminating the organic cause of the stimulus. However, as empirical observations accumulated, pain's elimination did not follow. Further, the stories of soldiers expressing little pain at war and medicine's inability to find the organic origins of pain both confounded and challenged 20th century investigators. It was the original work by Melzack and Wall that began to dismantle the Cartesian relationship between stimulus, perception and expression^[1].

What was originally viewed as an obligatory relationship between stimulus and expression can now be understood as two fundamental parts: stimulus and its relationship to experience and the relationship of that experience to pain's expression. The reaction to aversive stimulus has been called the expression of pain - an objective and quantifiable behavior that occurs alongside the private aversive sensational experience.

Clinicians might not consider the relationship between the sensation and the expression of pain a necessary division but it demands considerable attention. Our own private experience serves a clear example of this difference - how often do we express pain differently in different social contexts? The distinction between internal and external causes of pain perception and the voluntary and involuntary expression pain is what psychology pain experiments seek to explain.

Psychological research has shown the limits of introspection for understanding human behaviors. Social psychologists have long shown that explicit verbal questioning of a subject does not lead to an accurate description of the causes of their behavior^[2-4]. The experience of pain is not exceptional in this respect. Individuals given an identical stimulus will report their pain differently based on the immediate social context they are embedded^[5-8]. Further this difference in reporting occurs outside the direct awareness of the subject^[9]. So where physiology has shown that a pain stimulus does not necessitate a painful experience, social psychology has shown that the

pain experience does not necessitate pain's expression.

The challenge for clinicians is to synthesize these diverse findings in a way that allow for their parsimonious use in the clinical setting. In order to do this we encourage the reader to take on a broader view than simply the medical treatment for the alleviation of pain. From a social psychological perspective, pain's expression could be viewed as accomplishing one very important biological goal: to decrease the immediate uncertainty that accompanies the pain experience *via* facilitating social contact and closeness.

Several animal and human studies of experimental pain have shown that uncertainty is a powerful modulator of pain's expression^[10-12]. From the human perspective this uncertainty can best be understood in both the fear and catastrophizing constructs that have been applied to pain^[13,14]. Both constructs uniquely help the clinician understand the aspects of uncertainty that the patient faces. This view is also supported by findings which demonstrate that areas commonly associated with processing affective behaviors - the insula, amygdala and cingulate - also process uncertainty^[15,16]. The cognitive and behavioral overlap between the shared aspects of physical and social pain^[17] has also been observed in social experiments^[18,19].

Returning to the division between the experience and expression of pain, the difference between the patient who chooses to express their pain and the one who does not may amount to the uncertainty that accompanies the aversive stimulus, as well as the uncertainty of social defection (social harm) of other people in the immediate context. Humans are the quintessential social animal and seek interpersonal certainty in their social environment. The patient seeks this certainty (about the present and future environments) when the expression of pain occurs^[20]. The updating of expectations can be due to characteristics of a health provider's interaction (implicit) as well as their explicit message. In other words what mediates whether an individual accepts a persistent pain experience as an inevitable part of the human experience or goes onto develop a chronic expression of pain can be the result of two dimensions: interpersonal trust (*i.e.*, safety and certainty in the social interaction) and the uncertainty of the aversive stimulus.

The dimensions of social and physical uncertainty interact during pain's assessment, which can both potentiate pain expression (*e.g.*, low uncertainty of social agents; intimacy-induced hyperalgesia) and attenuate pain expression (*e.g.*, high uncertainty of social agents; fear-induce hypoalgesia). Following this reasoning, it is the uncertainty of one's physical condition that accompanies the aversive experience that motivates the patient to find a sympathetic ear to express their pain, and the perception of trustworthiness (lack of threat) of people in the immediate social context that moderates the translation of pain sensations into momentary pain expression^[21].

To put this in a more clinically concrete example, the clinician who does not engender the patient's trust

is likely to inhibit the patient's expression. Likewise a clinician who earns more of the patient's trust will in turn receive more of the patient's expression. A clinician may be tempted to hope that the inhibition of a patient's expression is the same as experiencing less pain. Yet no such guarantee can be given. Further, the only way to for the clinician to encourage a dialogue about the significance and the meaning of one's pain - in order to reduce the averseness of physical uncertainty - is by its expression. Therefore in crafting an empathetic dialogue it is imperative for a clinician to work at earning the patient's trust.

Turning to interventions for pain, in the absence of signs of serious pathology, perhaps the best treatment is the genuine message by providers that the patient is physically safe (*i.e.*, physical damage is not continuing to occur) and that there is no reason to expect that a recovery will not occur. This might be as simple as saying "you're alright" but often might involve more than just direct explicit messaging. For example, the use of therapeutic touch, empathetic listening or allowing the patient to fully tell their story may all be necessary parts of the therapeutic ritual (referred to as the placebo mechanism) that may provide the contextual security the patient is seeking^[22,23]. Further, rather than the provider following the inclination to provide immediate relief we strongly feel that having open empathetic conversations about the relation of the pain experience to patients' values and functioning is the best way proceed.

Finally, we find ourselves full-circle by concluding that acute pain and chronic pain are different, each in terms of their precipitating stimuli, contextual influences and associations with other aspects of affect (*e.g.*, emotional valence). Experimental social manipulations of pain are performed acutely and no model exists to experimentally induce chronic pain in humans. Additionally, chronic pain represents an unruly challenge to the patient-provider relationship. For example, one challenge may be to reinterpret the patient's expression, an expression that could have persisted because the uncertainty in one's condition was never fully addressed. Instead of allowing for expression to occur providers may be tempted to promise relief alongside treatment and while this promise may provide the temporary certainty that the patient craves, when the pain returns, doubt is likely to creep back in. Repeated enough times, the patient in this situation may become caught in a cycle. Breaking this cycle may not necessarily be about fixing the patient but improving the provider's ability to form an open and empathetic discourse about pain.

We humbly accept that treatment of pain is a course that is littered with challenges and even this parsimonious perspective will not fully account for all the variability encountered along the way. A social psychological perspective has much to contribute to the study of pain. Given the extensive evolutionary history that the expressive role of pain has played in our survival and its biological robustness it may be counterproductive and even professionally stifling to consider a world where

the elimination of human pain is possible. As providers we cannot control nor predict and thus must remain tentative about the unanticipated physical, social and/or emotional traumas that our patients can and will experience. However, after the patient's expression of pain to an empathetic clinician and serious disease related pathology is ruled out, what remains for the clinician is building a relationship that allows for the genuine forecasting that life is (and will be) alright for the patient. It is when this message is delivered carefully, responsibly and empathetically that the patient can learn to face the uncertainty of the experience of pain with less averseness.

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Pharmacokinetics and pharmacodynamics of lignocaine: A review

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Abstract

Lignocaine is an essential drug on World Health Organisation essential drug list, considered efficacious, safe and cost-effective for any health-care system. Despite its ubiquitous use in medicine and surgery, there are few detailed reviews of its pharmacokinetics and pharmacodynamics. Being an amide-type local anesthetic and Class 1b antiarrhythmic, lignocaine is most frequently used clinically for its anesthetic and antiarrhythmic benefits. However, lignocaine has important antinociceptive, immuno-modulating, and anti-inflammatory properties. Information pertaining to the pharmacokinetics and pharmacodynamics of lignocaine was examined by performing a literature search of PubMed, Embase and MEDLINE (*via* Ovid), pharmacology textbooks and online sources. We present a focused synopsis of lignocaine's pharmacological composition, indications for use and mechanisms of action, focusing on its anti-inflammatory, immuno-modulating and analgesia effects. In addition we review the dosing regimes and infusion kinetics of lignocaine in the clinical setting. Finally, we review the evidence for lignocaine's modulation of the inflammatory response during major surgery and its specific effects on cancer recurrence. These indirect effects of local anesthetics in tumor development may stem from the reduction of neuroendocrine responses to the stress response elicited by major surgery and tissue damage, enhanced preservation of immune-competence, in addition to opioid-sparing effects of modulating tumor growth.

Key words: Lignocaine; Humans; Pharmacokinetics; Pharmacodynamics; Adult

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Core tip: Lignocaine is a widely used amide-type local anesthetic and Class 1b antiarrhythmic. In addition to its anesthetic and antiarrhythmic effects, lignocaine has

important analgesic, antinociceptive, immuno-modulating, and anti-inflammatory properties. Understanding the pharmacokinetics and pharmacodynamics of lignocaine will enable clinicians to safely prescribe lignocaine in a variety of clinical settings.

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INTRODUCTION

Lignocaine, commonly referred to as "Lidocaine", is an amide local anesthetic agent and a Class 1b antiarrhythmic. Lignocaine is an essential drug on World Health Organisation essential drug list, considered efficacious, safe and cost-effective for any health-care system. Despite its ubiquitous use in medicine and surgery, there are few detailed reviews of its pharmacokinetics and pharmacodynamics. We present a focused synopsis of lignocaine's pharmacological composition, indications for use and mechanisms of action, focusing on its anti-inflammatory, immuno-modulating and analgesia effects.

SEARCH

Search strategy

Information pertaining to the pharmacokinetics and pharmacodynamics of lignocaine was examined by performing a literature search of PubMed, Embase and MEDLINE (*via* Ovid), pharmacology textbooks and online sources. Only articles in the English language and human studies were considered. There were no date restrictions applied to the MEDLINE and Central searches. The last search update was in November 2014. The online databases were searched for the following terms: "lidocaine", "lignocaine", "humans", "pharmacokinetics", "pharmacodynamics", "adult". Specifically, clinical information relevant to the pharmacokinetics and pharmacodynamics of lignocaine was included in this literature review.

Search results

Using a combined search strategy, a total of 7311 articles were revealed. A further search confining the results to "humans" and "English language" revealed 216 information sources and titles, of which 81 references were examined for analysis. A detailed review was undertaken that included the screening of manuscript or abstract titles against the key search criterion. A total of 120 articles were included in this review.

BACKGROUND

Nils Löfgren, Bengt Lundqvist, and Holger Erdtman

were the three pioneers who were instrumental in the development of LL30, later developed into the solution known today as "lignocaine". Lignocaine, as detailed by Professor Wildsmith^[1-3], was first synthesized in 1942, approved for use in humans and launched in 1948 in Sweden, patented in United States in 1948, and launched in 1949 after Food and Drug Administration approval. Lidocaine and Xylocaine were the original proprietary and trade names chosen for LL30: Lidocaine because it is an acetanilide, and Xylocaine because m-xylylidide is the major reagent in its synthesis. In the United States the "e" was added to each, hence the names Xylocaine and Lignocaine. Lignocaine was the generic name in the United Kingdom from 1950 until Recommended International Non-proprietary Names were required by European law. The name was derived from the Greek "xylo", or the Latin, "ligno", both meaning "wood" originally^[4].

Interestingly, cardiologists discovered the antiarrhythmic effects of lignocaine accidentally during surgical procedures requiring the local anesthetic's use. Previous pharmacologic screening for novel cardiovascular drugs led to the discovery of anti-arrhythmic and local anesthetic activity of local anesthetic agents. In this context it was demonstrated that local anesthetic agents were effective in suppressing ventricular arrhythmias, a property common to all Class 1 antiarrhythmic agents.

PHARMACOLOGICAL COMPOSITION

Lignocaine, 2-diethylaminoaceto-2',6'-xylylidide ($C_{14}H_{22}N_2O$), is a amide local anesthetic and a Class 1b antiarrhythmic agent according to the Vaughn Williams classification^[5]. A Class 1b antiarrhythmic agent binds to open sodium channels during phase 0 of the action potential, therefore blocking many of the channels when the action potential peaks. Lignocaine is a stable, crystalline, colourless solid whose hydrochloride salt is water soluble^[6]. Solutions for injection are available with or without adrenaline. All lignocaine solutions should be protected from light and maintained at a room temperature of approximately 25 degree Celsius or 77 degree Fahrenheit^[7].

INDICATIONS

The indications of lignocaine include the requirement for local, neuraxial, regional or peripheral anesthesia by infiltration, block or topical application, or the prophylaxis or treatment of life-threatening ventricular arrhythmias. It has also been extensively used for chronic and neuropathic pain management, and more recently as an intravenous infusion for the management of postoperative analgesia and surgical recovery.

MECHANISM OF ACTION

Local anesthetic blockade

Similar to other local anesthetics, the mechanism of action of lignocaine for local or regional anesthesia is by

reversible blockade of nerve fibre impulse propagation^[7]. Some local anesthetic is removed by tissue binding and circulation when lignocaine is infiltrated near a nerve^[8]. The remaining anesthetic enters the nerve cells by diffusion through membranes. Lignocaine then binds to sodium channels, causing a conformational change that prevents the transient influx of sodium, therefore depolarisation^[9]. All potentially excitable membranes are affected, however sensory fibres are blocked preferentially because they are thinner, unmyelinated and more easily penetrated^[10]. Lignocaine's onset of action is rapid, and blockade, whilst dependent of dose given, concentration used, nerves blocked and status of the patient, may last for up to 5 h when administered as a peripheral nerve block^[7].

Antiarrhythmic effects

An important indication for lignocaine is prophylaxis or treatment of life-threatening ventricular arrhythmias. The mechanism of action of lignocaine for its antiarrhythmic action is by direct effect on mammalian Purkinje fibres. By decreasing the slope of phase 4 and changing the excitability threshold, lignocaine reduces automaticity^[9]. This results in a decrease of both the action potential length and the refractory period duration of the Purkinje fibres^[11]. The PR interval, QRS and QT durations are not commonly effected by lignocaine^[9]. There is no evidence of any important interactions between lignocaine and the autonomic nervous system, thus lignocaine has minimal effect on autonomic tone^[11].

Antinociceptive effects

The antinociceptive effects of lignocaine are thought to be attributable to the blockade of neuronal sodium channels and potassium currents^[12,13], and the blockade of presynaptic muscarinic and dopamine receptors^[14,15]. Local anesthetics have also been shown to block sodium and potassium currents centrally at a spinal cord level, specifically targeting the spinal dorsal horn neurons, in addition to their generally accepted peripheral nerve blockade^[13]. The mechanisms of these actions at the molecular level are complex and further characterization will be integral in our understanding of central neuraxial anesthesia.

Anti-inflammatory effects

Lignocaine has potential utility as a potent anti-inflammatory agent, although to date well-designed studies are lacking to substantiate its use in most clinical settings. A variety of lignocaine's actions on inflammatory cells have been described. Accumulating data suggests that lignocaine's powerful anti-inflammatory properties may be superior in many ways to nonsteroidal anti-inflammatory drugs and steroids, the traditional anti-inflammatory agents^[16,17]. However lignocaine is not approved for this specific indication and potential risks of toxicity (see below), particularly in unmonitored patients, may negate its beneficial anti-inflammatory effects. Unfortunately, the specific

molecular mechanisms involved in the migration of polymorphonuclear granulocytes and free radicals are not well known. Sodium channel blockade can be however excluded. Firstly, because *in vivo* local anesthetic solutions are active at lower concentrations than those required for blockade of the sodium channel, and secondly because sodium channels *in vitro* are often not even detectable in the cell lines that are being investigated^[17].

Whilst lignocaine's antinociceptive effects are thought to be secondary to the blockade of neuronal sodium channels and potassium currents^[12,13], and the blockade of presynaptic muscarinic and dopamine receptors^[14,15], its anti-inflammatory effects are complex and multifactorial. *In vitro* pre-incubation of human polymorphonuclear granulocytes or monocytes with varying concentrations of lignocaine have been reported to inhibit leukotriene B4 release^[18]. Both leukotriene B4 and prostaglandin E2 can induce edema; therefore the blockade of these cells may explain lignocaine's beneficial effects on tissue inflammation and edema prevention^[19]. In these studies, the treatment of the peritoneum with intravenous local anesthetic solutions resulted in a reduction of the amount of Evans blue-albumen extravasated from areas of inflammation, with histological examinations supporting these clinical findings. However, in the perioperative setting, development of edema is complex and multifactorial. To evaluate the effects of intravenous lignocaine on the development of edema in this setting, further clinical studies are required.

Lignocaine has been documented to block the release of interleukin-1 (IL-1), an inflammatory mediator acting on polymorphonuclear granulocytes, which in turn activates phagocytosis, respiratory burst, degranulation and chemotaxis^[16,17]. This reduction in the release of interleukins may also contribute to lignocaine's anti-inflammatory effects. *In vitro*, lignocaine, at concentrations of 0.2-20.0 mmol/L, has been shown to inhibit IL-1 production in peripheral blood mononuclear cells^[18]. *In vivo* studies have shown that at high micromolar concentrations, lignocaine can inhibit histamine release from human leukocytes, mast cells, and cultured basophils^[20]. Accordingly, the anti-inflammatory actions of lignocaine are thought to be attributable to lignocaine's direct effects on macrophage and polymorphonuclear granulocyte function, in addition to its inhibition of the release of several critical markers of the inflammation cascade.

Arachidonic acid (released from phospholipids) and the subsequent generation of bioactive eicosanoids have a critical function in the regulation of tissue preservation and the patho-physiological response to organ injury and ischemia^[21]. This critical sequence of biological processes is modified by lignocaine's action on the enzymes phospholipase A2, cyclooxygenase and lipoxygenase. Lignocaine interacts in a dual manner with phospholipase A2; causing inhibition of its activity at high concentrations and stimulating activity at lower concentrations^[22,23]. Lignocaine has been shown to inhibit

spontaneous prostaglandin biosynthesis, in early *in vitro* studies^[24,25]. Lignocaine administration significantly inhibited prostanoid release and biosynthesis from human gastric mucosa in response to experimental damage^[26-28]. In dogs with cardiac arrhythmias the release of prostaglandin was seen to be inhibited during systemic administration of lignocaine^[29]. Lastly, topical lignocaine has been shown to inhibit prostaglandin release when used clinically for the treatment of burns in an animal model^[30], confirming other studies that report reduced prostaglandin release from gastric mucosa as a result of lignocaine intervention^[26]. These inhibitory effects on prostaglandin release may explain some of the powerful antinociceptive and anti-inflammatory effects of intravenous lignocaine described in patients with severe burns^[31,32].

Numerous *in vivo* and *in vitro* studies demonstrate the effects that lignocaine have on thromboxane B2 release^[26,28,33]. Lignocaine has an inhibitory effect on thromboxane induced platelet aggregation, which may contribute to reduced incidence of venous thrombosis^[34,35]. In addition, early studies demonstrate that lignocaine at low concentrations can powerfully inhibit the release of histamine from activated mast cells^[36,37]. Lignocaine also has important effects on oxygen free radical production. The inhibition of free oxygen radical formation (such as superoxide anions) by lignocaine has been eloquently demonstrated in clinical trials^[38,39]. The mechanism of action of this direct scavenging effect is due to lignocaine's interaction with protein and phospholipid membranes, the interference with mitochondrial radical formation^[40], and the prevention of free radical production^[41].

Antibacterial activity

Lignocaine has also been shown to possess antibacterial activity^[16]. The potent effects of lignocaine on antimicrobial activity are related to lignocaine's concentration and pharmacological structure. Structure is of lesser importance as both amide and ester type local anaesthetics can inhibit bacteria in high enough concentrations^[42]. Lignocaine has been shown to have important inhibitory actions on various strains of bacterium, including important Gram-positive cocci such as *Staphylococcus aureus* and *Streptococcus pneumoniae*, and Gram-negative bacteria such as *Haemophilus influenza* and *Pseudomonas aeruginosa*^[16,43-46]. Lignocaine's anti-bactericidal effects are poorly understood, however complex interactions between the local anesthetic solutions and the bacterial wall^[47] or with macromolecules at the surface of the bacterium^[44] have been implicated. Functional changes, which include the alterations in the membrane proteins and reductions of membrane fluidity that may be induced by electrostatic interactions between anionic membrane components and cationic local anesthetics, have been implicated mechanisms^[45,48,49]. Consequently, various cell and membrane functions such as the DNA binding properties of the cell and membrane-bound ATPase activity may be inhibited^[50,51]. The immunomodulating and anti-inflammatory effects of lignocaine

are summarized in Table 1.

PHARMACOKINETICS

History

One of the earliest studies evaluating the pharmacokinetic properties of lignocaine was by Friden^[52] in 1965. It was observed that lignocaine displayed a rapid onset of action, but of very short duration (between 10-20 min) after the intravenous administration of either 50 or 100 mg boluses doses. In the same year, Beckett *et al*^[53,54] reported that lignocaine had a half-life of approximately 10 to 20 min one hour after the administration of an intravenous bolus. Two years later, Gianelly *et al*^[55] reported that patients with occlusive coronary artery disease who were administered a continuous intravenous lignocaine infusion, without an initial loading dose, achieved acceptable plateau plasma concentrations within a 30 to 60 min period, suggestive of a 10 to 20 min half-life. Rowland *et al*^[56] studied the ability of intravenous lignocaine to control ventricular arrhythmias in order to understand its disposition kinetics, and thus was able to establish safe and effective dosage regimens. Rowland reported a rapid early fall in lignocaine plasma levels after the administration a 50 mg bolus dose. The mean half-life was 7 min. However, they also reported a significantly slower phase (a mean half-life of 108 min), related to the drug's elimination. After a 4-h lignocaine infusion, the average elimination time of 108 min was similar to the elimination half-life of 96 to 108 min reported by Beckett *et al*^[54]. Rowland found that lignocaine was primarily eliminated by metabolism, since urine collected 24 h after the bolus contained less than 4% of unchanged lignocaine. The range of elimination half-life was relatively narrow (73 to 133 min) among the subjects evaluated^[56]. Beckett *et al*^[54] also put forward that de-ethylation of lignocaine to monoethylglycine xylidide was the drug's primary metabolic pathway.

Absorption

Lignocaine's pharmacokinetics have been studied in a variety of clinical models, which include healthy volunteers, subjects with chronic pain syndromes, and patients with cardiac failure^[56-59]. The speed of onset of lignocaine is 1 to 5 min after local infiltration, and 5 to 15 min after peripheral nerve blockade. Lignocaine's absorption is dependent upon the total dose administered, the route by which it is delivered, and blood supply to the site of injection^[7]. In 1972, Scott *et al*^[57] found that upon injection of lignocaine 400 mg, serum levels were highest following infiltration of vaginal mucosa and lowest following subcutaneous abdominal infiltration. Major nerve blocks and epidurals result in intermediate peak plasma levels. Irrespective of the administration site, peak serum levels occurred 20 to 30 min following injection. The addition of adrenalin (1:200000) to the local anesthetic solution reduced peak levels and delayed the rate of absorption.

Table 1 Immuno-modulating and anti-inflammatory effects of lignocaine

Effects	Immuno-modulating and inflammatory actions
Anti-nociceptive and analgesic effects ^[12,16,17,34,101]	Interaction with nociceptive pathways Blockade of neuronal sodium channels Blockade of potassium currents Muscarinic receptor antagonist Blockade of dopamine receptors Glycine inhibitor Reduction in excitatory amino acids Reduction in thromboxane Release of endogenous opioid peptides Reduction in neurokinins Release of ATP-adenosine triphosphate
Wound healing effects ^[19,38, 39,102-104]	Retardation by reduction of mucopolysaccharide and collagen synthesis Reduction in recruitment and metabolic response of Inhibition of thrombus formation Antithrombotic activity Inhibition of platelet aggregation <i>via</i> blockade of calcium influx Mobilization of intracellular calcium stores Inhibition of oxygen free radical production Inhibition of inflammatory cytokines Inhibition of vascular permeability Inhibition of edema formation
Inhibition of immune cell mediators from monocytes ^[18,105]	Inhibition of interleukin 1 α Inhibition of interleukin β Inhibition of interleukin 8 Inhibition of tumor necrosis factor
Inhibition of immune cell mediators from neutrophils ^[18,24-26,28,33,102,106]	Inhibition of prostaglandins Inhibition of thromboxanes Inhibition of leukotrienes Inhibition of lysosomal enzymes Inhibition of free radicals
Inhibition of immune cell mediators from mast cells ^[36]	Inhibition of histamine release
Anti-bactericidal effects ^[16-18,43-46,107]	Inhibitory actions on <i>Pseudomonas aeruginosa</i> Inhibitory actions on <i>Escherichia coli</i> Inhibitory actions on <i>Staphylococcus aureus</i> Inhibitory actions on <i>Haemophilus influenza</i> Inhibitory actions on <i>Mycobacterium tuberculosis</i>
Anti-viral and anti-fungal effects ^[16,17,108]	Inhibitory actions on Herpes simplex virus Inhibitory actions on <i>Candida albicans</i>
Clinical effects in inflammation-related disease ^[109-117]	Protective effects in acute lung injury Protective effects in septic shock Protective effects in cardiac ischemia Beneficial effects in ischemia-reperfusion injuries Protective effects in interstitial cystitis Protective effects in ulcerative colitis Protective effects in ulcerative proctitis Protective effects in burn injuries Accelerated return of bowel function in major surgery Blockade of airway hyperactivity in asthma Treatment of intractable hiccups Beneficial effects in traumatic brain injury

Protein binding

When lignocaine is given intravenously to normal subjects, the volume of distribution is 0.6-4.5 L/kg^[60]. The plasma binding of lignocaine is inversely proportional to the drug concentration. It is 60% to 80% protein-bound at concentrations of between 1 and 4 mcg/mL^[7]. Binding fraction also depends on the plasma levels of the acute phase reactant alpha-1-glycoprotein^[9]. Lignocaine has been shown to cross the placenta and blood-brain barrier by simple passive diffusion. Given that proportion of maternal protein binding is greater than that foetal protein binding, the maternal total plasma concentration will be

higher, however free lignocaine concentrations will remain the similar in both mother and fetus^[7]. Fetal lignocaine concentration may be increased by transmembrane pH gradients, such as fetal acidosis, and associated ion trapping^[9]. Lignocaine may exist in ionised or unionised form depending on the pH of the environment. As a weak basic drug, lignocaine tends to be more unionised and able to cross cell membranes in basic media^[10]. In fetal acidosis lignocaine crosses the placenta in unionised form, becomes ionised given the acidic environment of the fetal circulation and becomes "trapped", thus increasing fetal lignocaine concentration.

Metabolism and elimination

Lignocaine is dealkylated in the liver by the cytochrome P450 system forming numerous metabolites. Monoethylglycine xylidide and glycine xylidide are the key active metabolites, both of which have reduced potency but have comparable pharmacologic activity to lignocaine^[9]. The only reported metabolite of lignocaine found to be carcinogenic in a rat model is 2, 6-xylidine^[61]. Its pharmacologic activity is unknown. After the intravenous administration of lignocaine, monoethylglycine xylidide and glycine xylidide concentrations equate to approximate 11% to 36%, and 5% to 11%, respectively, of the total plasma lignocaine concentrations^[62].

Hepatic blood flow appears to be a limiting factor in lignocaine's metabolism. The rate of metabolism is slower reduced in patients with congestive cardiac failure, chronic liver disease and hepatic insufficiency, and after acute myocardial infarction^[63]. Lignocaine and its metabolites are predominantly renally excreted. Less than 10% of lignocaine is excreted without being metabolised^[53,64].

The total body plasma clearance of lignocaine in healthy volunteers has been reported to be approximately 10-20 mL/min per kilogram^[62]. The majority of lignocaine elimination occurs in the liver, and since the total body plasma clearance of lignocaine is about 800 mL/min and hepatic blood flow is about 1.38 L/min^[65,66], up to 60% of an oral dose is metabolised before entry into the systemic circulation. This accounts for the low plasma lignocaine concentrations observed following a the oral administration of 500 mg lignocaine hydrochloride^[67].

Elimination half-life is defined as the rate at which a local anesthetic is removed from the blood. Therefore, the time necessary for 50% reduction in lignocaine blood level is one half-life; two half-lives equates to a 75% reduction, three half-lives to an 87.5% reduction, four half-lives to a 94% reduction, five half-lives to a 97% reduction and six half-lives to a 98.5% reduction. The half-life of lignocaine has been shown to be approximately 100 min following either an infusion lasting less than 12 h or a bolus injection. In this setting lignocaine demonstrates linear pharmacokinetics^[56]. However, following an intravenous infusion greater than 12 h, lignocaine exhibits nonlinear, or time-dependent pharmacokinetics. Patients who received prolonged lignocaine infusions following a myocardial infarction, were found to have lignocaine concentrations that continued to rise for approximately 48 h, with the half-life extending up to 4 h^[68].

Maximum doses

The maximum doses for lignocaine is based primarily on manufacturer recommendations and animal studies. Animal studies are frequently used to calculate a drug's therapeutic index. This is derived or calculated from the median toxic dose and median effective dose ratio. It is important to note that the complexities found within human populations are not replicated in animal studies. General recommendations based on site of administration, use of vasoconstrictors, and patient factors such as age,

hepatic, renal, cardiac diseases, and pregnancy have been attempted. However due to the lack of quality data, specific recommendations regarding generic maximum doses cannot be definitively made. Furthermore, recommended doses from manufacturers vary between countries. The intrathecal ED50 of lignocaine for a motor block (defined as the development any motor block in either leg within a five-minute-period) has been shown to be approximately 13.7 mg (95%CI: 13.1-14.4 mg)^[69]. According to most manufacturers recommendations, the maximum dose of lignocaine for infiltration and regional nerve block techniques is 300 mg (approximately 4.5 mg/kg) or 500 mg (7 mg/kg) with 1:200000 adrenalin (based on a 70 kg patient). However, for neuropathic pain treatment in human subjects, the ED50 and ED90 of lignocaine has been reported as 372 mg and 416 mg respectively, although the resulting plasma levels were not evaluated^[70]. Generally, however, from animal data, the ED50 of intravenous lignocaine for CNS toxicity is approximately 19.5 mg/kg (95%CI: 17.7-21.3 mg/kg) and 21 mg/kg (95%CI: 19.0-23.4 mg/kg) for electrocardiographic evidence of cardiac toxicity^[71].

Infusion kinetics

As discussed above, plasma concentrations of lignocaine differ widely, depending on the total dose administered, the method and route of delivery, and the vascularity of the site where it is injected. Plasma levels of between 0.5 and 5.0 mcg/mL (2-20 µmol/L) are required for many of reported clinical effects after both intravenous or subcutaneous administration^[72]. A infusion of intravenous lignocaine administered at a dose of 2 to 4 mg/min results in plasma levels of between 1 and 3 mcg/mL after 150 min^[73]. After 15 min of the same infusion, a 2 mg/kg intravenous bolus of lignocaine leads to peak plasma levels of 1.5 to 1.9 mcg/mL^[74]. Subcutaneous lignocaine infusions may be advantageous over intravenous drug delivery methods because plasma levels are more stable, and therapeutic benefit may be achieved whilst avoiding the toxic effects of peaks and troughs associated with episodic drug administration or a prolonged continuous intravenous infusion^[75].

The aim of an intravenous lignocaine infusion is to achieve a therapeutic steady-state concentration while minimising systemic toxicity. The pharmacokinetic implication of using a lignocaine bolus dose prior to a continuous infusion is important. This technique increases plasma concentrations allowing therapeutic ranges to be achieved more quickly. Hsu *et al.*^[59] evaluated the lignocaine's pharmacokinetics during 2-d infusion in patients who underwent cardiac surgery. These researchers concluded that lignocaine plasma concentrations are more accurately described using a two-compartment pharmacokinetic model, and advocated that lignocaine infusions should be dosed by body weight, with the infusion dose reduced after 24 h to avoid toxicity. The authors advocated that the ideal lignocaine continuous infusion protocol is a bolus/loading dose of 1 mg/kg, then an infusion at 50 mcg/kg per minute

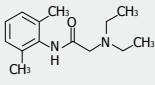
Systematic name	2-(diethylamino)-N-(2, 6-dimethylphenyl)acetamide (International Union of Pure and Applied Chemistry nomenclature)
Class	Amide
Vaughan Williams classification	Class IB antiarrhythmic agent
Molecular formula	C ₁₄ H ₂₂ N ₂ O, HCl, H ₂ O
Structural formula	
pKa	7.86
Molecular mass	234.34 g/mol
Pregnancy Class	Australia: Class A United States: Class B
Trade names	Xylocaine
Preparation	Clear and colorless Sterile and preservative-free Isotonic
Mechanism of action and effects	Myocardial depolarization: decreases Myocardial automaticity: decreases Ventricular excitability during diastole: decreases (by a direct action on Purkinje network) Autonomic system: no effect Contractility: no effect Blood pressure: no effect Atrioventricular conduction: no effect Absolute refractory period: no effect ^[9,118]
Distribution	Intravenous route: volume of distribution: 0.6 to 4.5 L/kg Transdermal route: lignocaine 5% patch ^[119] Approximately 70% bound alpha-1 glycoprotein Absorption: depends on duration of application and the surface area When 2100 mg (3 × lignocaine 5% patches) applied over intact skin for 12 h: dose absorbed: 64 ± 32 mg; C _{max} : 0.13 ± 0.06 mcg/mL; T _{max} : 11 h
Protein binding	60% to 80% protein bound
Biotransformation	90% hepatic Metabolites: monoethylglycinexylidide and glycinexylidide (less potent toxic effects ^[120]) Following intravenous dosing, monoethylglycinexylidide and glycinexylidide in plasma range from 11% to 36%, and from 5% to 11% of lignocaine concentrations
Half-life	Transdermal application (lignocaine 5% patch): negligible metabolite concentrations ^[119] 60 to 120 min Dose-dependent Biphasic distribution phase (7 to 9 min after intravenous loading dose) During prolonged (approximately 24 h) intravenous infusions: > 3 h Time to steady-state plasma concentration Limited data regarding subcutaneous infusion.
Therapeutic plasma concentration	1.5 to 5 mcg/mL > 5 mcg/mL: toxic effects described
Duration of action	Intravenous route: 10 to 20 min
Elimination	Renal excretion: 10% unchanged Not reliably removable by dialysis Systemic clearance: 10-20 mL/min per kilogram

Figure 1 Summary of the pharmacokinetics of lignocaine.

infusion for the first hour, then 25 mcg/kg per minute for the second hour, then 12 mcg/kg per minute for the following 22 h, and finally 10 mcg/kg per minute for the remaining 24 h. The pharmacokinetics of lignocaine are summarised in Figure 1.

ADVERSE REACTIONS AND TOXICITY

Generally, lignocaine toxicity can result when either the correct dose of lignocaine is inadvertently administered or delivered *via* the intravascular route, or when doses, even if given by the correct route, are excessive^[76]. There are a number of factors that influence or directly affect the severity of lignocaine toxicity. These include the vascularity of the site of injection, speed of the

injection, acid base status, and underlying hepatic or renal impairment. Lignocaine is metabolised by the liver, therefore severe hepatic dysfunction will significantly increase the both the risk and severity of toxicity^[9]. In addition, given that lignocaine is protein bound, severe hypoalbuminemia may also predispose to toxicity risk^[9]. Acidosis increases the risk of toxicity because due to lignocaine dissociating from plasma proteins^[7]. Lignocaine's pharmacokinetics and antiarrhythmic effects may be potentiated or altered by beta-blockers, ciprofloxacin, cimetidine, clonidine, and phenytoin^[6]. Beta-blockers such as propranolol and metoprolol can reduce lignocaine's metabolism, whilst cimetidine and amiodarone reduce its clearance. Lignocaine's interactions with phenytoin and ciprofloxacin are thro-

Table 2 Adverse effects of lignocaine toxicity

System	Effects
CNS	Biphasic effects Early: CNS excitation with seizures Late: CNS depression, termination of convulsions, reduced level of consciousness, leading to respiratory depression and/or arrest Mechanism: Local inhibition of inhibitory CNS pathways (CNS stimulation), then inhibition of inhibitory and excitatory pathways (CNS inhibition) Symptoms and signs Anxiety Dizziness or light headed Confusion Euphoria Tinnitus Blurring of vision or diplopia Nausea and vomiting Twitching and tremors Seizures with reduced consciousness
Cardiovascular	General effects Conduction block of neural impulses Prevention of passage of sodium through sodium channels Stabilization of excitable membranes Prevention of the initiation and transmission of nerve impulses Attenuation of phase 4 diastolic depolarization Reduction in automaticity Reduction in absolute refractory period Increase in the ratio of effective refractory period: action potential duration Decrease in action potential duration Ventricular fibrillation threshold: raised Higher serum concentrations Blockage of sodium channels Depression of rate of depolarization during phase 0 of the cardiac action potential Re-entrant arrhythmias Suppression of conduction through the sinus and atrioventricular nodes Symptoms and signs Bradycardia Hypotension Cardiovascular depression Cardiac arrest
Respiratory	Symptoms and signs Tachypnea Respiratory depression Respiratory arrest
Allergic reactions	Extremely rare Symptoms and signs Cutaneous lesions: urticaria, edema Anaphylaxis

CNS: Central nervous system.

ugh their effects on the liver's cytochrome system.

Adverse effects of lignocaine and other amide local anesthetic agents are similar in nature^[7]. These are summarised in Table 2. Low plasma concentrations of lignocaine (less than 5 mcg/mL) are used in the clinical setting to suppress cardiac ventricular arrhythmias and status seizures, but seizure activity may be induced at higher concentrations. Seizures result from selective depression of central nervous system inhibitory tracts. As plasma lignocaine levels increase, all pathways are suppressed, resulting in respiratory arrest, cardiovascular collapse and coma^[76]. Lignocaine toxicity may commence at concentrations greater than 5 mcg/mL, although convulsive seizures most often occur at concentrations greater than 10 mcg/mL.

The adverse systemic effects of lignocaine toxicity are summarised in Table 2.

CARCINOGENICITY AND MUTAGENICITY

Toxicity studies of 2, 6-xylidine, a lignocaine metabolite, have documented the development of nasal cavity adenomas and carcinomas in rats^[6,77]. Nasal tumors were reported with daily doses of 900 mg/m² (150 mg/kg) 2, 6-xylidine, but not with low dose (15 mg/kg) or control animals.

LIGNOCAINE AND CANCER OCCURRENCE

Whilst clear *in vitro* and *in vivo* evidence exists for

the anti-inflammatory properties of lignocaine and its modulation of the inflammatory response during major surgery, the question of whether lignocaine can influence cancer outcomes following cancer surgery is a debatable topic. The indirect effects of local anesthetics in tumor development may stem from the reduction of neuroendocrine responses to the stress response elicited by major surgery and tissue damage, enhanced preservation of immune-competence, in addition to opioid-sparing effects of modulating tumor growth^[78]. The plasma concentrations of local anesthetic agents, even when administered as part of a regional anesthetic technique or from infiltration around neoplastic tissue, are frequently in the millimolar range. These concentrations have been shown to have cytotoxic properties *in vitro*^[79]. Other actions of local anesthetic agents on cancer cells may be through direct sensitisation of chemotherapy^[80]. Protection against tumor cell invasion and suppression of tumor proliferation has been found with the infiltration of local anesthetic agents^[79]. Furthermore, local anesthetics can modulate tumor biology^[81], and lignocaine has been suggested to be a potent demethylating agent with cancer treatment potential^[81].

A retrospective study in patients with breast cancer who received paravertebral anesthesia with local anesthetic solutions during mastectomy showed considerable benefit with regard to metastatic spread^[82]. These promising finding could not however be replicated in abdominal cancer patients^[83-85]. When epidural anesthesia with a local anesthetic solution was utilized as part of a standardised anesthetic, Gupta *et al*^[86] reported a reduction in all-cause mortality after resection of rectal cancer; but not after resection of cancer of the colon. Intraoperative epidural analgesia has been linked to increased three and five-year survivals, and increased recurrence-free interval in patients with from ovarian malignancy^[87]. Patients with cervical cancer showed no significant survival effect associated with epidural anesthesia during brachytherapy^[88], however the use of epidural anesthesia in patients hepatocellular carcinoma undergoing percutaneous radiofrequency ablation was not associated with a significant decrease in survival^[89]. The equivocal results of these small observational studies indicate that there is distinct biological heterogeneity of the cancers being investigated, or that regional anesthesia with local anesthesia has no effect.

Multiple factors can hamper perioperative immune competence. Surgery itself can result in significant cytokine and neuroendocrine responses, which can impair several immune functions and attenuate the adverse effects of natural killer cell function. Natural killer cells play an important role in preventing tumor spread^[90]. Lignocaine may reduce the stress response to surgery; hence enhance natural killer cell response^[91]. Perioperative immune competence may also be influenced by opioids, which have been shown to suppress multiple immune functions, including both humoral and cellular immune function^[92-95]. If lignocaine is used as part of a patient's anesthesia regime, less opioid may be required, resulting in

less immune compromise. Appropriate analgesia may also reduce metastatic spread of cancer through preservation of natural killer cell function^[96]. Finally, morphine is pro-angiogenic and may promote the release of factors that enhance tumor growth^[97]. Lignocaine, therefore, may help to maintain immune function in the perioperative period by minimising the need for postoperative opioids and reducing general anesthesia requirements.

The use of lignocaine in patients with prostate cancer remains equivocal^[98-100]. Wuethrich *et al*^[98] performed a retrospective study examining prostate cancer-related outcomes and the effects of the anesthesia technique in patients undergoing open radical retropubic prostatectomy. The authors reported a reduction in the risk of clinical cancer progression in a cohort of patients receiving epidural analgesia. However, there were no statistical differences in overall survival, cancer-specific survival, and biochemical recurrence-free survival. Similarly Biki *et al*^[99] investigated recurrence of cancer of the prostate in men who underwent open prostatectomy under a general anesthetic with postoperative opioid for analgesia, or general anesthetic with epidural anesthesia/analgesia. They observed a significantly reduced risk of biochemical cancer recurrence when open prostatectomy surgery was performed with general anesthesia in combination with epidural analgesia. In contrast to these two retrospective analyses, more recently Tsui *et al*^[100] performed an observational study investigating disease free-survival in patients undergoing open radical retropubic radical prostatectomy. There was no difference in clinically evident or biochemical occurrence of prostate cancer when comparing epidural and control groups. In summary, the question of whether lignocaine can modulate cancer recurrence has not yet been answered unequivocally. It is probable that only specific cancer types may be affected by the tumor-suppressive effects of lignocaine^[81].

CONCLUSION

Lignocaine is a unique amide local anesthetic and a Class 1b antiarrhythmic agent with ubiquitous use in medicine and surgery. Its use as a local and regional anesthetic agent and for the treatment and prophylaxis of life-threatening ventricular arrhythmias is well known. However, accumulating data suggests that in addition to its sodium channels properties, lignocaine possesses a wide range of *in vitro* and *in vivo* immunomodulating, anti-inflammatory and anti-cancer effects that show immense promise in a variety of other clinical applications. These effects are often exerted at lower concentrations than needed for sodium channel blockade, and result from lignocaine's complex interactions with other cellular systems^[16,17,34].

The clinical applications of utilising lignocaine in the pharmacological armament for treating inflammatory conditions such as inflammatory bowel disease, acute lung injury, sepsis, burns, peritonitis, infections, myocardial infarction and reperfusion injury, and cancer recurrence

continue to be areas of intense clinical research. In the context of anesthesia, patients where perioperative epidural analgesia is contraindicated, intravenous infusion of lignocaine could also be considered as an alternative intervention to modulate the postoperative inflammatory responses^[17,34]. Lignocaine may be an important pharmacological agent in the influence and modulation of these responses in the practice of modern perioperative medicine. Finally, defining the roles of lignocaine in these clinical settings are necessary to obtain a more detailed appreciation of the complex mechanisms of lignocaine's clinical utility. Maximizing lignocaine's clinical benefits with its risks of toxicity and harm must be of paramount importance at all times. Well-designed large scale clinical trials are awaited to assess whether the immuno-modulating, anti-inflammatory, analgesic, and anticancer effects of lignocaine observed in both *in vitro* and *in vivo* experiments and small clinical trials can be safely applied to routine clinical practice^[17].

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Observational Study

Transthoracic echocardiography assists appropriate pulmonary artery catheter placement: An observational study

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment. All study data was de-identified for analysis.

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Abstract

AIM: To investigate the utility of transthoracic echocardiography in confirming appropriate pulmonary artery catheter (PAC) placement.

METHODS: Three commonly used transthoracic echocardiography (TTE) views were used to confirm PAC position in 103 patients undergoing elective cardiac surgery - the parasternal short axis right ventricular inflow-outflow view; the subcostal short axis right ventricular inflow-outflow view; and the parasternal short axis ascending aortic view. All PACs were inserted by the managing anesthesiologist under pressure waveform guidance alone, who was blinded to all sonographic information. A sonographer blinded to all pressure waveform information confirmed visualisation of an "empty" PA before PAC insertion, and visualisation of the PAC balloon in the main PA (MPA) or right PA (RPA) after attempts at placement were complete. Agreement, sensitivity and specificity of TTE in confirming appropriate PAC placement was compared against pressure waveform

guidance as the “gold standard”. The successful view used was compared against patients’ anthropomorphic indices, presence of lung hyperinflation, and insertion of PAC during positive pressure ventilation. Agreement between TTE and pressure waveform guidance was analysed using Cohen’s Kappa statistic. The relative proportion of total RPA seen by subcostal *vs* parasternal TTE views was also compared with a further 20 patients’ computed tomography (CT) pulmonary angiograms (CTPA), to determine efficacy in detection of distal RPA PAC placement.

RESULTS: Appropriate positioning of the PAC balloon, and its to-and-fro movement consistent with a non-wedged state, within the MPA or RPA was confirmed by TTE in 98 of the 103 patients [sensitivity 95% (95%CI: 89%-98%)], and absence of the PAC balloon before insertion correctly established in 100 patients [specificity 97% (92%-99%)]. This was in very good agreement with pressure waveform guidance [Cohen’s Kappa 0.92, (0.87-0.98)]. The subcostal view was the best view to visualise the PAC tip when it was placed in the right pulmonary artery (OR 70, $P < 0.0001$), was more successful in patients with COAD (OR 9.5, $P = 0.001$), and visualized 61% (*vs* 44% by parasternal views, $P < 0.001$) of mean RPA lengths compared with CTPA; however the parasternal views were more successful in patients with higher body mass indexes (OR 0.78 for success with subcostal views, $P < 0.001$). There was a trend towards insertion during intermittent positive pressure ventilation favoring visualisation by subcostal views (OR 3.9, $P = 0.08$). The subcostal view visualized a greater length of the RPA than parasternal views (3.9 cm *vs* 2.9 cm, $P < 0.0001$). PACs were more often placed in the MPA than RPA (80 *vs* 18 patients). Three patient’s pulmonary arteries were not visible by any TTE view; in a further 2 patients, despite pre-insertion visualisation of their pulmonary arteries, the PAC balloon was not visible by any view with TTE where correct placement by pressure waveform was unequivocal.

CONCLUSION: TTE can assist appropriate PAC placement by visualization of an unwedged PAC balloon in the PA.

Key words: Transthoracic echocardiography; Pulmonary artery catheter; Main pulmonary artery; Right pulmonary artery; Pulmonary artery rupture; Intensive care unit

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Core tip: Transthoracic echocardiography (TTE) is an efficacious adjunct to pressure waveform guidance for guiding appropriate pulmonary artery catheter (PAC) placement. With the required equipment and expertise, TTE is a rapid and safe tool for confirming whether the PAC is placed too far (the PAC balloon seen beyond the proximal RPA) or not far enough (the body of the PAC seen in the right ventricle but the PAC balloon not seen in the main PA or right PA). This application may assist

in reducing complications related to PA rupture or PAC induced arrhythmias.

Tan CO, Weinberg L, Story DA, McNicol L. Transthoracic echocardiography assists appropriate pulmonary artery catheter placement: An observational study. *World J Anesthesiol* 2015; 4(2): 30-38 Available from: URL: <http://www.wjg-net.com/2218-6182/full/v4/i2/30.htm> DOI: <http://dx.doi.org/10.5313/wja.v4.i2.30>

INTRODUCTION

Pulmonary artery catheters (PACs) are variably used in critical care^[1] and cardiac anesthesiology^[2]. In proficient hands, complication rates are low^[3] but include a 1:650-1:4300 risk of death secondary to pulmonary arterial rupture^[4], with inappropriate balloon inflation or catheter advancement beyond the main pulmonary artery (MPA) as presumed contributory factors. Conversely, failure to advance the PAC beyond the right ventricle (RV) may result in endocardial irritation and arrhythmias; these complications may occur not only during insertion but also subsequently due to retrograde catheter migration. Pressure waveform analysis, X-ray guidance, and transesophageal echocardiography (TEE)^[5] have all been used to confirm placement of the tip of the catheter in the PA. Pressure waveform analysis is the most commonly used technique^[6] because of its accuracy and accessibility. Pressure waveform guided placement is usually straightforward, however fast or irregular heart rates, low pulmonary pressures, or gross waveform distortion by widely varying intrathoracic pressures may make pressure waveforms difficult to interpret. This situation occurs more frequently in the ICU setting where patients requiring PACs often display severely abnormal haemodynamic states, at times also with tachyarrhythmias.

TEE is an ultrasound modality that offers advantages over transthoracic echocardiography (TTE) but is semi-invasive, and its use is difficult to justify for PAC placement as a primary indication. Portable X-ray offers ideal information on PAC position but may not be immediately available during PAC insertion and also utilises ionising radiation. TTE however is non-invasive, utilises no ionising radiation, and is usually immediately available in most critical care settings. It has also been used to successfully visualise PACs in a small sample in a non-surgical scenario^[7]. We aimed to explore how TTE could serve as an adjunct to pressure waveform guidance for confirmation of PAC placement in the MPA or RPA, as well as how TTE could assist in ideal final positioning of the PAC tip in the MPA to assist prevention of hazardous distal or proximal PAC migration.

We hypothesized that: (1) use of three basic TTE views could reliably confirm PAC placement in the MPA or RPA when pressure waveform analysis is used as the primary technique; (2) particular TTE views

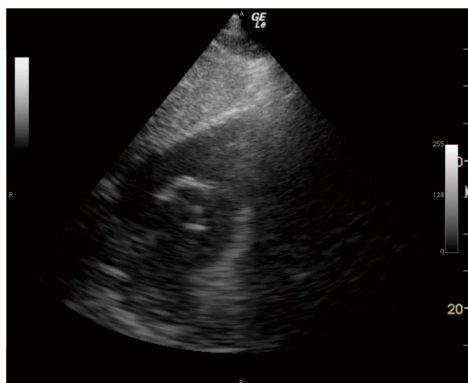


Figure 1 Subcostal right ventricular inflow outflow view confirming absence of the pulmonary artery catheter from the main pulmonary artery and right pulmonary artery prior to pulmonary artery catheter insertion. Cardiac chamber identification labels have been omitted for clarity.

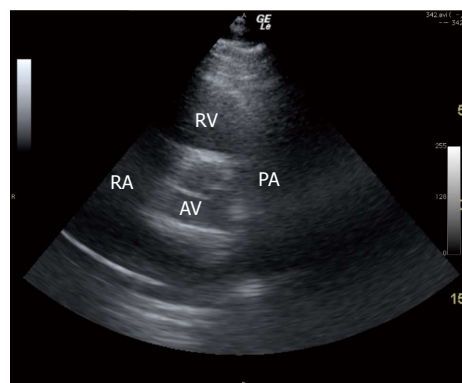


Figure 3 Parasternal right ventricular inflow outflow view, sonogram. RA: Right atrium; RV: Right ventricle; PA: Pulmonary artery; AV: Aortic valve.

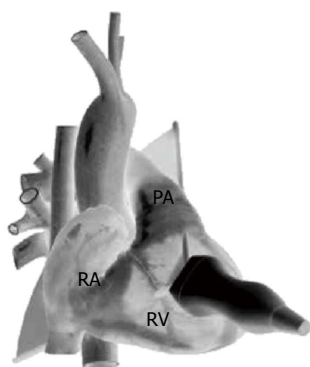


Figure 2 Parasternal right ventricular inflow outflow view, anterior projection. Schematic diagram demonstrating transthoracic echocardiogram probe position and alignment of scanning plane. Reproduced in part with permission from Toronto General Hospital, Perioperative Interactive Education Virtual TTE (<http://pie.med.utoronto.ca/TTE>). TTE: Transthoracic echocardiogram; RA: Right atrium; RV: Right ventricle; PA: Pulmonary artery.

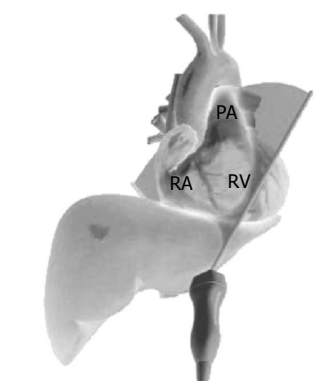


Figure 4 Subcostal right ventricular inflow outflow view, antero-inferior projection. Schematic diagram demonstrating TTE probe position and alignment of scanning plane. Reproduced in part with permission from Toronto General Hospital, Perioperative Interactive Education Virtual TTE (<http://pie.med.utoronto.ca/TTE>). TTE: Transthoracic echocardiogram; RA: Right atrium; RV: Right ventricle; PA: Pulmonary artery.

could visualise a greater proportion the distal RPA as determined by CTPA, assisting confirmation of ideal PAC placement proximal to the RPA 1st division; and (3) that other factors including: chronic obstructive airways disease (COAD), body mass index (BMI), concomitant intermittent positive pressure ventilation (IPPV) or final PAC position influenced which echocardiographic view used to successfully visualise the MPA, RPA and PAC.

MATERIALS AND METHODS

This study was approved by the Austin Health Human Research and Ethics Committee (H2012/04776) and was carried out in compliance with the Helsinki Declaration on research involving human participants. Written informed consent was obtained from all participants. We recruited 103 cardiac surgery patients who were planned for PAC insertion as part of their anaesthesia care. The PACs inserted were the Swan-Ganz VIP+ (Edwards Lifesciences, CA, United States). Information on patients BMI and previous diagnosis

of COAD or asthma were obtained preoperatively. The study protocol was as follows.

All PACs were inserted preoperatively by observation of the pressure waveform during advancement of the catheter.

A single anesthesiologist experienced in TTE, who was not the patient's treating anesthesiologist at the time, performed all ultrasound examinations and was blinded to all pressure waveform information obtained during PAC insertion.

Three commonly used TTE views were used in the following sequential order to visualize the MPA and right pulmonary artery (RPA) prior to PAC placement.

The MPA and RPA were visualised and confirmed as "empty" of the catheter before PAC insertion to establish the specificity of the technique (Figure 1).

The 3 TTE views used were: (1) the parasternal short axis right ventricular inflow-outflow (PSRVIO) view (Figures 2 and 3); (2) the subcostal short axis right ventricular inflow-outflow (SCRVIO) view (Figures 4 and 5); and (3) the parasternal short axis ascending aortic (PSAscAo) view (Figures 6 and 7).

These particular views were selected as they offer

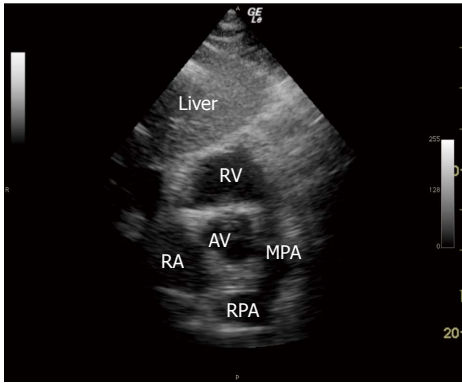


Figure 5 Subcostal right ventricular inflow outflow view, sonogram. RA: Right atrium; RV: Right ventricle; MPA: Main pulmonary artery; RPA: Right pulmonary artery; AV: Aortic valve.

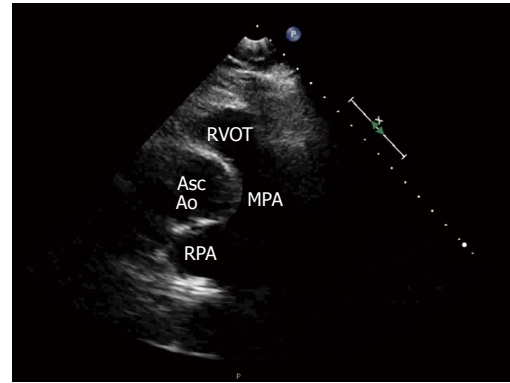


Figure 7 Parasternal ascending aorta short axis view, sonogram. RVOT: Right ventricular outflow tract; AscAo: Ascending aorta; MPA: Main pulmonary artery; RPA: Right pulmonary artery.

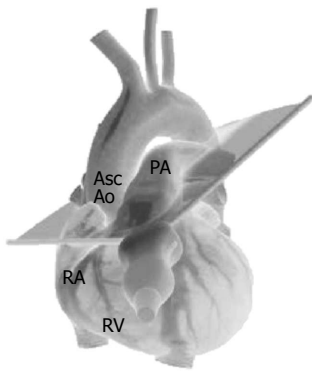


Figure 6 Parasternal ascending aorta short axis view, left anterior oblique projection. Schematic diagram demonstrating TTE probe position and alignment of scanning plane. Reproduced in part with permission from Toronto General Hospital, Perioperative Interactive Education Virtual TTE (<http://pie.med.utoronto.ca/TTE>). TTE: Transthoracic echocardiogram; RA: Right atrium; RV: Right ventricle; PA: Pulmonary artery; AscAo: Ascending aorta.

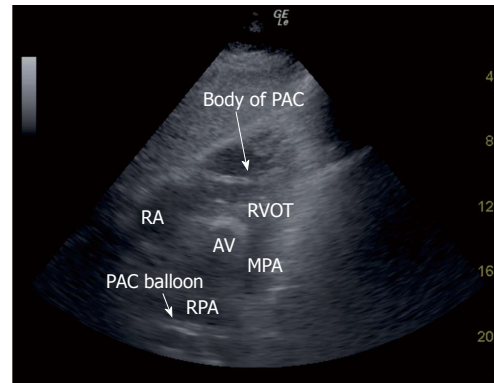


Figure 8 Subcostal right ventricular inflow outflow view showing the body of a pulmonary artery catheter in the right ventricle. RA: Right ventricle; RVOT: Right ventricular outflow tract; AV: Aortic valve; MPA: Main pulmonary artery; RPA: Right pulmonary artery; PAC: Pulmonary artery catheter.

optimal visualisation of the MPA and RPA, with the structures in question positioned in the near field.

Patients in whom none of the three TTE views of the MPA and RPA were attainable were noted and included in the results of the study.

The sonographer was then notified by the proceduralist inserting the PAC that attempts at insertion had begun.

The sonographer then used the same TTE view that was successfully used to visualise the MPA and RPA to examine for the appearance of a PAC balloon or tip, and the right ventricular outflow tract (RVOT) visualised to examine for the presence of the body of the PAC line (Figure 8).

The sonographer was notified by the proceduralist inserting the PAC that attempts at correct placement were complete. The sonographer was not given any information about presumed success or failure of appropriate PAC placement according to pressure waveform information.

If the PAC balloon or tip were not already seen in the PA, or PAC body in the RVOT, then any of the 3 remaining views not used were henceforth utilised in the above described sequence to examine for those structures.

If either PAC line in the RVOT or PAC balloon in the PA were seen by TTE, the case was recorded as a "test positive" for the first view used that, in the above sequential order, was able to identify those structures. We did not attempt to visualise PAC structures further by different views once positively identified. If not seen, the case was recorded as a "test negative".

If the PAC balloon had not been seen in the MPA or RPA by any of the 3 designated TTE views, but examination of the RVOT positively identified the body of the PAC, the PAC tip was presumed to be placed in the distal RPA beyond the view of TTE.

All sonograms were recorded and de-identified, then reviewed independently at a later date by a second anesthesiologist skilled in perioperative TTE to confirm absence or presence of the PAC balloon or tip in the PA, and PAC body in the RVOT. The second assessor was blinded to the diagnosis of "test positive" or "test negative" by the initial sonographer. Disagreement between observers was recorded as interobserver variability.

A single portable ultrasound machine (LogiqE, GE, New York) and 2-5 MHz phased array ultrasound probe (3S, GE, New York) was used to perform each

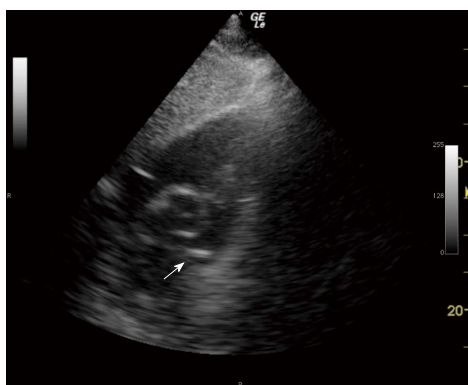


Figure 9 Subcostal right ventricular inflow outflow view confirming presence of the pulmonary artery catheter balloon in the main pulmonary artery after pulmonary artery catheter insertion (arrow). Cardiac chamber identification labels have been omitted for clarity. Movie clip 1: Subcostal right ventricular inflow outflow view showing appearance of pulmonary artery catheter balloon in the main pulmonary artery as it is appropriately placed.

sonogram. The probe was positioned on the praecordium and subcostal region carefully under the patient's sterile drapes. PAC balloon position was identified by the hyperechoic appearance of its air-filled balloon and motion away from the transducer in concert with ventricular systole (Figure 9, Movie Clip 1). The body of the PAC was identified as a hyperechoic line positioned between and distinct from the RVOT free wall and anterior border of the aortic root (Figure 8). Insertion was performed by a cardiac anesthesiologist or a supervised cardiac anaesthesiology registrar, both of whom were blinded to all sonographic information. In keeping with the majority practice in our department of PAC insertion until PA pressure waveforms were observed, in all cases bar those inserted by a single anesthesiologist, PACs were advanced until this point, the balloon then deflated, and the catheter position secured. The remaining practitioner deliberately obtained a pulmonary capillary wedge pressure waveform before balloon deflation, 1-2 cm withdrawal, and fixation of catheter position. Patients were awake and spontaneously ventilating or anaesthetised and positive pressure ventilated (IPPV) as per the cardiac anesthesiologist's preference. Difficulties in placing the PAC under pressure waveform guidance were recorded by the inserting proceduralist but not communicated to the sonographer at any time.

To establish how TTE could assist in confirming a PAC placed potentially too distally or proximally, the distance from MPA bifurcation to the furthest point of RPA visualisation in each sonogram was also measured and compared between views. This was then compared with the dimensions of the RPA at its narrowest point, and its 1st divisions, measured from the CT pulmonary angiography scans (CTPA) of 20 adult patients. With this information the approximate expected wedge position was estimated by comparison of the known width of the inflated PAC balloon^[8]. TTE measurements were performed offline (Pixmeo, Geneva, Switzerland). CTPA RPA measurements were taken at the narrowest points of the vessels with the midpoints of bifurcation

(MPA to RPA, RPA to 1st divisions) used as measurement endpoints. CTPA measurements were performed *via* Impax Web1000 (Agfa, Mortsel, Belgium).

Statistical analysis

All calculations were performed using SPSS V21 (IBM, New York, United States) statistical software. As described by Gwet^[9], based on a minimum limit of agreement of 70% between TTE and pressure waveform guidance by Cohen's Kappa statistic, 51 subjects were required. We chose a convenient sample of 100 patients anticipating difficulty in obtaining appropriate MPA and RPA views. Continuous data was assessed for normality by histogram frequency distribution analysis and the Kolmogorov-Smirnov normality test, and was considered suitable for parametric testing using unpaired *t*-tests, or one-way ANOVA for multiple groups. Single independent variable, binary outcome data was analysed with Fisher's Exact test. Multivariate logistic regression was used to identify the effect of simultaneous patient factors and PAC position in the MPA or RPA on likelihood of successful TTE views used. We reported this study using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines^[10].

RESULTS

One hundred and three patients were recruited (Table 1). Three patients' pulmonary arteries were not visible in any of the 3 TTE views [2% (95%CI: 1%-8%)]. Appropriate placement of the PAC balloon within the MPA or RPA was confirmed by TTE in 98 patients [sensitivity 95% (95%CI: 89%-98%)], measured against pressure waveform guidance as the "gold standard". Absence of the PAC balloon in the MPA or RPA before PAC insertion was correctly established by TTE in 100 patients [specificity 97% (95%CI: 92%-99%)]. Confirmation of correct PAC placement by TTE was in very good agreement with pressure waveform guidance [Cohen's Kappa 0.92, (95%CI: 0.87-0.98)]. There was no interobserver disagreement found regarding presence or absence of the PAC balloon. Visualisation of the body of the PAC in the RVOT was confirmed in 76 patients [74% (95%CI: 63%-82%)] more often by parasternal than subcostal views (69% vs 21%, *P* < 0.0001). PACs were more often placed in the MPA than the RPA and the PAC balloon most often seen in the PSRVIO view (Table 1).

All PACs were successfully floated into the MPA or RPA. When the PAC was visualised during insertion, the PAC balloon was easily visible in its transition from RV to PA. Three patients suffered from rapid atrial fibrillation preoperatively, making the pressure waveform transition from RV to PA difficult to interpret. In these instances the balloon was clearly seen on TTE in the MPA. In 2 patients, despite detection of the body of the PAC in the RVOT and clear confirmation of correct placement in the PA by pressure waveform analysis, the inflated balloon of the PAC was not visible by TTE; in one of

Table 1 Patient study parameters

Parameter	Number (proportion or 95%CI) or mean (SD or 95%CI)	
Age (yr)	67 (10)	
BMI (kg/m ²)	29.6 (5.6)	
IPPV during PAC insertion	24 (24%)	
Diagnosis of COAD or Asthma	28 (28%)	
Final PAC position in MPA	80 (72%-88%)	<i>P</i> < 0.0001
Final PAC position in RPA	18 (13%-29%)	<i>P</i> < 0.0001
TTE view in which PAC was seen		
PSRVIO	52 (43%-63%)	<i>P</i> < 0.0001
SCRVIO	33 (26%-45%)	<i>P</i> < 0.0001
PSAscAo	13 (6%-24%)	<i>P</i> < 0.0001

BMI: Body mass index; IPPV: Intermittent positive pressure ventilation; COAD: Chronic obstructive airways disease; PAC: Pulmonary artery catheter; MPA: Main pulmonary artery; RPA: Right pulmonary artery; TTE: Transthoracic echocardiography; PSRVIO: Parasternal right ventricular inflow outflow view; SCRVIO: Subcostal right ventricular inflow outflow view; PSAscAo: Parasternal ascending aorta short axis view.

these patients, despite good visualisation of the PA in all 3 views, and in the other where only the PSRVIO view was able to be obtained. Neither of these 2 patients had a preoperative diagnosis of COAD, were positively pressure ventilated, or had a BMI over 30.

Successful PAC visualisation by subcostal views compared to parasternal views was more likely in patients with preoperative diagnoses of COAD, PAC insertion during IPPV and PAC positioning in the RPA (Table 2), but less likely in patients with higher BMI. All factors except insertion during IPPV reached statistical significance in the multivariate logistic regression model.

Length of RPA visualised by TTE and CTPA measured dimensions of the RPA and its 1st divisions at their narrowest points are presented in Tables 3 and 4. The SCRVIO view consistently visualised a greater length of the RPA compared with parasternal views, and hence a greater proportion of the complete RPA as established by CTPA (61% vs 45% of the complete RPA length respectively, *P* < 0.0001).

DISCUSSION

The use of TTE in acute medicine continues to enjoy rapidly increasing uptake and application in many areas of acute care^[11]. Point-of-care ultrasound machines now offer high quality imaging and are smaller and more affordable, making their use in the critical care setting ideal. Although now superseded, the point-of-care machine used in our study was fully enabled to perform quantitative spectral and colour Doppler analyses. Focused TTE training for critical care physicians outside of conventional cardiology and sonography training has demonstrated utility in assisting clinical decision making^[12,13].

We conducted a prospective observational study of focused transthoracic echocardiography used to confirm appropriate pulmonary artery catheter placement in the main or right pulmonary artery in patients undergoing elective cardiac surgery. Consistent with our hypotheses

Table 2 Influence of patient factors and pulmonary artery catheter position on successful pulmonary artery catheter visualisation by subcostal views¹

	Odds ratio	<i>P</i> -value	95%CI
Diagnosis of COAD or Asthma	9.5	0.001	2.5-36
Insertion during IPPV	3.9	0.08	0.8-17.8
BMI (kg/m ²)	0.78	< 0.0001	0.67-0.89
RPA PAC position	70.0	< 0.0001	9.6-502

¹Data are expressed as [number, (proportion)] or [mean, (SD)]. COAD: Chronic obstructive airways disease; IPPV: Intermittent positive pressure ventilation; BMI: Body mass index; RPA: Right pulmonary artery; PAC: Pulmonary artery catheter.

Table 3 Transthoracic echocardiogram length of right pulmonary artery visualised

TTE	Length (cm)		<i>P</i> -value
	Mean (SD)	Range	
Parasternal views: RPA	2.9 (0.8)	1.2-4.8	< 0.0001
SCRVIO view: RPA	3.9 (0.8)	2.8-5.6	

Data are presented as mean (SD). TTE: Transthoracic echocardiogram; RPA: Right pulmonary artery; SCRVIO: Subcostal right ventricular inflow outflow.

Table 4 Computerised tomographic pulmonary angiogram measurements of the right pulmonary artery and 1st divisions

CTPA	Length (cm)		Width (cm)	
	Mean (SD)	Range	Mean (SD)	Range
RPA	6.4 (1.0)	4.5-8.1	2.0 (0.4)	1.1-2.6
RPA 1 st division (anterior)			0.8 (0.02)	0.4-1.4
RPA 1 st division (posterior)			0.7 (0.02)	0.4-1.3

Data are presented as mean (SD). CTPA: Computerised tomographic pulmonary angiogram; RPA: Right pulmonary artery.

we found that: (1) Use of three basic TTE views could reliably confirm appropriate PAC placement in most patients, by direct visualisation of a mobile "to-and-fro" PAC balloon in MPA or RPA, and by the presence of the body of the PAC catheter in the RVOT confirming adequate PAC advancement; (2) Subcostal TTE views visualised a greater proportion of the RPA as defined by CTPA than parasternal TTE views, allowing more reliable estimation of ideal ("not too far") PAC positioning; and (3) that patient factors and final PAC position affect the type of echocardiographic view successfully used for PAC visualisation.

Tempe *et al*^[14] demonstrated a mean distance from PA to wedge pressure trace of 6.8 cm. The MPA is known to be approximately 5 cm in length; as our data suggests that as the mean length of the RPA is 6.4 cm, in the majority of cases a PAC would wedge in proximal-to-mid RPA. Such a wedge position is consistent with our CT pulmonary angiogram data suggesting that small RPAs at their distal narrowest point may not accommodate an inflated PAC balloon (Table 3), as

the balloon is purported to be 1 cm in diameter when inflated^[8]. Hence a PAC placed approximately halfway between the origin of the MPA and 2 cm beyond the MPA bifurcation should have the least likelihood of migrating too distally to spontaneously wedge in the RPA, as well as too proximally causing RV irritation. Even the TTE parasternal views, which visualized less of the RPA than the SCRPIO view, consistently visualized the proximal RPA (Table 3). Hence successful use of any view that captures the PAC balloon, together with visualization of its to-and-fro motion over the cardiac cycle, should confirm placement of a PAC balloon within this "safe" depth of proximal to mid RPA.

Use of parasternal views also offered good visualization of the body of the PAC in the RVOT more frequently; this was most likely because the lie of the PAC in the RVOT is perpendicularly aligned to the incoming ultrasound beams, and is in the near field, in these views. In practice, if the body of the PAC is seen in the RVOT, but to-and-fro movement of the PAC balloon is not seen in the MPA or RPA, it is highly likely that the balloon is wedged; additionally, if the catheter is not seen in both the RVOT and the PA/MPA in this instance, then the PAC must be inserted "not far enough" (*i.e.*, placed proximal to the RVOT). Hence, TTE should be used to: (1) confirm that a PAC is not unintentionally wedged; (2) confirm that a PAC is inserted distal to the RVOT; (3) assist "ideal" PAC balloon final positioning approximately 3-4 cm beyond the origin of the MPA; and (4) confirm subsequently by repeat examination that proximal or distal PAC migration has not occurred if the monitored PAC pressure waveforms become equivocal.

Where the PACs were placed in the RPA, the SCRPIO was significantly better at visualizing the PAC balloon than parasternal views. This may be because the caudo-cranial direction of the ultrasound beams from the SCRPIO are well aligned with the final path taken by the PAC from RVOT to RPA (Figures 5 and 6).

In the 2 patients where the balloon of the PAC was not seen when an obvious PA waveform was displayed, one case was most likely because the SCRPIO was not obtained and the PAC positioned in the RPA. In the other patient, despite good visualization of the MPA and RPA in both parasternal and subcostal views, the PAC balloon was not seen. It is possible that further non-standard views not utilised in this study, such as the parasternal long axis RV outflow view^[15], may have assisted in PAC visualisation.

Although serious complications are rare with the use of PACs, should pulmonary artery rupture occur, the associated mortality is up to 70%^[16]. The important pressure waveform transitions to recognize during insertion are the changes from RV to PA, and if this is unrecognized, the transition from PA to wedge. Even in experienced hands these changes can occasionally be obscure. Patients who have received a sedating premedication can partially obstruct their airway and create large baseline swings in their intrathoracic, and

hence cardiac, pressures. Right ventricular systolic failure and hypovolemia may also reduce the pulse pressures in RV and PA whilst raising the central venous pressure a, c and v waves. Absolute changes between systolic and diastolic pressures from RA, RV, PA and then to wedge are difficult to appreciate in these circumstances. The dicrotic notch seen in a PA pressure trace may be subtle and hidden within an underdamped pressure trace, and the falling diastolic phase seen when in the PA can be hard to distinguish from the flat or rising diastolic phase of the RV during rapid and/or irregular heart rates; for example in rapid atrial fibrillation or other supraventricular tachycardias. All of these confounders may mislead even experienced practitioners in identifying appropriate PAC placement; in our study 3% of patients had rapid atrial fibrillation making pressure waveform interpretation difficult. These situations will be more frequent in the emergency cardiac surgery or intensive care setting. Scenarios in which TTE would provide utility in confirming appropriate PAC placement are summarized in Table 5.

Our study is limited by its single centre sample and observational design. Selection bias cannot be excluded as only elective patients in whom a PAC was deemed necessary for the operative procedure were included in the study. The moderate sample size used also precludes any conclusions when lack of a statistical difference between compared samples was found. The designation of TTE in the study as an adjunct to pressure waveform guidance, rather than as a sole alternative was purposeful; in most cases, insertion of a PAC is straightforward with the latter technique. Whilst we have not investigated a direct comparison between the two insertion techniques, we believe this would not have practical significance as use of pressure waveform guidance should remain the proceduralist's insertion technique of choice. Catheter migration due to unfolding PAC loops, changes in patient position, and/or unintentional catheter manipulation is known to occur after insertion. To take full advantage of the potential for TTE to assist in the prevention of PAC related complications, repeated examinations would be required to exclude further PAC migration into the RPA or regression back to the RVOT. The sequential, rather than systematic use of TTE views from PSRVIO to PSAscAo then SCRPIO may have also skewed the proportion of "true positive" views in favor of the parasternal approach. This was again a deliberate aspect of the study design as the author's experience in teaching TTE is that parasternal views are more intuitive and easier to apply in a beginner's hands. Finally, the fact that in 3 patients no TTE views were obtained is a reminder that despite the excellent sensitivity and specificity of the technique when the MPA and RPA are visualized, there remains a very small proportion of patients in whom the technique will not provide useful information.

We conclude that TTE is a highly sensitive and

Table 5 Situations where utilisation of transthoracic echocardiogram for pulmonary artery catheter positioning may be of assistance

Timing	Utility
Pre-insertion	Identify RV dilation, suggesting a longer than standard PAC insertion distance until the MPA/RPA is reached by the PAC balloon Identify small calibre MPA/RPA dimensions, usually associated with hypovolemia, and possibly predisposing to shorter depths of insertion from RV to “wedge” Quantify RA, TV and PV abnormalities and/or degree of regurgitation prior to PAC insertion
Insertion	Establish absence of the body of the PAC within the RVOT, suggesting PAC coiling or failure of passage past the TV Establish presence of the body of the PAC within the RVOT, confirming that the PAC balloon (1) is not coiled in the RV and (2) must be either in or distal to the MPA/RPA Visualisation of an “un-wedged” PAC balloon by the appearance of “to-and-fro” movement of the echogenic air-filled PAC balloon in the MPA or RPA Imply a wedge position and/or “too distal” placement of the PAC balloon if (1) the body of the PAC is seen within the RVOT and (2) the PAC balloon is not seen in the MPA or RPA Optimise final PAC balloon position to distal MPA/proximal RPA
Post-insertion	Repetition of the above TTE signs to identify proximal or distal migration of the PAC from the initial insertion point When in doubt, confirmation of the PAC balloon inflation status by visualisation of the “to-and-fro” movement of the echogenic air-filled PAC balloon Quantify possible contribution of decline in RV/TV/PV function with presence of the PAC

TTE: Transthoracic echocardiogram; BMI: Body mass index; PAC: Pulmonary artery catheter; MPA: Main pulmonary artery; RPA: Right pulmonary artery; RV: Right ventricle; PA: Pulmonary artery; RVOT: Right ventricular outflow tract.

specific second line technique when confirmation of appropriate PAC placement is required. Visualization of the air-filled PAC balloon in the MPA or RPA, together with its free “to-and-fro” movement, assists in confirming that a PAC is not wedged, whereas visualization of the body of the PAC in the RVOT confirms PAC placement beyond the RV. TTE used to guide final PAC positioning approximately 3-4 cm beyond the MPA origin, and used again as needed in the postoperative period, could assist in reducing the incidence of complications related to proximal or distal migration. Parasternal views are useful in patients with higher BMI, for PACs placed in the MPA and for visualisation of the PAC body, whereas subcostal views are more successful for PACs placed in the RPA. With the appropriate equipment and an available practitioner with experience in perioperative TTE relevant to obtaining views of the pulmonary artery, use of focussed TTE as an adjunct to pressure waveform guidance may assist in reducing complications related to PAC malposition.

COMMENTS

Background

With the advent of point-of-care ultrasound machines with high quality imaging, more and more applications of ultrasound in critical care are finding their place. Transthoracic echocardiography (TTE) in particular was previously the sole domain of cardiologists and cardiac sonographers; however with the use of a focussed TTE examination critical care physicians can obtain reliable and useful information. Appropriate placement of pulmonary artery catheters (PAC) is usually a routine procedure with the use of pressure waveform guidance, but can be challenging in certain circumstances. The authors explored how focussed TTE could assist in confirming appropriate PAC placement.

Research frontiers

Other examples of new applications of point-of-care ultrasound (U/S) in critical care include U/S diagnosis of pneumothorax, U/S localisation of the cricothyroid membrane for cricothyrotomy, and U/S estimation of stomach residual volumes to assist decision making on pre anaesthesia aspiration risk.

Innovations and breakthroughs

Point-of-care TTE utilised by critical care physicians has added great value to cardiovascular aspects of clinical decision making (Potter A. Echocardiography in acute medicine: a clinical review. *Br J Hosp Med* 2010; 71: 626-630). Guidance on degree of volume replacement, requirement for administration of inotropes or vasoconstrictors, and postoperative level of care planning decisions have all been assisted by information by TTE (Cowie B. Three years' experience of focused cardiovascular ultrasound in the peri-operative period. *Anaesthesia* 2011; 66: 268-273). However, use of echocardiography to guide invasive procedures outside of U/S guided regional anaesthesia has been restricted to case series of transoesophageal echocardiographic confirmation of PAC placement (Tempe DK, Datt V, Banerjee A, *et al* (2004). Case 5: Transesophageal echocardiography-guided insertion of a pulmonary artery catheter. *J Cardiothorac Vasc Anesth* 2004; 18: 657-662). This study is the first of its kind to be used in a large sample in the perioperative context demonstrating the utility of the less invasive transthoracic modality. The authors have successfully shown how TTE can safely and efficaciously confirm appropriate TTE placement.

Applications

With appropriate training and available equipment, PAC positioning in the main or right pulmonary artery can be confirmed reliably when PAC insertion by pressure waveform methods are equivocal. This can be performed rapidly and safely in time critical situations. Other applications of the technique may include pre-insertion quantification of right heart conditions that may be affected by PAC insertion, as well as post-insertion assessment of placement when catheter migration may have occurred.

Terminology

TTE: Transthoracic echocardiography; TEE: Transesophageal echocardiography; RV: Right ventricle; RVOT: Right ventricular outflow tract; RA: Right atrium; PAC: Pulmonary artery catheter; PA: Pulmonary artery; MPA: Main pulmonary artery; RPA: Right pulmonary artery; PSRVIO: Parasternal right ventricular inflow-outflow view; SCRVIIO: Subcostal right ventricular inflow-outflow view; PSAscAo: Parasternal ascending aorta short axis view; CTPA: Computerised tomographic pulmonary angiogram; COAD: Chronic obstructive airways disease; IPPV: Intermittent positive pressure ventilation; ICU: Intensive care unit; BMI: Body mass index; ANOVA: Analysis of variance statistical test.

Peer-review

This is an interesting and well conducted study reinforcing the usefulness of TTE during invasive procedure.

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Anesthesia for bronchoscopic amniotic membrane grafting to treat non-healing bronchial dehiscence

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Abstract

Airway complications after lung transplantation remain a significant cause of morbidity and mortality. Many of these occur at the anastomotic sites, which are susceptible due to poor collateral circulation. Of the possible complications, bronchial dehiscence is particularly formidable. These cases have been successfully treated bronchoscopically with metallic stents, which likely promote healing through granulation tissue formation. However, limited options exist in cases where the dehiscence fails to heal following stent placement. Here, we present the case report of a 65-year-old male who developed bronchial dehiscence status post bilateral lung transplantation for idiopathic pulmonary fibrosis that failed to heal with simple stent placement. Eventually, the patient underwent amniotic membrane grafting with stenting as a novel therapy for non-healing bronchial dehiscence, for which we describe the anesthetic management. His anesthetic plan included inhalational induction with sevoflurane, propofol infusion for total intravenous anesthesia, rocuronium for muscle relaxation, and closed-circuit assisted ventilation. His existing tracheostomy was used as the airway for oxygenation and induction. In summary, our anesthetic plan for the lung transplant patient was effective; future amniotic membrane grafting for bronchial dehiscence through bronchoscopy may follow a similar technique. Ultimately, the choice of anesthesia in this patient population requires judicious consideration of the requirements of the procedure as well as the pathophysiology of the transplanted lung.

Key words: Bronchial dehiscence; Amniotic membrane;

Grafting; Bronchoscopy; Lung transplantation; Anesthesia

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Core tip: Bronchial dehiscence is a significant airway complication following lung transplantation and most commonly occurs at anastomotic sites due to poor collateral perfusion. This complication is often difficult to treat, especially when widespread. Severe disease has been treated with the temporary placement of metallic stents within the airway to promote healing, but limited options exist when stenting fails. This case report presents the anesthetic considerations for a lung transplant patient undergoing bronchoscopic placement of an amniotic membrane graft as a novel solution for non-healing bronchial dehiscence after multiple failed attempts with metallic stent placement.

Feng TR, Gildea TR, Doyle DJ. Anesthesia for bronchoscopic amniotic membrane grafting to treat non-healing bronchial dehiscence. *World J Anesthesiol* 2015; 4(2): 39-43 Available from: URL: <http://www.wjgnet.com/2218-6182/full/v4/i2/39.htm> DOI: <http://dx.doi.org/10.5313/wja.v4.i2.39>

INTRODUCTION

Since the first human lung transplantation, improvements in patient selection, surgical technique, and immunosuppression have led to increased overall survival^[1-3]. Nevertheless, airway complications remain an important cause of morbidity and mortality^[4,5]. The incidence of complications at most centers ranges from 7%-18% with a 2%-4% mortality rate^[1]. These complications arise partly because bronchial arterial circulation is not reestablished during transplantation and requires approximately 2 wk for rearterialization^[4-6]. Thus, initial bronchial perfusion depends on retrograde collaterals from the pulmonary artery, making the anastomotic sites particularly susceptible to ischemia^[1,4,5,7].

Of the anastomotic complications, dehiscence is particularly difficult to treat, especially when widespread and clinically significant^[2]. Partial dehiscence is often managed conservatively with surveillance and aggressive antibiotic therapy. More severe cases have been treated with temporary placement of metallic stents, which promote healing through excessive granulation tissue formation^[1]. Other methods have also been used, including endoscopic application of cyanoacrylate glue^[8] and surgical repair with homograft aorta^[9].

Here, we present the anesthetic management of a lung transplant recipient with non-healing bronchial dehiscence treated with the novel application of amniotic tissue grafting *via* bronchoscopy. As interventional bronchoscopic procedures have become more sophisticated and capable of treating more severe disease, anesthesia for bronchoscopy has evolved alongside

them. In providing anesthesia for such patients, thorough preoperative evaluation with ample consideration of transplanted lung physiology and requirements within the bronchoscopy suite setting is imperative.

CASE REPORT

A 65-year-old male underwent bilateral lung transplantation for end-stage lung disease secondary to idiopathic pulmonary fibrosis. Though he tolerated the procedure well, his immediate post-operative course was complicated by cardiac insufficiency, pulmonary hypertension, acute kidney injury, hypotension, and coagulopathy. He soon underwent percutaneous tracheotomy due to debilitation and extended ventilation requirement.

Three weeks later, he developed acute hypoxic decompensation with sepsis, pneumomediastinum and pneumothorax. Bronchoscopy revealed partial dehiscence of the right anastomosis with a large fistula into the mediastinum. A non-covered metallic stent was placed in the right main stem bronchus and was subsequently replaced and repositioned several times. However, the dehiscence continued to worsen and extend. *Pseudomonas aeruginosa* was also isolated from the bronchial wash and treated with antibiotics. The decision was made to place an amniotic membrane graft *via* bronchoscopy.

Pre-anesthetic assessment demonstrated a patient status post tracheostomy and ASA class IV, weighing 78 kg. His blood pressure was 119/57 mmHg, pulse was 90 beats/min, temperature was 35.5 °C, and arterial oxygen saturation was 99% on 4 L *via* tracheostomy collar. He had bilateral chest tubes in place and bilateral rhonchi on auscultation. His hemoglobin and hematocrit were 8.7 g/dL and 26.3%, respectively. Serum electrolytes were within normal limits. Chest X-ray showed no pneumothoraces.

His tracheostomy was used as the airway for oxygenation and for pure sevoflurane inhalational induction at 5 L/min over 2-3 min. We then switched to total intravenous anesthesia (TIVA) using a propofol infusion, starting at 125 mcg/kg per minute and rate adjusted to a Bispectral Index of less than 50 throughout the case. Following induction, the patient's blood pressure dropped to 82/51 mmHg, which was treated with propofol titration to 100 mcg/kg per minute and 200 mcg of phenylephrine. A 50 mg dose of rocuronium was given for paralysis.

After the patient was anesthetized and stabilized, rigid bronchoscopy was performed. A closed circuit was attempted due to the large fistula into the mediastinum; wet gauze was packed into the mouth to facilitate ventilation and limit circuit leaks. The stent was peeled out of granulation tissue with forceps and then removed with flexible instruments. A 2 cm by 4 cm EpiFix amniotic tissue graft was draped over a balloon and deployed over the fistula and the defect in the posterior wall and the mediastinal fistula of the right main bronchus as planned. An uncovered Ultraflex stent was passed through the rigid bronchoscope into the right main stem bronchus

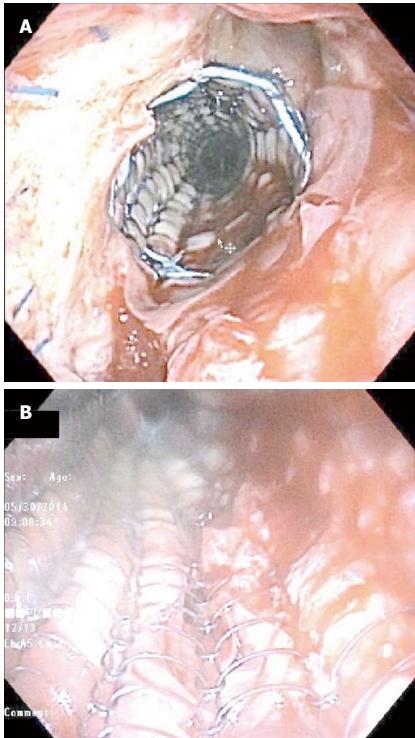


Figure 1 Two views of a bronchoscopically placed amniotic membrane graft underneath a self-expanding metallic stent used for treatment of bronchial dehiscence after lung transplantation. The image (A) shows the blue-colored sutures used for the bronchial anastomosis as well as the stent covering the graft, while the image (B) provides a view from inside the stent.

and was deployed over the amniotic tissue. However, the amniotic tissue was dislodged and required repositioning; its final location was under the stent and partially covering the fistula, which was the best positioning possible (Figure 1).

Throughout the case, a high oxygen flow rate of 15 L/min was maintained due to expected circuit leaks and suctioning from bronchoscopy. An assisted ventilation setting was used with a respiratory rate of 12-15 respirations/min. Two more 10 mg doses of rocuronium were given during the case. Due to a down-trending blood pressure, the patient was started on a phenylephrine infusion at 30 mcg/min; he was later titrated to 40 mcg/min.

Prior to emergence, the propofol infusion rate was decreased to 75 mcg/kg per minute and 5 mg of neostigmine with 0.6 mg of glycopyrrolate were given for reversal of rocuronium. Ondansetron 4 mg was given for nausea prophylaxis. Once the patient was confirmed to be breathing spontaneously at 14 respirations/min, he was switched to blow-by oxygen through mask on 6 L/min. He was transported to the post-anesthesia care unit (PACU) without any post-operative complications. His blood pressure in the PACU was 103/42 mmHg with a pulse of 70 beats/min, temperature of 35.1 °C, and oxygen saturation of 100% on room air.

Weeks later, the patient passed away due to complications related to liver failure and sepsis; bronchoscopy cultures prior to death were negative.

DISCUSSION

Management of airway complications varies depending on clinical symptoms and severity, and can range from medical management to interventional bronchoscopy to open surgical repair^[1]. Among the various methods to treat airway complications, stent placement is becoming increasingly popular and is effective for several types of complications^[1,7]. The different types of stents and their associated advantages and disadvantages have been described at length in the literature^[1,6,7,10-13]. In bronchial dehiscence, bronchoscopically deployed uncovered metallic stents have been useful in treatment, as they promote excessive granulation tissue formation that provides a platform for healing^[6]. They also have the added benefit of preventing stenosis through a constant outward radial force, which is important at the anastomosis due to its tendency to become stenotic upon healing^[2,6].

Amniotic membrane grafts are processed from human placenta and comprise the innermost layer of the amniotic cavity. Due to its anti-inflammatory, stem cell proliferating, and epithelialization-promoting effects, these grafts are particularly useful in healing and have been used in ophthalmology and for reduction of post-laminectomy epidural adhesions^[14-17]. Furthermore, Kheirkhah *et al.*^[18] demonstrated its antibacterial effects in treating acute *Pseudomonas* keratitis. Though its mechanism of action is poorly defined, its structure and properties likely lend to epithelial cell migration and attachment^[15]. Thus, in this case report, amniotic tissue was bronchoscopically placed as a potential substrate to treat the bronchial dehiscence and *Pseudomonas* infection.

As bronchoscopic procedures gradually became more sophisticated, anesthesia for bronchoscopy evolved alongside them. The increasing complexity and duration of bronchoscopic cases inevitably require deep sedation or general anesthesia^[19,20]. Rigid bronchoscopy is most often performed under general anesthesia with neuromuscular blockade^[19]. TIVA is preferred with a continuous variable rate infusion of propofol, as this is thought to minimize undesirable cardiorespiratory effects compared to bolus doses^[19,21]. The benefits of propofol are its rapid onset (< 2 min) and rapid offset (< 15 min)^[19,22,23]. It has also been shown to have the lowest complication rate and improved patient neuropsychometric recovery^[22], as well as improved tolerance, total amnesia, and decreased cough^[19,21]. Drug choice for neuromuscular blockade depends on the required duration of action; typically rocuronium or vecuronium is used^[19,23].

The choice of inhalational induction vs intravenous induction depends on both clinical circumstance and patient preference. Our patient's existing tracheostomy lent itself well to inhalational induction with sevoflurane since this merely involved connecting the tracheostomy tube to the patient breathing circuit. The switch to TIVA is typically made once the rigid bronchoscope is placed

to prevent room contamination, as the anesthetic circuit is not closed^[19,24]. Gauze packing in the nose and mouth can help with circuit leakage^[19]. A study by Thwaites *et al.*^[25] comparing sevoflurane to propofol use on induction demonstrated a significantly slower onset with sevoflurane, but a lower incidence of apnea and shorter time to establish spontaneous ventilation^[25]. Other advantages of sevoflurane included smoother transition to maintenance, less associated hypotension, and earlier emergence^[25]. However, patient preference appeared to lean towards propofol^[25].

Several ventilation strategies can be employed during bronchoscopic procedures, including spontaneous ventilation, high-frequency jet ventilation, and closed-circuit positive pressure ventilation^[19]. Spontaneous ventilation is typically ideal^[19,24]; thus, muscle relaxants are only recommended for coughing, movement, or dangerous airway manipulation^[24]. Unfortunately, spontaneous ventilation is often not feasible due to the deeper sedation required for cough and sympathetic drive suppression during bronchoscopy^[19]. Jet ventilation is a poor choice due to the added risk of further dissecting into the mediastinum through the fistula. The high airflow would also make amniotic tissue graft positioning difficult due to the graft's paper-like consistency and propensity to become displaced. Furthermore, an attempt to maintain a closed circuit is recommended in patients with airway fistulas due to the possibility of further exacerbation of existing pneumomediastinum and pneumothorax.

In lung transplant recipients, thorough consideration of transplanted lung physiology is also prudent. In the immediate post-operative month, total lung capacity and FEV₁ tend to decrease; significant improvement in respiratory function and gas exchange of the transplanted lungs is only gradually seen with time^[26]. Furthermore, transplanted lungs are highly susceptible to pulmonary edema from fluid overload as lymphatic drainage is interrupted during harvesting^[26]. In single lung transplants, ventilation and perfusion in the native and transplanted lungs may also be unequally distributed due to a difference in compliance^[26]. In single lung transplants for emphysema, ventilator flow is mostly directed toward the more compliant native lung, whereas the opposite is true for single lung recipients with pulmonary fibrosis^[26]. Bilateral transplantation does not appear to require ventilator precautions other than avoiding barotrauma due to an overall decrease in compliance^[26]. Barotrauma and aggressive tracheobronchial stimulation can be avoided with gentle intubation and moderate-to-deep anesthesia^[26]. Fiberoptic bronchoscopic intubation may also be helpful in avoiding complications at the site of bronchial anastomosis^[26].

In conclusion, our anesthetic plan for the lung transplant patient was effective for the procedure; future amniotic membrane grafting for bronchial dehiscence through bronchoscopy may follow a similar technique. Ultimately, the choice of anesthesia in this patient popu-

lation requires judicious consideration of the requirements of the procedure as well as the physiology of the transplanted lung.

COMMENTS

Case characteristics

A 65-year-old male with a history of bilateral lung transplantation complicated by bronchial dehiscence that failed treatment with metallic stent placement, who underwent bronchoscopic amniotic membrane grafting as a novel therapy for non-healing bronchial dehiscence.

Clinical diagnosis

He initially presented with acute hypoxic decompensation with sepsis, pneumomediastinum and pneumothorax, and bronchial dehiscence of the right anastomosis with a large fistula into the mediastinum was confirmed via bronchoscopy. Prior to his procedure, he was hemodynamically stable and presented with a tracheostomy, bilateral chest tubes, and bilateral rhonchi on physical exam.

Laboratory diagnosis

Hemoglobin 8.7 g/dL; hematocrit 26.3%; serum electrolytes within normal limits.

Imaging diagnosis

Chest X-ray showed no pneumothoraces pre-procedurally.

Treatment

The patient underwent bronchoscopic placement of an amniotic membrane graft underlying a stent as a potential substrate to treat the non-healing bronchial dehiscence and superimposed *Pseudomonas* infection.

Related reports

The reported cases of amniotic membrane grafting as a treatment have been mainly in the domain of ophthalmology and for the reduction of post-laminectomy epidural adhesions; use of amniotic membrane grafting for the treatment of bronchial dehiscence has not been reported in the literature and the anesthetics for this procedure has not been discussed.

Experiences and lessons

This case report outlines an anesthetic plan that was successful for the grafting procedure and can be used as a guideline in the future when bronchoscopically treating non-healing bronchial dehiscence with amniotic membranes. In this patient population, it is particularly important to carefully consider the comorbidities of the patient, the requirements of the procedure, and the physiology of the transplanted lung.

Peer-review

This is an interesting case report on the anesthetic management of bronchoscopic amniotic membrane grafting. The procedure is new for this kind of application and thus the paper is original and has merit. The report will be a useful reading for all anesthesiologist involved in lung surgery. The manuscript is well written and easily readable.

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Bradycardia and hypotension during pediatric scoliosis surgery-hypovolemia or spinal shock?

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Abstract

We present the case of a 13-year-old boy undergoing scoliosis repair utilizing skull-femoral traction who developed sudden, sustained bradycardia and hypotension during scoliosis repair, associated with loss of somatosensory evoked potentials and motor evoked potentials to all four limbs. A diagnosis of spinal shock and hypovolemia was made after ruling out primary cardiac causes, sepsis, anaphylaxis and intra-spinal pedicle screw placement. Acute complications of surgical scoliosis repair are reviewed along with anatomy of the sympathetic nervous system. In this case spinal shock may have been due to hypovolemia as well as spinal cord manipulation during T12 vertebral column resection that was needed to effect scoliosis correction. Treatment included volume expansion and inotropic support. Anesthesiologists caring for these patients should be mindful of the possibility of spinal shock during correction of severe scoliosis, particularly when vertebral column resection is undertaken.

Key words: Spinal shock; Scoliosis; Hemorrhagic shock; Vertebral; Sympathectomy

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Core tip: A child undergoing scoliosis repair developed sudden bradycardia and hypotension, associated with loss of somatosensory and motor evoked potentials to all four limbs. Spinal shock and hypovolemia were diagnosed after ruling out other causes. Acute complications of scoliosis repair are reviewed along with sympathetic nervous system anatomy. Spinal shock was likely due to hypovolemia and spinal cord manipulation during vertebral column resection that was needed to effect scoliosis correction. Treatment included volume

expansion and inotropic support. Anesthesiologists should be mindful of the possibility of spinal shock during correction of severe scoliosis, particularly when vertebral column resection is undertaken.

Karsli C, Strantzas S, Finnerty O, Holmes L, Lewis S. Bradycardia and hypotension during pediatric scoliosis surgery-hypovolemia or spinal shock? *World J Anesthesiol* 2015; 4(2): 44-48 Available from: URL: <http://www.wjgnet.com/2218-6182/full/v4/i2/44.htm> DOI: <http://dx.doi.org/10.5313/wja.v4.i2.44>

INTRODUCTION

Surgical correction of scoliosis may be associated with complications such as spinal cord or nerve root injuries^[1], hypovolemic shock, superior mesenteric artery syndrome^[2] and subtle sympathetic trunk/chain lesions^[3]. We present a case of acute intraoperative spinal shock likely exacerbated by hypovolemia during thoracic vertebral column resection (VCR).

CASE REPORT

Our patient was a 13-year-old male with Prader-Willi syndrome and severe scoliosis, Cobb angle 128 degrees, (Figure 1A) who presented for posterior spinal instrumentation and fusion with the use of skull-femoral traction. Anesthesia was maintained with propofol and remifentanyl to optimize somatosensory evoked potentials (SEP) and motor evoked potentials (MEP) monitoring throughout the case. The use of skull-femoral traction to aid in deformity correction was abandoned after repeated alerts in MEP monitoring during the surgical exposure. With attempted rod insertion, the MEPs were completely abolished from the lower extremity muscle groups bilaterally, and responses from the abdominal recti were decreased in amplitude by more than 50% of baseline. The mean arterial blood pressure was elevated to aid the patient tolerate sagittal plane correction of the spine. However, with the persistent absence of MEPs, the decision was made to eliminate the corrective forces by removing the rod. This resulted in an immediate return of all MEPs. With each subsequent attempt at rod insertion there was an associated loss of MEPs and the responses normalized only when attempts to correct the scoliosis were abandoned. It was decided to proceed with a vertebral column resection at the level of T12 in an effort to aid with the reduction of the severe curvature.

During the VCR there was an acute, complete loss of the left lower extremity MEPs and a significant reduction in amplitude of the right lower extremity MEPs to less than 10% of baseline (Figure 2A). Blood loss during the VCR was significant and over the next hour an estimated 60 mL/kg bleeding occurred. This was associated with a drop in mean arterial pressure from 70 to 35 mmHg and a slight increase in heart rate from

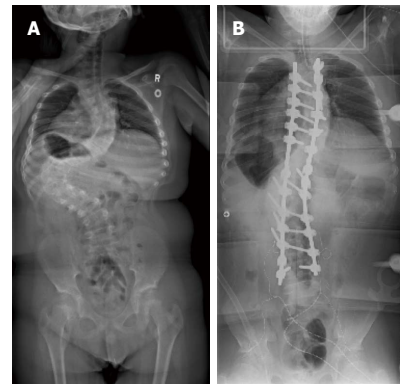


Figure 1 A-P X-ray of the patient. A: Preoperative A-P X-ray of the patient with severe scoliosis, Cobb angle 128 degrees; B: Postoperative A-P X-ray showing spinal instrumentation and final correction.

60 to 70 BPM. Coinciding with the drop in mean arterial pressure, the remaining small response from the right lower extremity MEPs disappeared. At this time, the upper extremity and abdominal rectus MEPs remained at baseline bilaterally. Aggressive fluid resuscitation included a total of one blood volume, comprising red blood cell concentrate: fresh frozen plasma at a ratio of 2:1. A dopamine 10 mcg/kg per minute infusion was initiated to address hypotension resistant to volume resuscitation and transfusion. Despite this, hypotension persisted and the heart rate remained between 60 and 70 BPM. With this the left and right upper extremity MEPs slowly declined in amplitude to less than 10% of baseline and the abdominal rectus responses were lost. This was followed by a complete loss of the upper extremity and greater than 50% amplitude decrease in the lower extremity SEP on both sides. The electroencephalography demonstrated burst suppression indicating global hypoperfusion.

With the instrumentation secured (Figure 1B) and continued fluid resuscitation with inotropic support, the mean arterial pressure improved over the next 20 min coinciding with partial return of MEPs, first in the right lower extremity followed by the left and right upper extremity. No improvement was seen from the left lower extremity MEPs (Figure 2B). Soon after, the left and right SEPs displayed recovery in both the upper and lower extremities. An intraoperative echocardiogram out-ruled hypovolemia or a primary cardiac cause for the decreased output and serum electrolytes and hemoglobin were in the normal range. With other causes ruled out, a diagnosis of acute intraoperative spinal shock was made. Upon emergence from anesthesia the patient was noted to be purposefully moving all but the left lower limb. This clinical presentation was consistent with the intraoperative findings of persistent complete loss of the left lower extremity motor evoked potentials.

Soon after intensive care unit admission dopamine was replaced with a norepinephrine infusion to maintain mean arterial pressure between 60 and 80 mmHg. Vasopressor support was discontinued on post-operative day 2 and the patient was transferred to the ward.

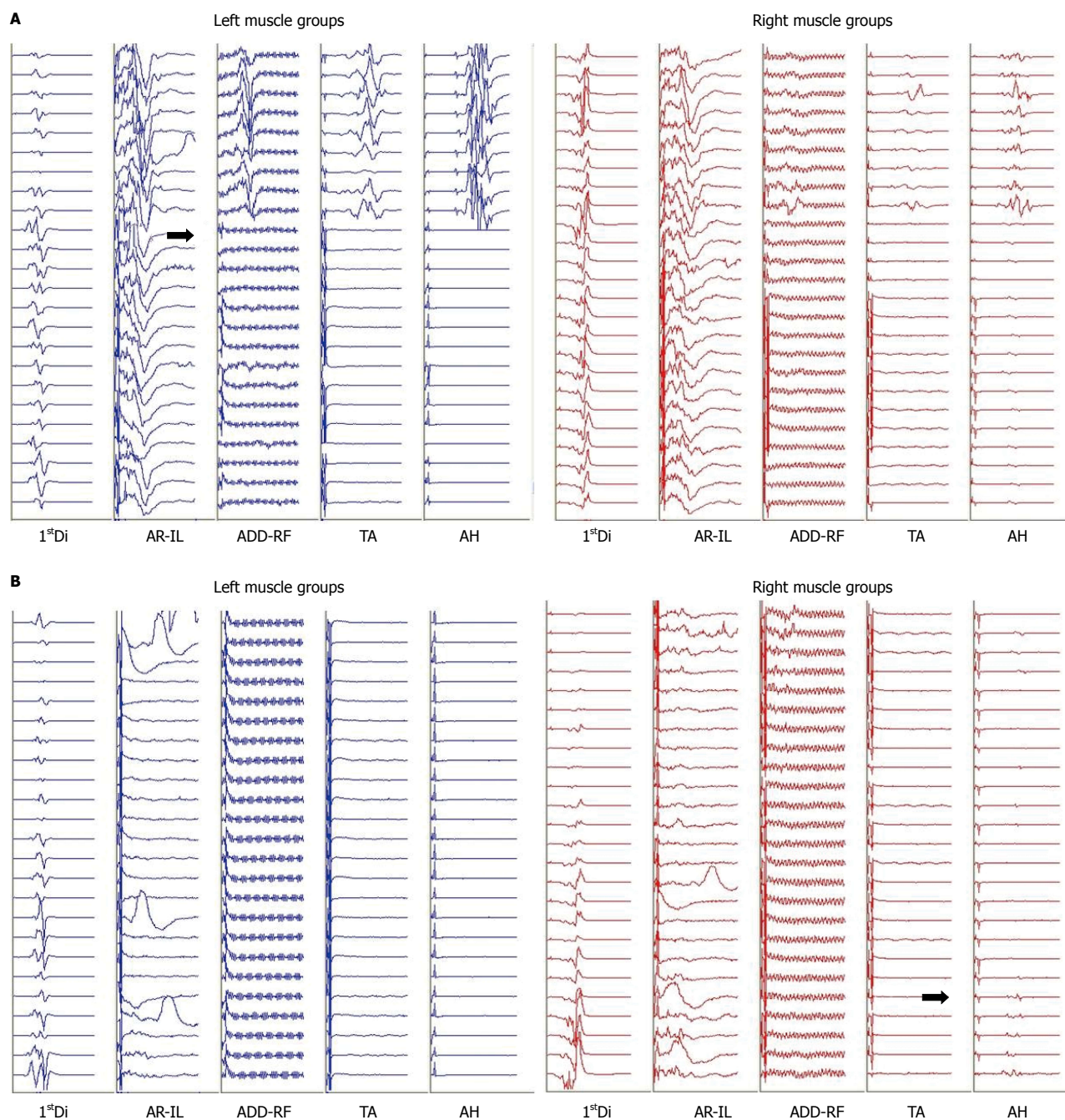


Figure 2 Motor evoked potentials during vertebral column resection (A) and at surgical closure (B). A: Abrupt loss of the left and right lower extremity motor evoked potentials (MEPs) during the vertebral column resection (dark arrows). Transcranial electric stimulation is delivered between two subdermal needle electrodes inserted 2 cm anterior to C1-C2 (International 10-20 System) overlying the motor cortex region. Trains of 5 to 9 pulses, spaced at an interstimulus interval ranging from 1.1 to 4.1 ms, are delivered with constant voltage (200-500 V) at the anode. Resultant compound muscle action potentials are recorded using subdermal needle electrodes, in a bipolar montage. These myogenic responses are recorded bilaterally from the first dorsal interosseous muscles (1stDi) in the upper extremity and lower extremity MEPs are recorded from the left and right abdominal rectus-iliopsoas (AR-IL), adductors-rectus femoris (ADD-RF), tibialis anterior (TA), and abductor hallucis (AH) muscles. Muscle groups are linked on occasion in order to maximize nerve root coverage. These unaveraged compound muscle action potentials are recorded through a 30-1000 Hz bandpass filter and are displayed in a 100 ms window; B: Closing left and right MEP responses. The dark arrow indicates the onset of a very small recovery of the right AH. There are no responses present from the left lower extremity muscle groups. Upon emergence from anesthesia the patient was noted to be purposefully moving all but the left lower limb coinciding with his MEP responses. Intermittent responses recorded from the left and right AR-IL were a result of movement artifact. Stimulation and recording parameters are similar to Figure 2A.

Some motor function had returned to the left leg by that time and the heart rate and blood pressure returned to pre-operative values. Clinical neurologic examination revealed a left sided Brown-Séquard syndrome at the T12-L1 level.

DISCUSSION

To our knowledge, this is the first reported case of acute intra-operative spinal shock in a pediatric patient undergoing scoliosis repair. This was a diagnosis of

exclusion, as many other confounding factors were present. There was significant blood loss during the VCR with hypovolemic shock and the absence of tachycardia in response to hypotension suggests a possible autonomic cause. The use of remifentanyl may have clouded the overall clinical picture and delayed the diagnosis of spinal shock in this case as it often results in a relative bradycardia. However the authors feel the persistent bradycardia was not due to remifentanyl as rises in heart rate were seen in response to incision and during deeper dissection earlier in the case. Trauma to the spinal cord as a result of a breached pedicle screw was ruled out using electrophysiological stimulation intraoperatively, and visual inspection of the X-rays post-operatively. It is possible during the VCR there was an insult to the left side of the spinal cord indicated by reductions in MEPs, and then confounded by ischemia during hemorrhagic shock. Despite aggressive resuscitation to normovolemia on ECHO, the need for inotropic support indicates a more sinister cause for the persistent shock. Given the acute and persistent loss of the left lower extremity motor evoked potentials during the VCR, and the clinical diagnosis of Brown-Séquard syndrome postoperatively, involvement of the spinal cord appears likely.

Spinal or neurogenic shock occurs usually after a serious injury to the spinal cord resulting in rapid loss of sympathetic output with persistent, relatively unopposed vagal tone causing the typical clinical picture of bradycardia with hypotension. The sympathetic nervous system includes preganglionic neurons in the lateral horn of the spinal cord from T1 to L2/3. Preganglionic axons exiting the spinal cord enter the white rami communicantes to join a network of the sympathetic chain, which run on either side of the vertebral bodies. Postganglionic axons follow the arterial tree to distal organs providing a constant balance between vasoconstriction and vasodilatation depending on clinical needs. Subtle sympathetic lesions have been reported after scoliosis repair and include altered sweating and sympathetic skin responses and an increase in temperature. We feel in this case two factors were at play: (1) a temporary but significant disruption in sympathetic activity due to spinal manipulation or vertebral column resection; and (2) hypovolemia from blood loss. The hypovolemia likely intensified the clinical picture of spinal shock. It is interesting that a single discrete injury at the level of T12 caused such rapid neurogenic shock. This scenario is more likely seen in high thoracic or cervical cord injuries. Hypovolemia leading to spinal cord ischemia likely aggravated the neurogenic shock. In caring for these patients the anesthesiologist should be mindful of this possibility and be prepared to treat spinal shock with fluids and vasopressor/inotropic support such as norepinephrine and dopamine.

Vertebral column resection is a challenging procedure that is reserved for patients with severe, rigid spinal deformity. Conventional methods such as posterior only instrumentation, or posterior instrumentation with anterior release, may not be adequate and a more aggressive

method may be required^[4]. It is associated with a higher degree of intraoperative blood loss and carries a risk of spinal or nerve root injuries, however, it has been performed safely and with excellent outcomes in several case series^[5-7]. In our particular case, VCR was performed after it was determined that the patient could not tolerate the sagittal corrective forces placed on the spinal cord by either skull-femoral traction or rod placement, as demonstrated by repeated MEP alerts. MEPs are highly sensitive in detecting ischemia to the anterior two-thirds of the spinal cord, and specifically the corticospinal tracts^[7]. Vertebral column resection reduces both the coronal and sagittal curves and aides in decompression of the spinal cord and reduces traction of the anterior spinal artery. Because of the high risk associated with VCR it is imperative that MEPs and SEPs be monitored to provide real time feedback and direct key surgical decisions^[7].

COMMENTS

Case characteristics

A child undergoing scoliosis repair developed sudden bradycardia and hypotension.

Clinical diagnosis

The clinical findings coincided with loss of somatosensory and motor evoked potentials to all four limbs.

Differential diagnosis

A diagnosis of spinal shock and hypovolemia was made after ruling out primary cardiac causes, sepsis, anaphylaxis and intra-spinal pedicle screw placement.

Laboratory diagnosis

Somatosensory and motor evoked potentials identified the acute neurologic changes, and intraoperative echocardiography ruled out primary cardiac causes.

Imaging diagnosis

X-ray was used to rule out intraspinal pedicle screw placement as a cause.

Treatment

Fluid resuscitation as well as inotrope and vasoconstrictor therapy was required to treat the hypotension and spinal shock.

Related reports

Spinal shock in pediatric scoliosis repair using vertebral column resection has not yet been reported.

Term explanation

Vertebral column resection is a surgical technique which involves resecting a or some segmental vertebral columns in their entirety in order to facilitate correction of severe scoliosis. It is associated with increased surgical blood loss and possible neurologic complications.

Experiences and lessons

In caring for pediatric patients undergoing scoliosis surgery the anesthesiologist should be mindful of the possibility of spinal shock and be prepared to treat it with fluids and vasopressor/inotropic support such as norepinephrine and dopamine.

Peer-review

It is an interesting case.

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