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Anaesthesia and pancreatic surgery: Techniques, clinical practice and pain management

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Abstract

Pancreatic cancer continues to pose a major public health concern. The incidence of the disease is nearly equivalent to the death rate associated with the diagnosis of pancreatic cancer. Thus, there exists a need for continued improvement in the diagnostic, therapeutic and palliative care of these patients. There have been significant advances made over the years in the areas of critical care, anesthesia, and surgical technique, which have led to improved mortality rates and survival after resection for pancreatic cancer. Resections are performed with the goals of negative margins and minimal blood loss and referral to high-volume centers and surgeons is encouraged. However, 5-year survival rate after curative resection still remains at less than 20%. Perioperative management of pancreatic and periampullary cancer poses a considerable challenge to the pancreatic surgeon, anesthesiologist and the intensive care team. Major morbidity is often secondary to pancreatic anastomotic leakage and fistula or infection. The anesthesiologist plays a crucial role in the perioperative management of such patients and in the pain control. Pancreatic ductal adenocarcinoma has a high rate of neural invasion (80%-100%) and can be associated with moderate to severe pain. In the recent past, new information has emerged on many is-

ues including preoperative biliary drainage, nutritional support, cardiovascular assessment, perioperative fluid therapy and hemodynamic optimization. Careful patient selection and appropriate preoperative evaluation can greatly contribute to a favorable outcome after major pancreatic resections.

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Key words: Pancreatic cancer; General anesthesia; Epidural anesthesia; Pain management; Pancreaticoduodenectomy; Perioperative optimization

Core tip: The aim of this editorial is to provide, from anaesthesiological point of view, practical recommendations for management of patients with pancreatic cancer.

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EPIDEMIOLOGY

Surgery for pancreatic cancer (PC) is widely viewed as a complex procedure associated with considerable perioperative morbidity and mortality^[1,2]. There is consensus that patients with distant metastases or local invasion of the surrounding organs are usually not surgical candidates. A decision analysis demonstrated that the best strategy to assess tumor respectability was based on computed tomography (CT) as an initial test and the use of endoscopic ultrasonography (EUS) to confirm the results of respectability by CT^[3]. Laparoscopic ultrasonography has been introduced as an additional procedure to in-

Table 1 Risk-reduction strategies

Preoperative
Encourage cessation of cigarette smoking for at least 8 wk
Treat airflow obstruction in patients with chronic obstructive pulmonary disease or asthma
Administer antibiotics and delay surgery if respiratory infection is present
Begin patient education regarding lung-expansion maneuvers
Intraoperative
Limit duration of surgery to less than 3 h
Use epidural or blended anesthesia
Use laparoscopic procedures when possible
Substitute less ambitious procedure for upper abdominal or thoracic surgery when possible
Postoperative
Use deep-breathing exercises or incentive spirometry
Use continuous positive airway pressure
Use epidural analgesia
Use intercostal nerve blocks

crease the detection of intrahepatic metastases, identify enlarged and suspicious lymph nodes and to evaluate local growth in the vascular structures^[4]. Surgery for the PC can be considered an high-risk surgery^[5]. The American Society of Anesthesiologists score is widely used and easy to apply, but excludes age from its risk analysis^[6]. Age is securely one of the most important, if not the single most predictive, risk factor for morbidity and mortality after major surgery, including major pancreatic surgery^[7].

PREANESTHETIC CONSIDERATIONS

The objectives of the preanesthetic evaluation include establishing a doctor-patient relationship, becoming familiar with the surgical illness and coexisting medical conditions, developing a management strategy for perioperative anesthetic care and obtaining informed consent for the anesthetic plan.

History of smoking

The risk of PC in smokers ranks second to lung cancer and is proportionate to the frequency, duration and cumulative smoking dose^[8,9]. The patients who smoke have an increased risk of intra- and postoperative complications, particularly of a pulmonary or cardiovascular nature, compared with nonsmoking patients^[10,11]. As carbon monoxide (CO) preferentially binds to hemoglobin in place of oxygen, the short-term effects of cigarette smoking include elevated blood CO levels that result in a 3%-12% reduction of oxygen availability in the peripheral vascular district^[12]. Moreover, nicotine stimulates a surgical stress response with increase in heart rate, arterial blood pressure and peripheral vascular resistance. Postoperative pulmonary complications are an important part of the risk of surgery and prolong the hospital stay by an average of 1-2 wk. A careful history taking and physical examination are the most important parts of preoperative pulmonary risk assessment. One should seek an history of exercise intolerance, chronic cough or dyspnea.

The physical examination may identify decreased breath sounds, dullness to percussion, wheezes, rhonchi and a prolonged expiratory phase that can predict an increase in the risk of pulmonary complications^[13]. The value of routine preoperative pulmonary testing remains controversial. There is consensus that such testing should be performed selectively in patients undergoing no-lung resection. It has been suggested that an increased risk of pulmonary complications is associated with a forced expiratory volume in one second (FEV₁) or forced vital capacity (FVC) of less than 70% of the predicted value or a ratio of FEV₁ to FVC of less than 65%^[14]. A partial pressure of arterial carbon dioxide greater than 45 mm Hg can't be considered as a risk factor for pulmonary complications. Several strategies can be adopted in the perioperative period reducing the risks of complications (Table 1).

Diabetes

Nearly 80% of PC patients have either frank diabetes or impaired glucose tolerance. Diabetes is usually diagnosed either concomitantly or during the two years preceding the diagnosis^[15,16]. The link between abnormal glucose and PC exists only for type II diabetes. Better glycemic control in diabetic patients undergoing major surgery has been shown to improve perioperative mortality and morbidity. Diabetics are at increased risk of myocardial ischemia, cerebrovascular infarction and renal ischemia because of their increased incidence of coronary artery disease, arterial atheroma and renal parenchymal disease. Increased mortality is found in all diabetics undergoing surgery and type I diabetics are particularly at risk of post-operative complications. Increased wound complications are associated with diabetes and anastomotic healing is severely impaired when glycemic control is poor^[17-19]. The immediate perioperative problems facing the diabetic patient are: (1) surgical induction of the stress response with catabolic hormone secretion; (2) interruption of food intake, which will be prolonged in PC surgery; and (3) circulatory disturbances associated with anesthesia and surgery, which may alter the absorption of subcutaneous insulin. Surgery evokes the "stress response", that is the secretion of catecholamine, cortisol, growth hormone and, in some case, glucagon. These hormones oppose glucose homeostasis, as they have anti-insulin and hyperglycemic effects. Although diabetics need increased insulin during the perioperative period, requirements for glucose and insulin in this period are unpredictable and close monitoring is essential, especially in the unconscious or sedated patients. The main concern for the anesthetist in the perioperative management of diabetic patients has been the avoidance of harmful hypoglycemia; mild hyperglycemia has tended to be seen as acceptable. High-dose opiate anesthetic techniques produce not only hemodynamic, but also hormonal and metabolic stability. Abolition of the catabolic hormonal response to surgery will abolish the hyperglycemia seen in normal patients and may be of benefit in the diabetic

Table 2 Continuous insulin infusion protocol

Initiating CII:	
Prepare solution: 1 unit per 1 mL of 0.9% normal saline	
Start CII when blood glucose level ≥ 140 mg/dL ($\times 2$)	
Patients with known diabetes treated with insulin can start CII when blood glucose ≥ 70 mg/dL	
Initial rate: divide blood glucose level (mg/dL) by 100, then round to nearest 0.5 UI	
Insulin infusion rate change:	
BG (mg/dL) instructions:	
> 200	↑ rate by 2 UI/h
> 160-200	↑ rate by 1.0 UI/h
> 120-160	↑ rate by 0.5 UI/h
80-120	No change in rate
60-80	If < 10% lower BG, rate by 1 UI/h
	Check BG within 30 min
	If > 10% lower BG, 2 rate by 50%
	Check BG within 30 min
< 60	Stop infusion (give IV dextrose 12.5 g IV bolus)
	Check BG within 30 min. When BG > 100 mg/dL, restart infusion at 50% of previous rate
Patient monitoring:	
Check capillary blood glucose every hour until it is within goal range for 2 h, and then decrease to every 2 h	
Hourly monitoring may be indicated for critically ill patients even if they have stable blood glucose	
If a patient is eating, hourly blood glucose monitoring is necessary for at least 3 h after eating	
Decrease insulin infusion rate by 50% if nutritional therapy (e.g., total parenteral nutrition or tube feeds) are discontinued or significantly reduced	

CII: Continuous insulin infusion; UI: 1 unit; BG: Blood glucose.

patients. Tight metabolic control in the perioperative period is imperative and is a goal which is attainable in most patients. IV infusion of insulin is the standard therapy for the perioperative management of diabetes, especially in type 1 diabetic patients and patients with type 2 diabetes undergoing major procedure^[20]. Recently, several insulin infusion protocols have been reported in the literature. Two main methods of insulin delivery have been used either combining insulin with glucose and potassium in the same bag (GIK regimen) or giving insulin separately with an infusion pump. The GIK is initiated at a rate of 100 mL/h in a solution of 500 mL of 10% dextrose, 10 mmol of potassium, and 15 UI of insulin. Adjustments in the insulin dose are made in 5 UI increments according to blood glucose measurements performed at least every 2 h. The combined GIK infusion is efficient, safe, and effective but does not permit selective adjustment of insulin delivery without changing the bag. Separate continuous glucose and insulin infusions are used more frequently than the glucose-potassium-insulin infusion^[21-24]. A proposed regimen for separate IV insulin infusion for perioperative diabetes management is shown in Table 2.

Nutritional status

Malnourished patients who require major operations are predisposed to infectious complications and poor outcome. A low preoperative body mass index (BMI, kg/m²) may be regarded as an overall indicator of the size of the patient's reserves; a BMI < 20 kg/m² is an accepted indicator of malnutrition. However, it has been recognized that acutely malnourished patients may still have a normal or even elevated BMI. Serum protein markers such as albumin (for evaluating long-term nutritional status) and prealbumin (for evaluating acute responses to nutritional support) have been shown to be useful addi-

tional measurements for assessing nutritional status. Low albumin levels have been identified as an independent risk factor for postoperative morbidity and mortality^[25]. It should be emphasized that, although preoperative enteral or parenteral nutritional support clearly benefits surgical cancer patients, a systematic review showed that "preventive" administration of parenteral support in non-malnourished patients did not positively influence outcome and may even be potentially harmful for certain patient subgroups^[26]. More recently, the concept of immunonutrition has evolved, in which enteral formulas are supplemented with arginine and glutamine, nucleotides or omega-3 fatty acids in an attempt to positively modulate the immune system, but the benefits of immunonutrition remain debatable. Whereas perioperative nutrition in the malnourished patient can improve postoperative outcome, immunonutrition seems to attenuate the inflammatory response and interferes with certain immune functions in selected patient groups.

Patient with jaundice

Jaundice results from an abnormally high bilirubin in the blood whose origin may be difficulty in eliminating, it is then an obstructive jaundice. This is the most symptom in patients with periampullary cancer (located near the Vater's ampulla) or cancer of the pancreatic head. It can be considered a risk factor for postoperative complications. Many studies concluded that it could be associated with a higher incidence of insufficient postoperative renal growth, but also of sepsis, hemorrhage, of liver failure and risk of mortality from about 16%^[27]. Jaundice causes a retention of acids and bile salts. In the long term, it may cause ascending cholangitis and secondary hepatocellular damage. In case of interruption of bile flow, bile acids and salts can't inhibit the phenomenon of translo-

cation and endotoxemia caused by gram-negative from the digestive tract. These bacteria will then multiply and, for a phenomenon of translocation, can contribute to the dissemination of endotoxins into the systemic circulation then creating a pro-inflammatory state with production of cytokines by activated macrophages and a subsequent risk of multiple organ failure, including the appearance of coagulation disorders. Since surgery in patients with jaundice is thought to increase the risk of postoperative complications, preoperative biliary drainage was introduced to improve the postoperative outcome. In several experimental studies preoperative biliary drainage reduced morbidity and mortality after surgery^[28]. In a multicenter, randomized trial, van der Gaag *et al.*^[29] compared preoperative biliary drainage with surgery alone for patients with cancer of the pancreatic head found that endoscopic preoperative drainage with placement of a plastic stent did not have a beneficial effect on the surgical outcome and early surgery without preoperative drainage did not increase the risk of complications. The preoperative oral administration of bile salts or lactulose has been proposed in order to reduce the risk of endotoxemia by blocking translocation phenomena bacteria from the gut. The effectiveness of this practice has not been validated. Anti-inflammatory and antibiotic prophylaxis should be avoided. In severe cases, a preoperative hemodiafiltration session can address the surgery with more serenity.

The general physical examination

The physical examination should be thorough but focused. Special attention is directed toward evaluation of the airway, heart, lungs and neurologic status. As a minimum the physical examination should include the following:

Vital signs, head and neck: Height and weight are useful in estimating drug dosages and determining volume requirements and the adequacy of perioperative urine output. Ideal body weight should be calculated in obese patients to help determine proper drug dosages and ventilator settings (*e.g.*, tidal volume). Blood pressure should be recorded in both arms and any disparity noted (significant differences may imply disease of the thoracic aorta or its major branches). At same time should be observed and noted the respiration rate and oxygen saturation. One should evaluate maximal mouth opening, the size of the tongue, the ability to visualize the posterior pharyngeal structures and Mallampati classification. A thyromental distance shorter or longer than three fingerbreadth may be a sign of a difficult intubation.

Laboratory studies: A routine laboratory screening tests are necessary to evaluate a recent hematocrit/hemoglobin level, the platelet activity and the coagulation status before surgery. An electrocardiograph (ECG) should be obtained in any patient with risk factors for coronary artery disease. It can also detect new dysrhythmias and be useful to evaluate the stability of known abnormal rhythms. A chest radiograph should be obtained in all patients to

evaluate the cardiovascular image and to document any tracheal deviation or cervical masses.

ANAESTHETIC MANAGEMENT

General anesthesia with mechanical ventilation is the rule. Spinal anesthesia is impractical owing to the length of the operation. However, epidural analgesia could, in theory, be used as the sole anesthetic technique. It's our belief that the length of surgery, insertion of central lines and the high likelihood of conversion to general anesthesia make epidural alone unsatisfactory. Epidural analgesia may be beneficial post-operatively in reducing venous thromboembolic events, reducing the incidence of respiratory failure and in providing superior analgesia in comparison with opioids. However, there may be clotting abnormalities perioperatively leading to an increased risk of neurological complications. Epidural anesthesia can make assessment of the patient's volume status more difficult and, with large fluid shifts occurring in this group, a period of hypovolemia could be worsened by concomitant vasodilatation secondary to the epidural analgesia. A balance of these risks needs to be addressed before embarking on an epidural. It's our practice to routinely use epidural analgesia as a part of combined general and regional anesthetic technique in these patients. Postoperative analgesia is then provided by a catheter left in place in epidural space. The choice of anesthetics must consider their pharmacokinetic: benzodiazepines should be avoided for premedication; propofol are the preferred induction agent; morphine should be used with caution in patients with hepatic or renal function (accumulation); muscle relaxants not metabolized by hepatobiliary system (atracurium, cis-atracurium) are to be used in the first intent with adequate monitoring. The antibiotic therapy is essentially for the control of *Enterobacteriaceae* (*Escherichia coli*) and *Staphylococcus* risk infection. Fluid and volume therapy is an important cornerstone of treating critically ill patients in the operating room. New findings concerning the vascular barrier, its physiological functions and its role regarding vascular leakage have led to a new view of fluid and volume administration. Avoiding hypervolemia, as well as hypovolemia, plays a pivotal role when treating patients both perioperatively and in the intensive care unit. The postoperative phase may be studded with complications: sepsis, hepatic dysfunction, coagulation and metabolic disorders, renal and pulmonary failure and, in addition to the typical risks associated with abdominal surgery, some specific to the Whipple procedure, the two most common are pancreatic fistula and delayed gastric emptying^[30]. Therefore the recovery in the post-anesthesia care unit (PACU) is necessary for these fragile patients.

PHARMACOLOGY OF ANESTHETICS

Benzodiazepines

Their use in the perioperative period is widely not rec-

commended because of their hepatic metabolism that exposed to an increased half-life, an extension the duration of action and delayed recovery. In premedication for anxiolysis, with the exception of jaundiced patients, midazolam 0.1-0.4 mg/kg is indicated; after i.v. administration, the onset of central nervous system effects occurs in 2-3 min. The benzodiazepines (BZP) enhance inhibitory neurotransmission by increasing the affinity of GABA_A receptors for GABA. Effects are terminated by redistribution, the metabolism is typically hepatic and renal the elimination. Administration of a BZP to a patient receiving the anti-convulsive valproate may precipitate a psychotic episode.

Induction agents

Thiopental no longer the place it has had for very many years. In addition, its use was largely dissuaded in the presence of hepatobiliary disease because of its hepatic metabolism *via* the cytochrome P450. Thiopental is metabolized to pentobarbital, an active metabolite with a longer half-life. Its use therefore exposed to delayed awakening. Similar to propofol, barbiturates facilitate inhibitory neurotransmission by enhancing GABA_A receptor function. They also inhibit excitatory neurotransmission *via* glutamate and nicotinic acetylcholine receptors. Absolutely contraindicated in patient with acute intermittent porphyria, variegate porphyria and hereditary coproporphyrin (barbiturates induce porphyrin synthetic enzymes such as alpha-aminolevulinic acid synthetase). Ketamine for a variable pharmacokinetic in the presence of extrahepatic biliary obstruction and postoperative hallucinatory effects have largely limited use in clinical practice. Propofol is the agent of choice, not only for the induction, but also for sedation in patients requiring postoperative ventilatory support. It has a short action and effect rapid metabolism is not influenced in the presence of liver failure. It is prepared as a 1% isotonic oil-in water emulsion, which contains egg lecithin, glycerol and soybean oil. Bacterial growth is inhibited by ethylene-diaminetetraacetic acid, diethylene-triaminepentaacetic acid, sulfite, or benzyl alcohol depending on the manufacturer (avoid the use of opened propofol after 6 h to prevent inadvertent bacterial contamination). Mode of action: facilitation inhibitory neurotransmission by enhancing the function of GABA_A receptors in the central nervous system; the modulation of glycine receptors, N-ethyl-D aspartate receptors, cannabinoid receptors and voltage-gated ion channels may also contribute to propofol's actions. Dose-dependent decreases in preload, afterload and contractility lead to decrease in blood pressure and cardiac output. Hypotension may be marked in hypovolemic, elderly, or hemodynamically compromised patients. Heart rate is minimally affected and baroreceptor reflex is blunted. Adverse effects are: irritation venous, lipid disorders, myoclonus and hiccups, "propofol infusion syndrome".

Opioids

Morphine and its derivatives are essential for the peri-

operative period (commonly used in general anesthesia) and are frequently used to ensure postoperative analgesia. Opioids, including morphine and fentanyl, have been accused of increasing the tonus of the bile ducts and spasm of Oddi's sphincter. However, the consequences in clinical practice are limited: the pressure is most often in the bile duct within normal limits and delay the passage of bile in the duodenum is not significant. The administration of a derivative nitrate was effective in treating the hypertension. Opioids differ in their potencies, pharmacokinetics and site effects. The mode of action is due to the interaction with specific receptors in the brain, spinal cord and peripheral neurons^[31]. After i.v. administration, the onset of action is within minutes for the fentanyl derivatives; hydromorphone and morphine may take 20-30 min for peak effect due to their lower lipid solubilities. The termination of effects for all opioids except remifentanyl is by redistribution. Elimination is primarily by the liver and depends on hepatic blood flow. In patients with renal failure, the accumulation of morphine-6-glucuronide, the active metabolite, may cause prolonged narcosis and respiratory depression. Fentanyl is metabolized by hydrolysis and N-dealkylation, and its metabolites are excreted in the urine. Function liver in the normal range is necessary to plasma clearance in case of repeated injections. The pharmacokinetics of alfentanil is also changed, with a longer duration of action and an initial effect over pronounced. The sufentanil is not altered, even in cases of moderate hepatic insufficiency. The short duration of action of remifentanyl (context-insensitive half-time) and especially its extrahepatic metabolism (by nonspecific esterases in tissues, primarily skeletal muscle) are purely an advantage^[32]. Opioids exert emetic effects and represent a significant cause of patient discomfort. Nausea and vomiting can occur because of the direct stimulation of the chemoreceptor trigger zone, of the vestibular apparatus, inhibition of gut motility^[33].

Halogenated

Inhalation agents represent a basic drug used in modern balanced anesthesia. Actually the most important halogenated in the clinical use are sevoflurane and desflurane. Desflurane is largely appreciated for its high stability. Less than 0.02% of desflurane is metabolized, thus, plasma fluorine levels are very low. The very low solubility of desflurane allows for a surprisingly rapid emergence from anesthesia. Nitrous oxide has a controversial role in the modern anesthesia. Its ability to diffuse into air filled cavities increases the likelihood of pneumothorax, air emboli and pressure in the cuff of the endotracheal tube. Nitrous oxide diffusion causes an increase in the middle ear pressure and distension of the bowel, possibly resulting in increases in postoperative nausea and vomiting. The results of a questionnaire proposed by the Association of Anesthesiologist of Great Britain and Ireland indicate that 49% of them had reduced their use of nitrous oxide^[34]. According to Baum, nitrous oxide should not be used routinely as a carrier gas and the safer mixture of

oxygen/medical air is able to replace this old anesthetic with some economical advantages^[35]. The combination of halogenated agents with short acting opioids results in the possibility of limiting the clinical application of nitrous oxide. Attempts to replace nitrous oxide with other gases has led to an increase in studies on Xenon. This inert gas does not undergo metabolic biotransformation and has no direct negative environmental effects. Xenon has a very low solubility in the blood and its potency is higher when compared to nitrous oxide solubility^[36]. Xenon cannot be synthesized and the available amount is very low. Consequently, at present, the cost of compound may be a limiting factor for the clinical use. The pharmacokinetic advantages of inhalation anesthetics are unique. By increasing or decreasing their inspired concentration, it is possible to increase or decrease their concentration in the blood and tissues, allowing for rapid changes in anesthesia depth and providing a simple method for inducing, maintaining and reversing general anesthesia. The flexibility of inhalation anesthesia cannot be reproduced with modern intravenous hypnotics or opioids. Furthermore, it is important to underline the protective effects of inhalation agents on several different organs.

Neuromuscular blocking drugs

Non depolarizing blockade is produced by reversible competitive antagonism of Ach at the alpha subunits of the AChRs. The principal pharmacologic effect is to interrupt transmission of synaptic signaling at the neuromuscular junction. The neuromuscular blocking agents in biliary excretion (*e.g.*, vecuronium) should be avoided in favor of those metabolized by Hoffman system (atracurium, cis-atracurium). In all cases, the use of a monitoring of neuromuscular blockade is essential^[37,38].

Monitoring

Standard monitoring for general anesthesia involves oxygenation (analyzer and pulse oximetry), ventilation (capnography and minute ventilation), circulation (ECG with ST-segment analysis, blood pressure and perfusion assessment) and temperature if necessary. Additional monitoring may be added such as invasive arterial and venous pressure monitoring, trans esophageal echocardiography, neuromuscular blockade and central nervous system monitoring. Invasive arterial pressure monitoring is imperative in the pancreatic surgery; there is potential for rapid swings in blood pressure and acid-base balance often needs managing (acidosis is common). Central venous access (CVC) is essential; ultrasound guidance can be useful in the patients that have had multiple previous cannulation. The central venous pressure (CVP) and cardiac output (CO) is monitored by CVC. Pressure is monitored at the level of the vena cava or the right atrium. The normal CVP is 2-6 mmHg. Positive-pressure ventilation affects both cardiac output and venous return. According to the Starling rule, the transmural pressure, which is the difference between the atrial pressure and extracardiac pressure, correlates with the cardiac output. At low level

of positive end-expiratory pressure (PEEP), the CVP increases with increased PEEP. At high levels of PEEP (over 15 cm H₂O), CVP increases as the cardiac output is depressed because of impaired right ventricular output. Common locations include internal jugular and subclavian vein. Multiple lumen catheters are directly inserted and are available with one to four lumens to provide access for multiple drugs, pressure monitoring and blood sampling. Temperature may be measured continuously; the limitation of more external methods of temperature determination is that they may not reflect changes in the core body temperature, especially in the presence of vasoconstriction. Oropharyngeal temperature monitoring is preferred in any lengthy laparotomy, which has potential for blood loss and perioperative clotting abnormalities. Ventilation is assessed by end-tidal carbon dioxide measurements and spirometry. Capnometry and capnography are often used as synonyms, as both analyze and record carbon dioxide, with the latter including a waveform. Capnography not only evaluates respiration but also confirms of endotracheal intubation and is diagnostic of pathologic conditions. Neuromuscular blockade is utilized, above all for patients with co-existing renal failure. The adductor pollicis response to ulnar nerve stimulation at the wrist is most often used, because it is easily accessible, and the results are not confused with direct muscle activation. Cutaneous electrodes are placed at the wrist over the ulnar nerve and attached to a battery-driven pulse generator, which delivers a graded impulse of electrical current at a specified frequency. For maximal twitch response, the negative pole (active) should be placed distally over the ulnar nerve at the wrist. Evoked muscle tension can be estimated by feeling for thumb adduction or measured by using a force transducer attached to the thumb. After administration of a neuromuscular blocking drug, the developed tension and twitch height decrease with the onset of blockade. Foley catheter is the rule in all patient ones, necessary for fluid management and the control of the renal functionality.

Conduct of anesthesia

The primary goals of general anesthesia are to maintain the health of the patient while providing amnesia, hypnosis (lack of awareness), analgesia and immobility. Secondary goals may vary depending on the patient's medical condition and the surgical procedure. Perioperative planning involves the integration of preoperative, intraoperative and postoperative care. Flexibility, the ability to anticipate problems before they occur and the ability to execute contingency plans are skills that define the expert anesthetist. An anesthetic plan developed prior to entering the operating room helps the anesthetist marshal appropriate resources and anticipate potential difficulties. Important elements to consider in the anesthetic plan include: risk assessment (ASA classification), specific homeostatic challenges, intravenous access, monitoring, airway management, medications, perioperative analgesia, postoperative transport and disposition. Preoperative

medication is realized with midazolam 0.1-0.4 mg/kg (except cases of jaundice) for anxiety control. It is also important to consider aspiration prophylaxis; drugs to neutralize gastric acid and decrease gastric volume are used: metoclopramide 10 mg and ranitidine 50 mg usually. Induction of anesthesia produces an unconscious patient with depressed reflexes who is dependent on the anesthetist for maintenance of homeostatic mechanisms and safety. The patient's position for induction is usually supine, with extremities resting comfortably on padded surface in a neutral anatomic position. The head should rest comfortably on a firm support, which is raised in a "sniff" position. Routine pre-induction administration of oxygen minimizes the risk of hypoxia developing during induction of anesthesia. High flow (8-10 L/min) oxygen should be delivered *via* a face mask placed gently on the patient's face. Commonly, for the induction of anesthesia, we use propofol 4-6 mg/kg, a non-depolarizing neuromuscular blocking agent (cis-atracurium 0.15 mg/kg is the usual choice) and sufentanil 0.1-0.5 mcg/kg per minutes. Hypertensive patients may have an exaggerated pressor response to laryngoscopy. To obtund this response, opioids or beta-blockers can be used. Tracheal intubation is performed with laryngoscopy usually. An appropriate endotracheal tube (ETT) size depends on the patient's age, body habitus. Proper placement of the ETT needs to be verified by the detection of carbon dioxide in end-tidal or mixed expiratory gas as well as inspection and auscultation of the stomach and both lung fields during positive-pressure ventilation. Tidal volumes of 8-10 mL/kg and a respiratory rate of 10-12 breaths/min are set and low level PEEP is beneficial. For the maintenance of anesthesia we use normally a mixture of oxygen and air (40%/60%) and a halogenated (sevoflurane or desflurane) with a continuous infusion of sufentanil until the end of operation. The infusion of sufentanil generally is continued in the PACU to better adapt the patient to the mechanical ventilation. If we decide for a blended anesthesia, before the induction of anesthesia, we perform a thoracic epidural anesthesia (T8-T10) with the patient in a sitting position.

Epidural anesthesia / analgesia

The epidural space contains nerve roots, fat, spinal arteries and lymphatics, as well as a valveless venous system that communicates directly with both the intracranial sinuses *via* the basovertebral veins and the general circulation *via* the azygous vein. Dorsal and ventral spinal nerve roots covered by dura mater pass across the epidural space and drugs within this space can act on any nerve that traverses it - whether it is motor, sensory or autonomic. Epidural analgesics may prevent the release of neurotransmitters from afferent pain fibres, block receptors to neurotransmitters released by primary afferent pain fibres or interrupt the transmission of pain-related information in the dorsal horn of the spinal cord. Drugs introduced into the epidural space also have the potential to pass into the brain and the general circulation depend-

ing on their pharmacokinetics. Epidural analgesia was originally achieved with local anesthetic agents but, more recently, with opioids or a combination of local anesthetics and opioids. This combination has a synergistic action that allows the concentration of each drug to be reduced, thereby limiting unwanted effect produced by higher concentrations. Ketamine, midazolam or clonidine has also been used in combination with local anesthetics and opioids to obtain the best intra- and post-operative pain control. Local anesthetics penetrate axonal membranes within the epidural space and bind to sodium channels in nerves. This inhibits sodium conductance and reduces action potential depolarization, thereby reducing nerve stimulus propagation. The drawback is that the effect is nonselective, involving both autonomic and somatic nerves. Thinner nerve fibers are affected by lower local anesthetic concentrations than thicker fibers, suggesting that neuronal block is a function of diameter. With increasing local anesthetic concentration, the thinner C fibers (pain and autonomic fibers) are blocked first, followed by B fibers (preganglionic sympathetic fibers) and finally the largest A fibers (touch, pressure sensation and motor fibers). Epidural analgesia aims to produce a differential nerve block, affecting predominantly nociceptive fibers with few motor effects. Opioids act on opioid receptors that are widespread throughout the nervous system, but more concentrated in the medullary dorsal horn of the spinal cord and the periaqueductal grey matter of the brain. Opioid receptors belong to the family of guanine nucleotide-binding protein receptors. They exist as three principle types (OP1, OP2 and OP3) and opioids acting at these receptors have the advantage of selectively blocking pain without affecting motor function or the sense of touch. Epidural opioids act mainly on presynaptic and postsynaptic receptors in the substantia gelatinosa of the dorsal horn of the spinal cord^[39]. The combination of thoracic epidural analgesia (TEA) and general anesthesia has become a widespread anesthetic technique for the perioperative treatment of patients undergoing major abdominal surgery. The neuraxial application of local anesthetics and opioids provides superior pain relief, reduced hormonal and metabolic stress, enhanced normalization of gastrointestinal function and thus a shortened postoperative recovery time, facilitating mobilization and physiotherapy. TEA is currently thought to mitigate this effect by blocking nociceptive afferent nerves and thoracolumbar sympathetic efferent routes. In a very recent cohort study van Lier *et al*^[40] demonstrated that epidural analgesia reduces postoperative pneumonia in patients with chronic obstructive pulmonary disease undergoing major abdominal surgery. Among the long-acting local anesthetics, the S-enantiomer, ropivacaine, is gaining increasing preference for continuous epidural analgesia. Ropivacaine has lower central nervous system and cardiac toxicity and a less frequent incidence of motor block (differential block) during mobilization than bupivacaine^[41]. Panousis *et al*^[42] evaluated the effect of different epidurally administered concentrations of ropivacaine on

inhaled anesthetic, fluid and vasopressor requirement and hemodynamic changes. They concluded that ropivacaine 0.5% compared with a ropivacaine 0.2% concentration led to a greater inhaled anesthetic-sparing effect at the same levels of IV fluid supply and vasopressor support. In a critical appraisal published on 2008, Pratt *et al.*^[43] concluded that although it may provide more effective initial pain control, epidural analgesia does not necessarily improve other critical outcomes after pancreatoduodenectomy. The authors explained it with the high propensity for rapid fluid shifts and excessive blood loss during this operation, which may negate the proposed benefits of administering analgesic medications by epidural infusion and they reinforced these results considering the frequent need to terminate epidural infusions because of hemodynamic compromise or inadequate analgesia. Spinal epidural hematoma (SHE) after epidural analgesia is a rare but serious complication. Most cases of SHE after epidural block are attributed to a bleeding tendency or anticoagulant therapy. Placement of an epidural catheter may cause SHE more often than expected, but most SEHs remain asymptomatic^[44]. The incidence of significant spinal bleeding (paraplegia requiring laminectomy) has been estimated at 1:1000000 in patients without clinically apparent coagulation disorders. Vandermeulen *et al.*^[45] found spinal bleeding immediately after removal of the epidural catheter in 15 of the 32 cases that he reviewed. Spontaneous SHE has been reported in a few cases^[46]. The maximum incidence of clinically important spinal bleeding after epidural catheter blocks without specific additional risk factors probably list between 1:190000-200000. Approximately 60%-80% of all clinically important spinal bleeding is associated with hemostatic disorders or a blood tap. Removal of an epidural catheter should be considered a significant risk factor for spinal bleeding because 30%-60% of clinically important spinal hematomas occurs after catheter removal^[47]. Where central neural block is contraindicated (*e.g.*, systemic sepsis, in anti-coagulated patients), or where epidural catheterization is technically impossible, bilateral paravertebral nerve blocks (PVB) is a suitable alternative. The paravertebral space is a potential space, which is turned into a temporary cavity by fluid. Anesthesia occurs because of direct penetration of local anesthetic (LA) into the neurological structures contained within the PVB (anterior and posterior ramus of the intercostal nerve, sympathetic chain, rami communicantes, sinu-vertebral nerve). The spinal nerve, lacking both an epineurium and part of the perineurium and with only a thin membranous root sheath is easily penetrated by LA and hence easily and efficiently blocked^[48]. We recommend the use of levobupivacaine or ropivacaine for bilateral blocks. Good preservation of postoperative pulmonary function has been demonstrated, particularly in thoracotomy, which is a significant benefit over epidural analgesia^[49]. The incidence of complications such as pneumothorax and hypotension is low. For bilateral PVB a variety of techniques, including loss of resistance, nerve stimulators and ultrasound, have been used. Potential or relative contraindications to the use of PVB are coagula-

tion disorders, tumor in the PVB and an empyema.

POSTOPERATIVE CARE

Postoperative analgesia

In patients with epidural catheter the analgesia can be continued with a volumetric or elastomeric pump at a rate infusion of 5-8 mL/h, by using local anesthetics alone or in combination with opioids. Generally we use ropivacaine 2 mg/mL and sufentanil 5 mcg/mL. In patients where was impossible the positioning of an epidural catheter the postoperative analgesia is performed with i.v. NSADs or opioids or mixture of them. Several protocols are reported in literature for i.v. analgesia, but generally morphine is the leader drug. The patient controlled analgesia is the best route of administration with a primary dose of 2-10 mg and a rescue dose of 0.5-2 mg with a lock-out of 5-10 min^[50]. A specific role have the COX-2 inhibitors. Parecoxib (40-80 mg) is disposable for intravenous administration^[51].

Pain and inoperable pancreatic cancer

Pancreatic diseases such as cancer can cause clinically significant pain in the upper abdomen, which may radiate to the back. Pain management for pancreatic cancer patients is one of the most important aspects of their care, as it is one of the most weakening symptoms. The best therapy involves adequate therapy with constant assessment. The current management of pancreatic pain follows the WHO three-step ladder for pain control, starting with non-opioid analgesics such as nonsteroidal anti-inflammatory drugs and progressing to increasing doses of opioid analgesics^[52]. For pain that does not respond to drugs, or when oral or topical medication leads to unacceptable side effects such as nausea, constipation, somnolence, confusion, dependence and addiction, an alcohol nerve block can be indicated. This provides pain relief by acting directly on the nerves (celiac plexus) that carry painful stimuli from the diseased pancreas to the brain. Pancreatic cancer causes severe pain in 50%-70% of patients. This kind of pain is multi-factorial (pancreatic duct obstruction and hypertension, neural invasion) and it is often difficult to treat^[53]. Different mechanisms perpetuate pancreatic pain: infiltration of nerve sheaths and neural ganglia, increased ductal and interstitial pressure and gland inflammation. Pancreatic pain is generally transmitted through the celiac plexus, a neural structure located in the upper abdomen, near the emergence of the celiac trunk from the aorta. Celiac plexus neurolysis was first described by Kappis (1919) and is done at the level of the L1 vertebral body, with the patient in a prone position^[54]. There are a number of variations on the technique^[55]. It has been described in the literature since the 1950s but the first prospective study was published in 1990 and the first randomized in 1992. Celiac plexus neurolysis can be done surgically under fluoroscopic guidance or under CT guidance. The target for celiac axis destruction are the splanchnic nerves and/or celiac ganglia. The splanchnic nerves cross the diaphragm, enter the abdominal cavity

and form the celiac plexus. The celiac ganglia are located around the celiac artery anterior to the aorta, in varying positions, from T12 to L2. They can be reached percutaneously by different routes, with one needle through the anterior approach (under CT or ultrasound guidance) or with one or two needles through the posterior approach. During abdominal surgical procedures for pancreatic cancer chemical splanchnicectomy can be achieved by injecting the neurolytic solutions directly into the junction area of the splanchnic nerves with the celiac ganglia in the retroperitoneal area. With the advent of EUS new therapeutic applications for endoscopy have been developed and a needle can now be guided safely in the celiac plexus^[56]. The celiac plexus is destroyed by alcohol injected under the guidance of real-time endosonography. First, using a linear array echo-endoscope, the region of the celiac ganglia is located from the lesser curve of the stomach, following the emergence of the celiac trunk from the aorta. The anterior approach avoids the retro-crural space and minimizes the risk of neurologic complications such as paraesthesia or paralysis. Anyway, although statistical evidence is minimal for the superiority of pain relief over analgesic therapy, the fact that CPB causes fewer adverse effects than opioids is important for patients.

CONCLUSION

Pancreatic ductal adenocarcinoma (90% of pancreatic cancers) remains a devastating disease. For a select group in which complete resection is possible, surgery prolongs survival. Pancreaticoduodenectomy, the “Cadillac” of abdominal operations, is a major surgery with significant morbidity and mortality. The pancreatic-enteric anastomosis has been the Achilles’ heel of this operation. Adequate nutritional support, reduction of invasiveness, shorter operation times, combined regional/general anesthesia and target-controlled fluid management are options for reducing postoperative morbidity. In recent decades, diagnostic modalities and the surgical and palliative treatments of PC have clearly progressed, although the overall prognosis has barely changed. The management of patient affected by PC is complex and requires expertise in many fields. Multidisciplinary teams are necessary to optimize the overall care. The anesthesiologist plays a crucial role in the perioperative management of a patient with unresectable PC (anesthesia and analgesia). Careful patient selection, individualized preoperative evaluation and optimization go a long way in improving the short-term and long-term outcomes of these patients. In the future new protocols are necessary for pain control, adjuvant strategies, palliative measures in patients with pancreatic cancer.

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Review of essential understanding of ultrasound physics and equipment operation

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Abstract

Ultrasound (US) is being extensively used as an imaging tool in regional anesthesia (RA) and pain practice. Although it was first used in a regional block in 1978, it was only in 1994 that the first direct use of US in RA was reported. Like any other medical tool, its utility is only realized when the performing physician is able to understand the principles behind its application. Efficient use of US also requires an understanding of physical variables which can be suitably modified to produce a clear image of the structure of importance. This brief narrative review summarises the advantages of US in RA and pain practice over the conventionally used localising or imaging tools. The second section deals with the physics behind US. It highlights the necessary physical concepts such as wavelength, frequency and generation of US waves. It also informs the reader about the possible US and tissue interactions, use of US transducers and their differences. The third section deals with understanding the control variables in a typical US machine and how they could be modified to improve the image quality. The final section highlights the various artifacts that could be associated.

reserved.

Key words: Ultrasound physics; Ultrasound in regional anesthesia; Essential concepts of ultrasound; Ultrasound basics; Artifacts

Core tip: This review summarises the essential concepts of ultrasound (US) physics and equipment operation. To make the best use of US in regional anesthesia and pain practice, it is important to obtain a quality image. Since anesthesiologists do not depend on any image technician, it is necessary for them to understand the operating principles of the equipment. The physician will also have to choose an appropriate transducer, and make suitable adjustments in gain and focus. All these concepts are detailed in simple terms along with necessary figures for easy understanding.

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INTRODUCTION

Ultrasound (US) is being increasingly employed in the field of anesthesiology and pain medicine. Medical use of US, for diagnostic brain imaging was first done by Dr Karl Theo Dussik^[1]. The published report of Doppler technology for regional block came in 1978^[2]. Subsequently it was not popularly used in the field of anesthesia until the last couple of centuries. The first direct use of US for regional block was performed in 1994^[3]. The number of physicians who use it in their daily practice has increased significantly. Although tremendously useful, it is still a machine and it is up to the physician using it to make the most of it. As Dr. Marhofer *et al*^[4] has said, informed scepticism should accompany an increasing

Table 1 Several potential advantages over the nerve stimulation methods

Advantages of ultrasound nerve localisation in regional anesthesia ^[4]
Real time imaging-helps to modify the technique based on individual differences in anatomy
Actual visualisation of neural structures
Guides approximate needle positioning (not too near or too far)
Lesser patient discomfort-motor confirmation/muscle twitches may not be necessary
Can visualise vascular structures-helps to avoid intravascular injections
Visualisation of local anesthetic spread-less volume block-decreases the chances of toxicity
Can visualise important organs and avoid injury-lung shadows in supraclavicular block, paravertebral block
Other advantages of ultrasound as compared to fluoroscopy or computed tomography scan
Easy to use-less bulky
Does not need a separate environment-such as radiation shielded walls
No radiation exposure-safe
Cheaper
Produces tomographic images
Does not need a technician to operate

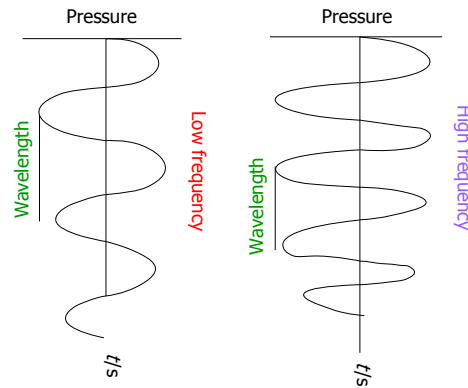
enthusiasm. The appropriate use of US technology in regional anesthesia (RA) requires a thorough knowledge of anatomy, an essential understanding of its working, and adequate training in the use of needling techniques. Accordingly essential categories of training in US guided interventional procedures are supposed to involve: (1) understanding device operations; (2) image optimization; (3) image interpretation; and (4) visualisation of needle insertion and injection^[5]. This review summarises the physical principles involved in US operation and also an understanding of the equipment involved and its appropriate use.

SECTION 1

Advantages of US as an imaging modality

US has several advantages over the conventional imaging or nerve localisation modalities. In the field of RA, US clearly has several potential advantages (Table 1) over the nerve stimulation method. Although improvement in patient safety during RA procedures could be debatable, there continues to be a surge of publications reporting better technical performance, lesser complications and increased safety with the use of US^[6].

In the field of interventional pain medicine (IPM), fluoroscopy to a major extent and computed tomography scan to some extent have been used as imaging modalities. There are important challenges for the use of US guidance in IPM. Most involve precision placement of needles around the neuraxis. However US is still very useful for injection of superficial structures such as stellate ganglion, inguinal nerves, intercostals nerves; deep intramuscular injections such as piriformis, trigger points, BOTOX injections. Narouze *et al*^[7] detail the pain interventions that can be done with the use of US. They also list the level of difficulty associated.

**Figure 1 Ultrasound waveform.**

SECTION 2

Understanding the physics behind the use of US

US waves are a form of sound waves. US wave frequencies exceed the upper limit of audible human hearing. Medical US frequencies are in the range of 1-20 MHz. Each US wave is characterised by a specific frequency and wavelength, which are inversely related (Figure 1). The higher the frequency, lower the wavelength. Frequency is the number of cycles per second and is measured in Hertz.

Wavelength is the distance between two consecutive, similar positions in the pressure wave. It is determined by the frequency of the wave, and the speed of propagation in the medium it is passing through. Actually the speed of sound is different based on the tissues through which it propagates: air-330 m/s, water-1525 m/s, bone 3000 m/s, fat-1450 m/s, muscle-1600 m/s and blood-1560 m/s. However it is averaged as approximately 1540 m/s for the entire body and is referred to as propagation velocity or acoustic velocity^[8,9].

The US waves are produced by piezoelectric effect, which was discovered by Curie brothers in 1880^[10]. It involves the generation of an electrical charge, by a piezoelectric material, when subjected to mechanical stress and the reverse piezoelectric effect involves such an electrical charge being converted to mechanical vibration. In the available US machines the transducer holding the piezoelectric material acts both as a generator and receiver of such signals. US used in medical imaging is referred to as B-mode (2D), meaning brightness mode display. This means the brightness of the pixel on the image is a representation of the strength of reflection.

A source of alternating current makes the piezoelectric crystals to vibrate at high frequency producing US waves. This is then transmitted to the patient through a conductive gel. These sound waves go through structures underneath the transducer and information is relayed back as reflected sound waves. A transducer acts as a generator of US waves for only 1% of the time and acts as a microphone to listen to the incoming waves for the rest 99% of the time. Frame rate refers to number of such pulses of US waves^[11]. Higher frequency produces more

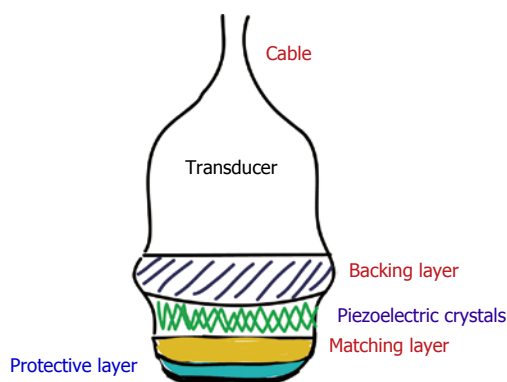


Figure 2 Typical transducer.

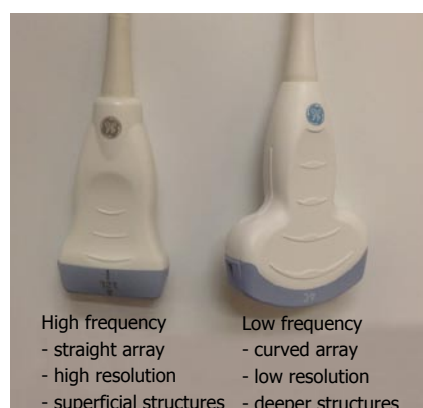


Figure 3 Commonly used transducers.

waves of compression and rarefaction in a given time and increases the resolution (ability to discriminate between 2 separate structures along the axial plane).

US equipment

Medical US utilises a transducer attached to a display monitor which also holds the operating console. A transducer (also known as probe) contains a damping material, piezoelectric crystals, a matching layer and a protective layer (Figure 2). Each crystal is isolated and hence transmits its own US wave. The damping layer, present just behind the crystals acts to reduce their resonance so that they are sensitive to the returning signal. The matching layer in front acts to reduce the impedance mismatch and is covered by a protective layer^[10].

There are several types of transducers and it is necessary to choose the right one for the procedure. Based on the frequency range, commonly 2 types of transducers are used for RA procedures^[10] (Figure 3). Some others give 3 varieties, based on the range: high- (8-12 MHz), medium- (6-10 MHz), and low- (2-5 MHz)^[12]. The smaller one with a straight contact surface is called a linear array transducer due to the linear arrangement of crystals. It also produces high frequency waves in the range of 8-12 MHz. Its penetration, and hence resolution is usually good for structures within 3-4 cm. The larger one with a curved contact surface is called a curved array or curvilinear transducer because of the curved arrange-

ment of crystals^[8,9]. It creates a wedge shaped US beam and produces a much broader view with the image of deeper structures being wider than the footprint of the probe. It is used to visualise deeper structures, beyond 4 cm. It is important to know that the width of the image is equal to the probe footprint size only at the uppermost part of the image and hence any determination of depth is tricky^[13].

US tissue interaction

Once generated the wave passes through various tissue structures and thereby interacts with them. This interaction results in various possibilities as shown in Figure 4. US waves are primarily influenced by physical changes involving reflection, refraction and attenuation. The reflected wave, which gives rise to the resulting signal, is dependent upon the underlying structures the waves encounter. This property is called acoustic impedance^[14]. It is unique to each tissue type and is defined as the density of the medium times the velocity of US wave transmitted through it. Less dense organs such as lungs have a lower impedance in contrast to bones which would have a higher impedance. The greater the differences in acoustic impedance between 2 adjacent tissues, more waves are reflected back. So it is not individual acoustic impedances but the relative difference of it among adjacent tissues that control the amount of energy reflected back^[15].

Specular reflection involves a large smooth surface, such as a needle. Depending upon the incident angle, a large amount of US waves are reflected back to the transducer. Scattered reflection involves an irregular surface giving rise to scattering and hence loss of signal. However due to the wide range of angles, regardless of the incident angle, some US energy is always reflected back. Most biological tissues fall into this category and give rise to the speckled appearance observed of most soft tissues^[16]. Refraction involves changes in the direction of US waves due to an interface of tissues with different speeds of sound transmission. This is similar to seeing a bent spoon when observed in a glass of water. This gives rise to loss of energy when not captured from the transducer^[16]. Even when captured, acts as a source of several artifacts (duplication error) commonly encountered^[15]. Attenuation refers to the loss of energy as the sound waves travel through increasing depth. It is related to the depth of beam penetration, type of tissue being imaged and the frequency of the wave. Due to friction, a vast amount of energy is lost as heat. More dense structures have higher attenuation coefficients as the oscillatory tissue motion produced by the sound wave creates more friction and heat^[15]. Higher frequency signals are attenuated more than the lower frequency signals. Hence a high frequency probe cannot be of much help in visualising deeper structures such as the sciatic nerve. Posterior acoustic enhancement, a commonly observed artefact, is largely due to an intrinsic compensating mechanism provided to counter the attenuation and loss of signal when imaging highly hyperechoic structures such as blood vessels^[15]. Transmission refers to loss of signal due to unop-

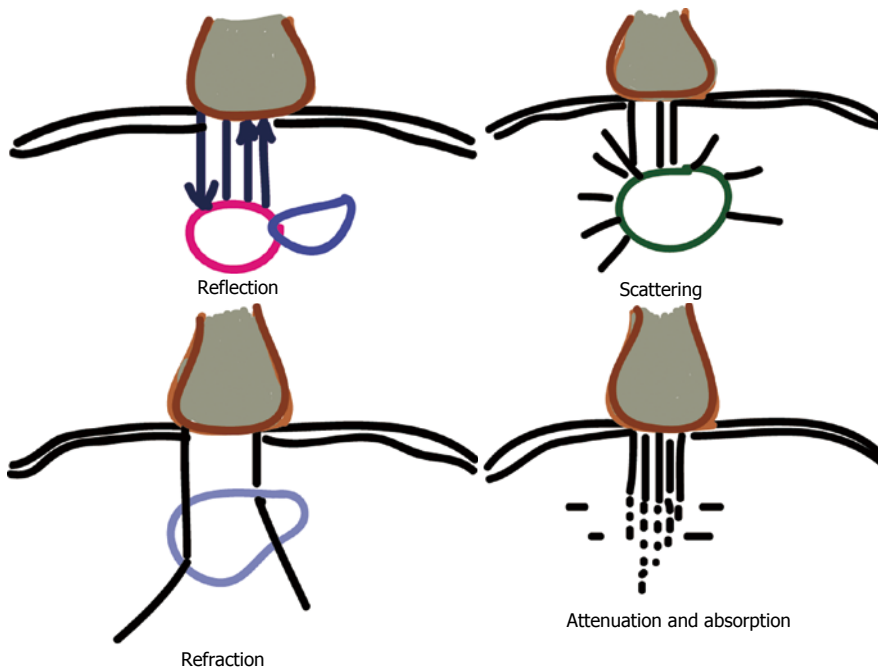


Figure 4 Ultrasound and tissue interactions.



Figure 5 Necessary operating controls to obtain an optimal image.

posed transmission away from the probe^[16].

SECTION 3

Understanding the controls and improving the image quality

A good use of US guidance can only be made when one understands how to operate the equipment and also how to modify the variables to get the best possible image. The following section gives an understanding of these elements (Figure 5).

Resolution: It describes the ability to separately identify to individual structures^[8,12]. Axial resolution refers to the possible differentiation between the 2 objects in the plane of US beam. Higher frequencies and superficial structures give better axial resolution^[10].

Temporal resolution refers to the rate at which consecutive images are visualised. It depends on the frame

rate or pulses. A transducer emits the next pulse only after it has received the previous pulse. Increasing the depth of US beam affects the temporal resolution. Similarly, using Doppler has the same effect as it requires more time to process the incoming signals and hence lower temporal resolution. Lateral resolution refers to separation of structures lying side by side. Inappropriate use of focus zone-as explained below can decrease the lateral resolution. Contrast resolution is referred to the optimal visualisation achieved in terms of hyper and hypo-echogenic structures displayed on the screen. To enhance visualisation and to improve resolution there are 3 important settings which can be altered.

GAIN: This simply refers to the strength of the signal. The brightness of the image is proportional to the strength of the signal received by the transducer. A highly reflective structure sends back proportionately more sound signals causing whiter shadow-hyperechoic, whereas less dense and less reflective structures send back less signals to the transducer causing blacker shadow-hypoechoic. Increasing the gain increases the signal strength and brightness in general. This may not be optimal as even the background structures (noise) are also increased^[12]. The optimal gain necessary for visualisation might be different from what is set as auto-gain and might need individual adjustments. Such well adjusted image is referred to as contrast resolution. Increasing the gain can also affect lateral resolution.

FOCUS: The sound waves converge to a point called focal zone and then diverge^[10]. The divergence of these waves beyond the focal zone can allow for missed information in a horizontal plane. To minimise this loss, it is

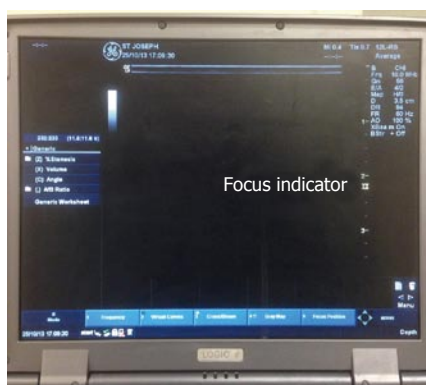


Figure 6 Focus Indicator shown on screen.

important to set the focal zone at the same level as the target of interest. It is achieved usually by a dial setting and is observed on the monitor as a small arrow on either side of the screen (Figure 6).

Time gain compensation: As the name suggests there is an increase in gain (signal strength) which is restricted to a set field of depth. Attenuation increases with increasing depth. To compensate for this time gain compensation (TGC) allows for stepwise increase in gain which can be adjusted for a particular depth. It is suggested that TGA adjustments are made less frequently than gain adjustments, which is not usually optimal^[6].

Frequency: Waves of higher frequency are more attenuated. One should choose a higher frequency probe for superficial structures, and low frequency probe for deeper structures.

Color doppler: This function helps to detect structures with movement, like blood flow. It is based on the doppler principle. Structures moving away from the probe appear blue and those towards the probe appear red. One important thing to remember is that the angle of incidence should be as less as possible. With an angle of incidence of 90°, no flow is detected and might provide a false negative implication. To help visualise even smaller vessels and also to be independent of the incident angle, newer machines have power Doppler^[9,13]. This function provides only a single color pattern.

SECTION 4

Artifacts associated with US imaging

The image produced on the monitor is a 2 dimensional image obtained from converting mechanical energy into electrical signals. The actual conversion of signals into images involves several assumptions on the part of equipment's software^[8,9]. These give rise to artifacts: could be a distortion in the image brightness, duplication, absence of echoes, etc.

It is difficult to avoid them altogether and hence must be able to distinguish them^[17]. Commonly understood

artifacts are described below.

Acoustic shadowing: This happens when a superficial structure has greater attenuation coefficient than the structures deep to it. Due to this the underlying structure appears less echogenic than normal. This is typically seen under a bone as a black shadow^[8,18].

Posterior acoustic enhancement: This is almost the opposite of shadowing. Due to the presence of a less attenuating structure superficially, the region behind that structure produces stronger echoes than the surrounding structures. This is typically seen underneath or posterior to a blood vessel and can be mistaken as a nerve due to its hyperechoic quality^[8,17].

Reverberation: It is the multiple representation of the same structure at different depths of display. It is usually caused by a specular reflector such as a needle. It reflects a strong signal back to the transducer, some of which is again reflected back to cause a repeat of the shadow at a different depth, because of the time delay involved. The lumen and the walls of a hollow needle can also give rise to reverberation artifacts due to differences in the time of reflected wave and appear as multiple but similar shadows. They also give rise to comet tail shadows^[19].

Mirror image: It is a type of reverberation artifact, commonly produced due to a significant mismatch in the acoustic impedance between 2 adjacent structures such as air-bone, soft tissue-lung etc. Interestingly this artifact appears in all modes including doppler.

Refraction: This is also called as bayonet effect^[20]. This appears as a subtle bend in the length of the needle due to refraction.

Dealing with artifacts^[8,17]: (1) Have a high degree of suspicion; (2) Confirm in 2 views, longitudinal and cross-sectional; (3) Change the position of transducer-move proximal or distal; (4) Reduce gain; and (5) Move the patient.

CONCLUSION

Appropriate and effective use of US requires a thorough knowledge of its operating principles. This helps one to utilise the controls to get an optimal image which is clear, with more signal transmission than background noise.

Key points include: selection of the right transducer, using focus adjustment, using TGC to allow for compensation at the required depth, using appropriate doppler imaging. All of these help to minimise the artifacts.

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No pain, no social gains: A social-signaling perspective of human pain behaviors

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Abstract

In this review article, we describe a social-signaling perspective of human pain and pain empathizing behaviors which is based on the premise that pain percepts evolved to serve both intrapersonal as well as interpersonal, communicative functions. This perspective offers a generative framework for understanding the natural origin and proximate expression of felt pain and pain empathizing behaviors. The basic thesis is that humans evolved sensory-behavioral heuristics for perceiving and inhibiting exogenous and endogenous pain sensations as part of more general expressive styles characterized by the demonstration of vulnerability gestures (*i.e.*, trustworthiness cues) versus empowerment gestures (*i.e.*, capacity cues), and these styles ultimately facilitate broader self-protection and social novelty-seeking life-history behavior strategies, respectively. We review the extant literature on how social contextual factors (*e.g.*, audience characteristics) and how structural and functional components of individual's social network appear to influence the expression of pain behaviors in ways that support basic predictions from the social-signaling perspective. We also show how the perspective can be used to interpret conventional findings of sex differences in pain percepts and pain empathizing behaviors and for predicting how the situational context and individual's peer networks modu-

late these differences *in vitro* and *in vitro*. We conclude the article by describing how pain researchers may better understand how varying levels and divergent directions of changes in affect tend to co-occur with systematic changes in internal *vs* external pain sensitivities, and thus why, from an evolutionary perspective, pain may occur in the presence and absence of physical tissue damage.

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Key words: Pain behaviors; Psychology; Social support; Sex differences; Communication

Core tip: This article introduces a social-signaling perspective of pain and pain empathizing behaviors, which hypothesizes that both exogenous and endogenous pain percepts evolved as part of more general expressive heuristics for demonstrating basic trait impressions (*e.g.*, empowerment *vs* vulnerability cues) to different types of affiliates. Prototypical sex differences in pain sensitivity/empathizing may then reflect specialized expressive styles for regulating distinct relationship dynamics throughout humans' natural history. We show how the perspective accounts for several findings on how social contextual factors (*e.g.*, audience characteristics) and how structural and functional components of the individual's social network appear to influence contemporary pain expression.

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INTRODUCTION

Scientists and health providers are currently limited in

their knowledge of many biopsychosocial processes that constitute a pain experience and how people subjectively evaluate pain suffering in others. Sensory pain perception is influenced by, and modulated through, processes that involve tissue stress and damage (*e.g.*, physical disease and injury), peripheral and central nociception (*i.e.*, afferent input and brain processing), mental thoughts (*e.g.*, memories), emotions, and social settings^[1,2]. Pain empathizing is similarly influenced by automatic (unintentional, reflexive) and controlled (intentional, reflective) reactions that are based on behavior and cognitive appraisals of the pain sufferer, trait attributes of the pain observer/pain sufferer, and situational factors in the immediate social context^[3-7]. Clinically, the reciprocal nature of the relationship between patient pain experiences and pain empathizing reactions of others forms the cornerstone of patient pain reports, health provider decision-making, and overall patient treatment quality.

A handful of contemporary pain theorists have independently derived similar conceptual models for predicting individual and group differences and circumstantial variability in the experience and expression of pain. These models have been referred to by various names, including “social communication”^[8], “socio-relational”^[9], and “social transactional” models of pain^[10,11], but they all rest on the general premise that humans experience pain and pain empathizing feelings/sensations in part to signal important social information to other people. This social-signaling perspective of pain perception and pain empathizing behaviors offers a generative framework for understanding the natural origin and proximate expression of these phenomena. The perspective uniquely focuses on the behavioral functions of pain percepts that originate from either exogenous (*e.g.*, skin abrasion) or endogenous sources (*e.g.*, muscle aches, menstrual pain, headaches) within a broader framework of human expressive behaviors.

In this review article, we provide a selective overview of the social-signaling perspective of pain perception and show how it can be used to predict how social contextual factors (*e.g.*, audience characteristics) and social environmental factors (*e.g.*, social network structure) influence exogenous (*e.g.*, experimental) and endogenous (*e.g.*, somatic) pain sensitivity. The framework is also generative for predicting situational- and environmental-modulation of sex differences in clinical and experimental pain reports and pain empathizing responses. We conclude the article by describing future conceptual directions from a social-signaling perspective, with a particular emphasis on ways to better understand how varying levels and divergent directions of changes in affect tend to co-occur with systematic changes in internal *vs* external pain sensitivities, and thus why, from an evolutionary perspective, pain may occur in the presence and absence of physical tissue damage.

SOCIAL SIGNALING MODEL OF PAIN

The degree to which felt pain is viscerally experienced (*i.e.*,

subjective pain intensity) is only measurable *via* pain behaviors such as facial grimaces, distinct body movements, and verbal reports^[11,12]. Recent applications of advanced neuroimaging techniques have led to claims that felt pain intensity can be objectively measured with this technology alone^[13,14]. Still, these studies are dependent on verbal reports of pain to assess the veracity of their outcome measures. Therefore, what pain researchers and treatment providers are largely measuring are pain behaviors and not painful sensations or pain percepts *per se*. The fact that felt pain is most evident and (arguably) conceptually and pragmatically relevant, as a behavior begets the plausibility that pain percepts evolved to serve both intrapersonal, as well as interpersonal, communicative functions.

At the most basic level, exogenous pain sensations serve the same basic, intrapersonal functions as all external sensory perceptual systems (*e.g.*, visual, auditory, olfactory, gustatory, tactile) that enable the individual to detect and discriminate certain types of stimuli in the environment. External pain sensations are also functional as an environmental warning system, by demanding attentional resources and promoting self-awareness (*e.g.*, to attend to and protect an injured body-part), and for facilitating operant learning (*e.g.*, to avoid dangerous stimuli^[15,16]). However, these basic intrapersonal functions do not explain why, from an evolutionary perspective, humans experience deep-tissue endogenous (*e.g.*, somatic) pain sensations that originate from within the body, often in the absence of physical tissue damage, that can neither be avoided, easily remedied, or directly learned from in and of themselves.

Instead, it makes more sense that the tendency for humans to experience endogenous pain percepts evolved so that the individual will modify their general activity levels and produce pain behaviors that signal salient social information, such as momentary vulnerability versus prowess, to other people *via* the presence or absence of pain gestures. Exogenous pain percepts are also able to provide such information, but they are distinct from intrinsic discomfort because external pain tends to occur during voluntary activities (*e.g.*, during physical labor, acts of bravery, acts of aggression) and hence under situations in which the individual usually has some degree of control. This distinction is important because it suggests that external and internal pain percepts have slightly different social signaling functions, with the latter being unavoidable, and therefore, better able at conveying sincere trait impressions (honest signaling) of the individual's current state of debilitation than may be possible *via* external pain behaviors. Finally, both external and internal pain percepts serve the functions of allowing the individual to assess the reliability and dependability (solicitousness tendencies) of other social agents in their environment. Each of these interpersonal functions can be characterized as communicative in nature, because they are modulated (*i.e.*, resulting in differential expression) by factors in the immediate social context, by factors in the individual's broader social environment, and by the individual's affect-

tive functioning, which tends to correspond to changes in perceived social-standing^[9].

EVOLUTION OF HUMAN EXPRESSIVE BEHAVIORS

Detailed models for explaining how and why the social context and individual's affective functioning influence pain and pain empathizing behaviors can be understood within the context of a broader framework on the evolution of human expressive behaviors. According to Vigil's Socio-Relational Framework of Expressive Behaviors (SRFB^[9]), all forms of heuristical expressive behaviors including discrete gestures that demonstrate "positive" *vs* "negative" affect (facial expressions, body movements, verbal reports, *etc.*) and gestures that demonstrate the presence or absence of felt pain evolved to modulate (*i.e.*, attract or avert) social interactions with other people. This occurs *via* the selective signaling of one or both of the two most parsimonious properties of human "reciprocity potential", or interpersonal value to other people. These constructs can be conceptualized as: (1) demonstrations of prowess, empowerment, and ultimately capacity cues, which exhibit one's ability to reciprocate with others; and (2) demonstrations of appeasement, vulnerability, and ultimately trustworthiness cues, which establish that one is non-threatening and willing/likely to reciprocate with others^[9,17]. Humans are predicted to continuously exploit both positive and negative life experiences and conditional circumstances along with the situational context for the opportunity to demonstrate these two basic trait impressions to other people.

For example, people heuristically respond to stochastic events that enhance the perception of one's capacity attributes (*i.e.*, enhanced material and/or social resources; experiential prosperity) with gestures that demonstrate empowerment cues to others (*e.g.*, verbal and nonverbal expressions of joy, confidence, lower pain). In contrast, humans respond to events that detract from or diminish one's capacity attributes (*i.e.*, material and/or social losses; experiential adversity) with gestures that demonstrate vulnerability (*e.g.*, sadness and depression) and ultimately trustworthiness cues to other people^[18-21]. This is because, under these latter conditions, the individual is less effective at conveying capacity impressions and should, therefore, utilize stochastic adversity and particularly repeated and uncontrollable hardships, and hence circumstances that the individual cannot escape or avoid, as an opportunity to advertise genuine (*i.e.*, honest-signaling) states of debilitation and compromise, and ultimately trustworthiness cues, to other people.

The SRFB also predicts that humans direct and utilize capacity gestures (*e.g.*, expressed joy and confidence) and trustworthiness gestures (*e.g.*, expressed sadness) to influence different types of relationship partners and to maintain different types of social network structures. Specifically, people are predicted to selectively direct capacity cues toward novel, prospective, and hence riskier

affiliates such as acquaintances and strangers^[9,17]. This is because affiliative, capacity attributes such as trait-happiness are highly attractive to prospective peers and are therefore effective at increasing the absolute number of reciprocators that individuals are likely to interact on the daily basis (see also^[18]). Increasing the size of one's social sphere necessarily limits the amount of time that can be devoted to individual relationship partners, and capacity traits (*e.g.*, physical prowess) are easier to verify than trustworthiness traits (*e.g.*, trait-kindness) through brief interactions with others. Capacity traits are also more indicative of the ability to provide expedient (*e.g.*, one-time) rather than continuous resources to others (*e.g.*, a mating opportunity, physical protection, interchange of socio-political or material resources). Finally, gestures that demonstrate capacity attributes (*e.g.*, facial expressions of joy, quick and open body movements) are more discernable from a distance than trustworthiness gestures (*e.g.*, facial sadness, slow movements). Collectively these patterns support the thesis that: humans evolved the behavioral heuristic to advertise higher levels of capacity gestures when they possess larger, less intimate (*e.g.*, time-investing), and more fluid peer networks and for maintaining these types of network structures, and thus when having a higher number of affiliates necessarily limits the amount of time that can be used to influence individual relationship partners^[9,17,18].

In contrast, people are predicted to direct trustworthiness cues (*e.g.*, expressed sadness and insecurity) toward intimate, continuous, and hence dependable affiliates such as family and close friends, and hence the types of relationship partners who are most likely to provide remedial social support to the individual in times of need^[9,18,22]. When individuals are experiencing vulnerability they tend to avoid less familiar and hence riskier affiliates and to express behaviors (*e.g.*, head bow, gaze aversion, expressed insecurity) that effectively dissuade interactions with these types of people^[23], ultimately resulting in the formation of smaller, more consolidated, and more secure peer networks. Moreover, the fact that trustworthiness impressions (*e.g.*, kindness, loyalty, prosocial motivations) require repeated interactions to effectively convey and to evaluate in other people, and the tendency for these types of cues to be more indicative of the probability of reciprocating continuous rather than expedient resources (*e.g.*, anticipated emotional and logistical assistance) support the thesis that: humans heuristically advertise higher levels of trustworthiness gestures when they possess smaller, more exclusive peer networks; and for maintaining these types of network structures^[9,18].

In other words, by responding to adversity with behaviors that operate to consolidate one's social network, the individual is able to avert interactions with less familiar and hence riskier affiliates while simultaneously spending more time with intimate and co-dependent relationships partners. The expression of vulnerability cues is also functional for providing these latter types of affiliates with the opportunity to project altruism and hence reciprocal

demonstrations of trustworthiness cues back towards the vulnerable individual, ultimately strengthening the dependability of individual's most intimate relationships. In essence, these "socio-relational" principles can be summarized by the omnibus thesis that humans evolved the behavioral heuristic to advertise empowerment cues (*e.g.*, expressed joy) in ways that promote a broader social novelty-seeking behavior strategy, whereas humans instead utilize vulnerability cues (*e.g.*, expressed sadness) to potentiate a self-protection behavior strategy^[9,18,24].

Evolution of pain-signaling behaviors

Thus, from the perspective of the SRFB, the behavioral expression of external and internal pain percepts, being pinnacle forms of vulnerability gestures, can be viewed as natural kinds of trustworthiness cues. Pain empathizing behaviors, being pinnacle examples of altruistic gestures, can similarly be viewed as distinct types of trustworthiness cues. In this sense, the human occurrence when pain is expressed and responded to by others can be viewed as a symbiotic transactional process in which people interchange reciprocal demonstrations of trustworthiness cues with intimate (*i.e.*, reliable and trusted) relationship partners^[8,9,10,25]. The idea that momentary vulnerability and altruism gestures share an underlying social-signaling function explains why for example people with higher trait empathy also show higher experimental pain sensitivity^[26]. The contra hypothesis, of course, is that pain concealment, pain tolerance, and hypoalgesia can operate at a social-signaling level to convey empowerment and hence capacity cues to other people. Similarly, the lack of pain empathizing behaviors, at least in theory, may be interpreted as part of an expressive style characterized by the inhibition of compromise and expressed altruism and thus as the projection of capacity cues in and of itself. According to the SRFB^[25], the tendency to heuristically express pain intensity and pain empathizing for advertising core components of human reciprocity potential (*i.e.*, capacity or trustworthiness cues) were set in cognition early in the course of human evolution.

Sex differences in expressive styles

Evolutionary psychology theories of sex differences in expressive styles, including sex differences in the expression of pain behaviors^[25-27] have attributed the differences to the unique sub-ecologies in which ancestral males and females evolved. These ecologies can be understood from an evolutionary history of male-male coalitional competition and male-biased philopatry (also referred to as patrilocality or female exogamy). In this type of social system, males tended to remain in closer proximity to their male kin, thus allowing them to form secure, kin-based coalitions, while females tended to emigrate into the social networks of their husbands upon marriage, which was historically upon the timing of sexual maturation (*i.e.*, during adolescence^[28]). Greater reliance upon non-kin and more distantly-related affiliates (particularly upon adolescence) would have constrained females to

develop higher cognitive thresholds for trusting peers as well as heightened motivations for forming fewer, more time-invested and intimate peer relationships. These proclivities would seem necessary for increasing the reliability of their relationships in the absence of inclusive fitness (*i.e.*, shared genes^[29-31]). From the perspective of the SRFB, such inclinations would have also co-evolved with the general heuristic for females to demonstrate higher levels of altruistic tendencies and vulnerability displays (*i.e.*, non-threat), and hence trustworthiness cues than males on average, thereby allowing females to strengthen the reliability and security of their peer relationships^[9,18]. This general thesis explains the conventional pattern of women reporting quantitatively and qualitatively (*e.g.*, menstrual pain) dimorphic pain experiences, including higher experimental and clinical pain sensitivity, along with higher levels of pain empathizing behaviors than men on average^[26,32-35].

In unison, a social-signaling perspective is useful for predicting how various social factors influence the expression of pain (*e.g.*, verbal reports) in home, clinical, and research settings. The basic premise of this approach is that the patterns in which people express pain and pain empathizing are partly governed by behavioral heuristics outlined by the SRFB^[9,25]. To date, three basic hypotheses have been testing when concerning the social-signaling of pain: (1) Males and females express different levels of pain and pain empathizing behaviors; (2) The immediate social context influences felt pain; and (3) Structural and functional components of individuals' social networks are linked to felt pain. These hypotheses are discussed in the following three consecutive sections.

SEX DIFFERENCES IN PAIN AND PAIN EMPATHIZING

It is well-established that biological sex modulates pain behaviors. As compared to males, females report greater prevalence, frequency, and duration of clinical pain and pain-related distress^[35-39]. Women also differ in their actual pain experiences when compared to men with women experiencing more internal pain events (*e.g.*, headaches, stomach cramps, menstrual cramps) as oppose to men who experience more external pain events (*e.g.*, concussion, broken extremity, physical violence^[40]). Experimental studies show that women report lower pain threshold and tolerance, and higher pain intensity associated with various types of noxious stimuli (*e.g.*, ischemic, pressure, electrical, and thermal^[32,34,36,38,41]). The magnitude of these group differences varies from moderate to large depending on sample size, nature of the stimulus, and whether pain sensitivity is indexed by threshold or tolerance^[27,32,34,36,41]. Sex differences in pain behaviors have also been detected as early as infancy^[42,43], and in both adults and in infants, the behavioral differences exist despite no clear evidence of associated sex differences in neurocortical responses to pain^[44]. Females have also been observed as showing a stronger correlation between facial displays and subjective

pain intensity^[45], which is perhaps more consistent with the hypothesis that males may inhibit the expression of pain behaviors, rather than the alternative possibility that females instead exaggerate the expression of pain.

Finally, it is important to note that females experience qualitatively different types of pain than males, including a variety of discomfort sensations that are associated with menstruation. Developmental research shows that sex differences in pain experiences, depression, and somatic symptoms correspond to the timing of pubertal transition in adolescent girls, more so than in same-aged boys; females experience rapid increases in depressive symptoms and self-reported distress upon puberty as compared to the relatively constant rates among boys^[46-48]. Sex differences in negative affect peak in early adulthood and then decline slowly but continue to exist throughout middle and late adulthood^[49-52]. These patterns are consistent with a human natural history of male-biased philopatry and the SRFB^[9] which predict that female emigration to the social environments of their husbands upon marriage required heightened tendencies for demonstrating trustworthiness cues to non-kin upon this stage in life. Still, it is important to note that, although this framework provides a plausible explanation of the epidemiology of higher pain sensitivity in biological females as compared to males on average, it does not fully account for additional factors, such as gender identity, which may partly influence external pain perception irrespective of biological (*i.e.*, chromosomal) sex. Several studies have found, for instance, within-sex variability in concomitants of gender identity such as sexual orientation and self-rated levels of dispositional masculinity/femininity are predictive of pain sensitivity^[53-55].

Experimental research shows that females report higher pain empathizing behaviors than males on average, for example, when asked to rate the pain levels of other people experiencing discomfort and distress in their physical presence^[6,23]. There is also some preliminary support that patient treatment may be influenced by their health-provider's gender. Studies have found that female physicians are more likely than male physicians to prescribe higher doses of analgesics to underserved categories of patients such as ethnic minorities and other females^[56,57].

People tend to show distinct brain activation when they experience pain empathy, which corresponds to the so-called "pain-matrix"^[58,59], yet only a few studies have found sex differences in empathy-related neurocortical activity^[60-63]. Other studies have not found these differences^[57,64-66], and there is some research that suggests that males and females show distinct patterns of associations between empathy-related brain functioning and behavioral indicators of empathy. Females show a stronger association between neurocortical and verbal indicators of pain empathizing than males^[67], while males tend to be more critical than females in their evaluations of others, which may attenuate neurocortical empathetic responses^[68]. Thus, while the extant research shows that females

are more likely to express felt pain and pain empathizing behaviors than males on average, this research also suggests that these differences are modulated by situational factors (*e.g.*, interpersonal appraisal processes) in the immediate social context.

SITUATIONAL VARIABILITY IN PAIN BEHAVIORS

Experiments have shown that active interaction with, and even the passive presence of others in the immediate social context influence subjective and autonomic pain responses^[69,70]. Observational studies show that people express heightened pain behaviors (*e.g.*, intensity reports and facial expressions) in the presence of intimate affiliates such as a significant other or parents during standard medical procedures^[71-75]. Instead, interactions with a non-deferential, unfamiliar, and more authoritative person preceding a pain task results in hypoalgesia^[76,77]. Even infants have been shown to respond to the social context, for instance, by expressing lower pain behaviors in the presence of a dismissive parent^[78]. These findings are consistent with the SRFB thesis that pain should be expressed most intensely in the immediate presence of intimate and familiar relationship partners (*e.g.*, family, significant other), because these types of affiliates are most likely to provide solicitous reactions toward the pain sufferer, and that interactions with less intimate, non-deferential, and unfamiliar people should instead predict inverse expressions^[25].

Likewise, the SRFB predicts that there should be systematic differences in the effects of male versus female audiences/targets on momentary pain percepts. Because women naturally form fewer, more intimate (*i.e.*, time-consuming and investing), and more exclusive relationships^[9,17,29,79] and demonstrate higher levels of parental investment and pain empathizing behaviors than males on average^[6], people are predicted to demonstrate greater pain sensitivity (*e.g.*, hyperalgesia) in the immediate presence of other women than in the presence of men^[25]. This prediction has been met with mixed support which suggests that the role of observer's gender on pain percepts is contingent on a multitude of factors. For example, several experiments have shown that people are more likely to demonstrate heightened exogenous pain sensitivity when they are processed by a female researcher^[77,80,81]. In our lab, we found that even minimal procedural interactions with female personnel (*e.g.*, processing consent procedures and explaining the research protocol) can lead to heightened experimental pain reports, particularly in women, even when the noxious stimuli is experienced in solitude, without the actual physical presence of another person^[82]. In another study, we found that the absolute number of female (strangers) but not males present during an ischemic pain task is linearly associated with hyperalgesia in women only^[6]. In contrast, there is some research that suggests that females may actually experience hypoalgesia in the immediate presence of a (real or simulated) male^[83]. This makes sense, given that men are

less likely to display empathy than females^[6], and thus offer less solicitous reinforcement for other people to express pain in their presence compared to the benefits of expressing pain to females.

The impact of the presence of women on the momentary pain intensity levels of men appears to be more dynamic. Our lab and others have found that, in men only, the presence (or simulated presence) of female researchers or other female strangers during an experimental pain test (*e.g.*, cold pressor, ischemic) results in hypoalgesia^[84,85]. Other research has demonstrated that this hypoalgesic effect is linearly related to the absolute number of female strangers in the room during the pain task^[6]. Thus it appears that among healthy young males, the presence of female strangers produces a hypoalgesic effect, although the opposite pattern (hyperalgesia in the presence of a female researchers) has also been reported^[77,80]. Clinical studies instead show that solicitous spousal responses are associated with increased pain behaviors^[86,87], and as we have found in our own lab (unpublished data), males in particular tend to report greater debilitating pain when they cohabit with a spouse than when they live alone (as described in the next section below). In other words, experimental and clinical pain studies are mixed on whether males report heightened or dampened pain sensitivity in the presence of other women.

From a social signaling perspective, the biological fitness costs and benefits to men for demonstrating heightened or lessened vulnerability to females should theoretically be contingent on implicit social expectations and other factors such as the momentary level of debilitation (*i.e.*, degree of pain severity) of the pain-sufferer^[8,9,11,25]. Females effectively serve as both an ecological and likely resource for consolation and caregiving for both sexes, as well as a potential reproductive partner for males. Since men tend to use empowerment gestures (*e.g.*, concealed pain behaviors) to attract prospective mating partners^[88], whereas they use vulnerability gestures (*e.g.*, explicated pain behaviors) to elicit solicitous responses from more established and intimate social partners (*e.g.*, female-kin) in times of need (*i.e.*, when the individual is physically debilitated)^[9], one would expect that the effect of women (hypoalgesic *vs* hyperalgesic) would depend on the relative state of debilitation (*e.g.*, degree of pain suffering) of the male.

We recently found evidence for these patterns, which we have come to refer to as the “Vigil-Alcock Effect”^[89]. This is the tendency for males to report attenuated pain intensity in the presence of female observers, when at relatively low pain levels, but to experience heightened pain intensity in the presence of female observers, at high pain levels. Using multiple chart reviews we compared the patient pain scores that were taken during standard triage assessments for people who were admitted for emergency care by either a male or a female health provider (*e.g.*, nurse). We found that male patients reported higher pain intensity levels to male practitioners, when initial pain intensity is low (scores of 3 or below on a 10-point

scale), and both male and female patients reported higher pain to female practitioners when initial pain intensity is high (scores greater than 4)^[89]. The statistical magnitudes of these effects were substantially larger than those from typical, non-pharmacological (*e.g.*, psychological, placebo) clinical interventions, suggesting that the influence of this interaction between examiner gender and patient condition on patient pain reports may be a pervasive feature in clinical and experimental settings.

Interestingly, other research has found that the absolute number of males or females in the immediate audience also influences the observational coding of other people’s pain suffering, irrespective of the sex of the pain sufferer and sex of the observer^[6]. In general, greater numbers of male audience members correlated with lower observer pain ratings, whereas greater numbers of female audience members correlated with higher observer ratings. Thus, it would appear that people most broadly learn to simulate the prototypical appeasement styles of males and females, with females demonstrating greater compassion for others than males, on average. An alternative explanation is that, male and female observers’ simulations of their own pain experiences influence their observational ratings of other people’s pain suffering.

ENVIRONMENTAL VARIABILITY IN PAIN BEHAVIORS

A social-signaling perspective of pain predicts that people’s close relationships should adaptively influence the phenotypic expression of exogenous (*e.g.*, experimental) and endogenous (*e.g.*, somatic) pain perception. Specifically, pain experiences should correspond to how often people interact with intimate (*e.g.*, in terms of shared time and interpersonal knowledge) relationship partners such as romantic partners, family, and close friends, and these associations should differ for males and females^[6,8,9,10,27]. The inverse would also be true, that dampened pain sensitivity should co-occur with the frequency of interactions with less intimate and riskier affiliates^[25]. An extension of this prediction is that the conventional finding of greater pain sensitivity in women^[6,27,33,34,38] should be modulated, in part, by structural and functional components of the individual’s social network^[9]. In theory, the level of intimacy that individuals share with their network partners should compound biological sex differences in pain sensitivity, and thus the typical pattern of females reporting higher pain intensity than males should be the most robust for females that have a high proportion of intimate types of affiliates (*e.g.*, lover and relatives *vs* non-kin) and more established (*e.g.*, longer formed) relationships.

Indeed, numerous studies have shown that higher levels of pain-related social support and solicitous behaviors from significant relationship partners are associated with greater clinical pain experiences^[90-94]. In a recent experiment, we also found consistent sex differences in how social network structures as well as intimate relationship functioning modulated experimental pain sensitivity^[22]. Us-

ing a cold pressor task, we found that comparing males and females directly revealed no group differences in reported pain intensity. However, when structural and functional components of individuals' social networks were considered, inverse sex differences emerged, hence otherwise obscuring the dynamic relations between biological sex and exogenous pain sensitivity. Females who listed a greater proportion of intimate types of relationship partners (*i.e.*, kin or a significant other) among their list of most significant people and females with more extensive (*i.e.*, longer established) relationships reported higher pain intensity than males. Instead, males with fewer intimate and less established peer relationships actually reported higher pain intensity scores than females, on average. The most robust sex differences were moderated by the amount of logistical support received from one's significant other such that greater logistical support was associated with heightened pain intensity ratings in females, but with dampened pain intensity in males. This makes sense based on the hypothesis that males' natural tendencies to form less intimate peer relationships resulted in their slightly greater tendency to utilize empowerment gestures including pain tolerance behaviors (when at relatively low pain-levels) for regulating (*i.e.*, attracting and maintaining) their peer relationships. The female tendency to utilize vulnerability gestures including pain reaction behaviors for accomplishing similar goals^[9,17,23,27] would then explain why women with more intimate relationships showed higher pain sensitivity than women with less intimate relationships.

As mentioned above, we have also found (unpublished data) that individuals, and particularly males, who reside with an intimate relationship partner such as a "significant other" (*e.g.*, boyfriend, girlfriend, spouse) are at greater risk for experiencing clinically debilitating pain interference than males with less intimate cohabitants and males who live alone. If females evolved a greater tendency than did males to regulate their relationships through trustworthiness demonstrations, including pain empathizing and related demonstrations of solicitude^[9,17,23,27], it makes sense that the males who resided with a (presumed) female significant other were likely to have experienced heightened levels of pain reinforcement behaviors (when at relatively high pain-levels). Other research shows that the association between pain catastrophizing and clinical pain experiences is stronger for people who live with a romantic partner than for those who live with someone else^[95]. Thus, while previous research has found that supportive (*e.g.*, functional) components of social networks are associated with health-related outcomes^[11,96,97], there is building evidence that structural dimensions of social networks are also associated with distinct and potentially adaptive (*i.e.*, epigenetically specialized) expression of exogenous and endogenous pain sensitivity in males and females.

FUTURE DIRECTIONS FOR A SOCIAL-SIGNALING PERSPECTIVE OF PAIN

Collectively, the extant literature on the associations be-

tween social situational and social network dynamics and pain perception are interpretable from the social signaling thesis that there is a reciprocal relationship between changes in pain percepts and changes in the social environment. That is, not only do individuals' verbal and non-verbal pain behaviors evoke specialized and functional reactions-sometimes reinforcing and sometimes aversive-from other people, but individuals' current relationship dynamics and the social context influence pain perception^[8,10-12,22]. This basic thesis can be used to construct more specific conceptual models that can guide the development of novel, evidence-based pain management treatment options.

One way that a social-signaling perspective can be useful is for providing a potential scaffold to better understand the current evolutionary and mechanistic paradoxes that characterize the discordant relations between affective functioning and pain perception. Emotion induction studies among healthy people, for instance, show that superficial (*e.g.*, non-salient, non-personal, and brief) sadness induction results in hyperalgesia to external or phasic (surface) skin painful stimuli, such as electrical, heat, and cold pressor pain^[98-100]. Clinically depressed people, instead, show the opposite pattern, of dampened ability to detect and more tolerance of many forms of exogenous pain sensations compared to healthy controls^[101,102]. These patterns are not always observed^[103-105], however, and this may be due to variability in pain induction techniques across the studies; depression is associated with hyperalgesia to electrical and thermal pain, but with hyperalgesia to ischemic muscle pain, which may be more similar to pain caused by endogenous forces^[106,107]. Thus, depression is associated with dampened ability to perceive exogenous pain, yet heightened experiences of daily deep tonic (*e.g.*, somatic) pain percepts^[108-110]. Similar discordances characterize the literature pertaining to positive affect, such that superficial happiness induction results in hypoalgesia, whereas dispositional optimism and high trait self-esteem have been linked to hyperalgesia, despite the tendency for optimistic people to report fewer somatic pain complaints^[109,110]. Currently, there are no conceptual models that can explain these seemingly antithetical observations, and conventional assumptions are that the discordances reflect a general dysregulation, or malfunctioning of a single (system-global) pain perception system. These suppositions can be re-interpreted from a social-signaling perspective.

We are developing and empirically testing a conceptual model for integrating and interpreting the complex relations between affective functioning and pain perception, which we refer to as a Divergent Affect Model of Pain Percepts (DAMPP). The main theses are that external and internal pain perception systems co-evolved for their distinct behavioral functions and the systems are differentially modulated by varying degrees, and divergent directions of changes in affect. From the perspective of the DAMPP, "positive" and "negative" affect ultimately facilitate broader behavioral strategies characterized by social novelty-seeking *vs* self-protection (as described

above), and external and internal pain percepts supplement these strategies in ways that are sometimes concordant (positively correlated) and other times discordant (inversely correlated). These patterns are systematic and may reflect logical correspondences between varying levels of affective functioning, different types of pain percepts, and systematic changes in the individual's social environment.

According to the SRFB^[9,25], non-salient and hence shorter-lasting demonstrations of positive or negative affect (*e.g.*, momentary emotive gestures) as well as exogenous pain percepts evolved for manipulating the immediate situational context, for instance, by signaling important social information (*i.e.*, capacity cues and/or trustworthiness cues) to facultative audiences and, in the case of pain detection, for operating at a basic sensory level (for discriminating environmental stimuli) as described above. Salient and longer-lasting demonstrations of affect (*e.g.*, trait optimism, trait depression) and endogenous (*e.g.*, somatic) pain percepts represent more canalized behaviors that function instead for controlling one's broader social environment. If sustained elated mood behaviors ultimately operate to attract less familiar and hence riskier affiliates, and if sustained depressed mood operates to avert interactions with unfamiliar people and to strengthen relationships with intimate and trusted confidantes, then the degree and hence duration of changes in either positive or negative affect (from a baseline state) should correspond to increasingly homogeneous social environments characterized by a disproportionate number of either risky or reliable affiliates. Likewise, since endogenous pain percepts are less avoidable than pain caused by extrinsic forces, the lack of or heightened ability to sense endogenous pain discomfort may be more functional for instilling trait-like (honest-signaling) impressions of capacity versus trustworthiness cues to others than is possible *via* exogenous pain percepts; hence, the social signaling functions of endogenous pain are probably more similar to those of salient/sustained changes (rather than superficial/momentary changes) in affect^[9,25]. In this sense, endogenous pain percepts are hypothesized to have evolved to regulate interactions with more distinct/sub-consciously chosen (risky *vs* reliable) types of social affiliates than did exogenous pain percepts and expedient affective gestures more generally.

According to the DAMPP, salient (environment-specific) states of positive *vs* negative affect are also accompanied by sustained changes (canalization) in basic sensory perceptual functioning in ways that may supplement social novelty-seeking and self-protection behavior strategies, respectively. Sustained positive affect should, in theory, co-occur with amplified global (system-wide) perceptual acuity for monitoring novel external stimuli in the environment (*e.g.*, visual, auditory, and tactile discrimination) and for potentiating interactions with riskier affiliates^[9]. Sustained negative affect should instead correspond to dampened perceptual acuities (multi-sensory agnosia) that effectively hinder the ability to navigate

novel environments, avert interactions with novel affiliates, and demonstrate phenotypic vulnerability and ultimately trustworthiness cues to intimate confidantes. This thesis explains why for instance positive mood is associated with a "broadening" of visual attention (*e.g.*, greater attention to peripheral stimuli and greater eye-gaze saccades^[111]), while low mood is instead associated with facultative decreases in one's visual field of view^[112] as well as a decrease in attentional focus on global *vs* local visual information^[113]. The current thesis is also consistent with fact that depression is associated with a general dampening of the ability to detect multiple forms of extrinsic information in the immediate environment including basic visual^[114-118], auditory^[119,120], olfactory^[121-123], gustatory^[124], and tactile stimuli^[125].

Finally, the DAMPP model assumes that the continuous, environment-specific, and preparatory functions of sustained affect (*e.g.*, perceptual calibration) should take precedent and hence be expressed over the expedient, situation-specific functions of momentary affect (*e.g.*, social signaling). This is because the former phenotypes represents heuristical reactions to more specialized environmental circumstances which generally offset the biological benefits of being able to variably respond to environment (*i.e.*, phenotypic plasticity). Collectively, these lines of reasoning suggest that individual's current state of socio-relational functioning, which is characterized by distinct structural and functional characteristics of their social environment and by the expression of varying levels of affect and exogenous and endogenous pain percepts, can be used to interpret the paradoxical findings in the literature on the association between affective functioning and sensitivity to clinical and experimental pain. The DAMPP model explains that: at low levels of affective functioning (*e.g.*, momentary happiness *vs* sadness), endogenous pain percepts are not affected, and hence under these conditions exogenous pain percepts are free to operate, at the social-signaling level, for demonstrating expedient demonstrations of capacity *vs* trustworthiness cues to others.

This phenomena may partly account for the placebo effect and research showing that exposure to contextual factors that may superficially (*e.g.*, momentarily) alleviate or dampen mood modulate exogenous pain perception. For example, some research has found that coming in contact with ibuprofen (*vs* a neutral object) results in hypoalgesia and that exposure to words that signify an act of victimization such as "sting" as oppose to "beware" induces hyperalgesia^[126,127]. Related studies show that people who are told that the exogenous pain they were exposed was the result of malicious intent by another person experience hyperalgesia^[128,129], presumably as a result of the brief/situationally-relevant impact of the experimental manipulation on momentary affect.

In contrast, and under conditions in which the individual is experiencing significant and sustain changes in affect (*e.g.*, trait-confidence *vs* depression), the DAMPP model predicts that the social-signaling functions of

demonstrating continuous capacity or trustworthiness cues to selective social audiences are going to be accompanied by changes in endogenous pain perception. Indeed, empirical studies show that loss of material or social resources (diminished capacity attributes) is associated with heightened endogenous pain percepts such as menstrual discomfort^[130]. Likewise, according to the DAMPP, continuous changes in positive and negative affect should be accompanied by a general heightening or dampening (respectively) of basic sensory acuity for navigating risky vs reliable environments. These changes in exogenous sensory acuities may be converse to sensory functioning when the individual is not experiencing salient mood states which, in theory, would have resulted in competing evolutionary selection pressures for expressing heightened external vs internal pain sensitivities under certain conditions.

This divergent affect model of internal vs external pain percepts appears to explain the empirical literature which shows discordant rates of internal (*i.e.*, somatic) and external (*i.e.*, experimental) pain sensitivities in people experiencing salient mood states, but not in healthy people who participate in conventional mood induction experiments. Additional factors such as individual differences in physical activity are also known to influence the relation between salient mood states such as depression and experimental pain thresholds^[131] and clinical pain reports^[132]. This makes sense from the DAMPP, which predicts that physical activity should partially mediate the relation between affective functioning and changes in exogenous and endogenous pain sensitivities in ways that facilitate broader behavioral strategies (novelty-seeking vs self-protection) characterized by differing mobility styles.

CONCLUSION

In summary, the social signaling perspective of pain-related behaviors provides a solid scaffold that can help clinicians and basic scientists predict how social situational and social environmental factors and how varying degrees of changes in affect may influence pain perception in the presence and absence of physical tissue-damage. The perspective is based on the general thesis that the human nervous system adaptively and systematically adjusts the heuristical expression of pain eliciting, pain concealing, and pain empathizing behaviors for manipulating interpersonal interactions and broader structural and functional components of the individual's social ecology. These heuristics appear to differ in males and females in specialized and functional ways that correspond to evolved sex differences in social relationship styles. Pain researchers may also choose to consider how the individual's current state of debilitation may modulate the influence of contextual factors (*e.g.*, audience characteristics) on pain percepts, and to consider how internal vs external pain sensitivities are related conceptually and mechanistically. There may be cost-benefit fitness tradeoffs associated with expressing discomfort that originates from either extrinsic or intrinsic forces that can

be empirically tested with a better understanding of the experiential determinants and behavioral consequences of these different natural kinds of pain percepts. At the very least, pain researchers and health providers should recognize that characteristics of the individual's social environment influence how they report their pain, and that pain reports differ according to several factors, including interpersonal characteristics of the pain sufferer and the pain observer, interpersonal tradeoffs associated with expressing pain under varying debilitation-levels, to whether pain originates from controllable/avoidable (*e.g.*, exogenous, tissue-related) or uncontrollable/unavoidable (*e.g.*, endogenous, non-tissue dependent) forces.

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Perioperative care and cancer recurrence: Is there a connection?

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ates, and non-steroidal anti-inflammatory drugs are reviewed along with recent literature and ongoing clinical trials in this area. Regional anesthesia is increasingly emerging as a safer option with less cancer recurrence potential as compared to general anesthesia. Blood transfusion, pain, stress, use of beta-blockers, and hypothermia are other potentially important perioperative factors to consider.

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Core tip: Cancer mortality is frequently related to metastatic disease. An altered balance between the tendency of the tumor to spread *via* metastasis and the body's anti defense processes is the most plausible mechanism of cancer spread. This comprehensive review summarizes the role of anesthetic technique and perioperative interventions and their influence in cancer recurrence. An exhaustive compilation of the latest research and ongoing clinical trials in this area is presented to the reader.

Abstract

Cancer is the second most common cause of death in the United States. Metastatic disease is a more important cause of cancer-related death relative to primary tumor progression. Surgical excision is the primary treatment for most malignant tumors. However, surgery itself can inhibit important host defenses and promote the development of metastases. An altered balance between the metastatic potential of the tumor and the anti-metastatic host defenses, including cell-mediated immunity and natural killer cell function, is a plausible mechanism of increased cancer metastasis. This article reviews the increasingly recognized concept of anesthetic technique along with perioperative factors and their potential to affect long-term outcome after cancer surgery. The potential effect of intravenous anesthetics, volatile agents, local anesthetic drugs, opi-

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INTRODUCTION

Cancer is a major source of morbidity and mortality throughout the world. Recent statistics from the Centers for Disease Control indicate that cancer is the second most common cause of death in the United States^[1]. Although age-adjusted death rates for cancer and heart

disease have slowly declined since 1991, approximately one in four deaths are still attributed to cancer. It is estimated that in the United States alone, there were over 1.6 million new cancer diagnoses in 2012 and over 577000 deaths from cancer^[2]. Of those cases, the most common cancer diagnoses are prostate in men (29%) and breast in women (29%), followed by lung cancer (14% in men and women), and colorectal cancer (9% in men and women). However, lung cancer remains the most common cause of cancer-related mortality in both men and women^[2].

Of the deaths due to cancer each year, only about 10% are due to complications of the primary tumor^[3]. The vast majority of cancer-related deaths occur due to metastatic disease. Local recurrence and metastasis rates are influenced by a multitude of factors. For example, one study of nearly 3000 women with Stage I, II, or III, breast cancer from 1985 to 2001 who underwent surgery followed by chemo- or hormonal therapy found an overall recurrence rate of 11% at 5 years and 20% at 10 years^[4]. However, recurrence rates at 5 years were nearly 50% lower in the subgroup that had Stage I breast cancer (7%) than those with Stage III breast cancer (13%) at diagnosis. Additionally, risk of recurrence differed substantially between those with hormone receptor positive versus negative tumors. Overall recurrence rates of breast cancer would likely be lower today, as treatment advances have been made since the time of this study, including the introduction of aromatase inhibitors and trastuzumab immunotherapy. However, this study illustrates that cancer recurrence is multifactorial, and even for a specific type of cancer can vary substantially based upon stage and grade at diagnosis, biologic characteristics of the tumor, initial treatment modalities, and host immune function.

Surgical excision is considered the first line of treatment for most solid organ tumors. However, even “curative” surgery leaves the possibility of microscopic residual disease^[3]. Tumor cells can be left at the excisional margins or released into circulation during the dissection and removal of the bulk tumor mass. It is also possible that primary tumor cells intravasate preoperatively and travel to distant organs, forming undetected micrometastases that continue to grow postoperatively^[5-7]. In addition, surgery and perioperative factors such as pain stimulate neuroendocrine and stress responses that suppress cell-mediated immunity (CMI) and promote tumor growth and metastasis^[5,7].

Metastases occur *via* a complex process of cellular changes and mutations balanced against host immune defenses. Primary tumors initially receive blood and nutrients from simple diffusion. As the tumor grows, it develops mutations in factors such as vascular endothelial growth factor (VEGF), which promote angiogenesis^[3,8]. Eventually, some tumor cells acquire mutations that allow invasion through the basement membrane into blood vessels and lymphatic channels, where they can be transported throughout the body. In patients with intact immune systems, most tumor cells are destroyed in circulation^[3].

However, surviving cells have potential to extravasate through capillary beds in distant organs, proliferate, and form micrometastases. Each primary tumor requires a particular biologic microenvironment to survive^[9]. Therefore, micrometastases tend to flourish in certain organs and not others. For example, prostate cancer typically metastasizes to the bone and colon cancer to the liver^[3].

The host cellular immune system is a critical defense mechanism against the development of metastases^[10]. Early on, cancer cells have weak antigenicity. With time, random mutations accumulate and the cells become more antigenic^[3]. Natural killer (NK) cells and cytotoxic T cells appear to be key players in immune surveillance^[11,12]. NK cells, which are activated by interleukin-2 (IL-2) and interferon- γ (IFN- γ), are able to spontaneously recognize and lyse tumor cells, as well as activate other immune cells^[5,13]. Loss of Major Histocompatibility Complex class I (MHC- I), which is almost universally expressed on normal cells, is a common mechanism for tumor cells to evade T-cell recognition. However, NK cells are able to recognize this abnormality and trigger apoptosis of the neoplastic cells^[13]. There is evidence from human studies that patients with depressed NK cell function have a higher incidence of cancer and of metastatic disease after “curative” surgery^[14-17]. There is also evidence that increased stress, like that occurring in the perioperative period, causes a reduction in NK cell activity^[17]. In animal models, decreased NK cell activity due to stress has been associated with increased tumor development^[18]. For all of these reasons, immunotherapies designed to enhance NK cell function are currently an area of extensive research for cancer treatments^[13].

The essential nature of immune surveillance in preventing the development of metastatic lesions is also seen in solid-organ transplant recipients. These patients, who are on life-long immunosuppressive therapy, have a significantly increased risk of developing metastases^[19]. Based upon the current evidence, identifying and targeting factors in the perioperative period that influence the immune system, and particularly NK cell function, could have a significant impact on development of metastases and long-term survival in cancer patients.

RATIONALE FOR REGIONAL ANESTHESIA

The curative treatment of cancer usually involves surgical resection of the primary tumor and/or metastases. Although complete eradication of the malignancy is the primary goal, the immune suppression associated with surgical stress may lead to tumor extension^[20]. On the other hand, with the marked decrease of anesthesia-related morbidity and mortality in the last decades and the difficulty in discriminating differences between anesthetic techniques, it has been suggested that new analyses on long-term anesthetic effects should focus on patient-centered outcomes, including but not limited to cancer recurrence^[21].

Effects of surgery and anesthesia on tumor cells

There is a large amount of data from anecdotal reports, observational and retrospective human studies and animal studies that emphasizes the so-called “deleterious” effects of general anesthesia and or surgical stress on cancer recurrence and outcomes. The authors would like to forewarn the reader that in the absence of large randomized prospective studies the clinician should not immediately change practices based on this data.

The immune response to cancer plays a pivotal role in recovery from oncologic disease. Cancer is characterized by the presence of genetic abnormalities that lead to alterations of regulatory processes^[22]. As a result, the malignant cells express different surface antigens that, coupled with MHC class I molecules, are presented to the immune system and recognized by CD8 T cells, leading to cytotoxic antineoplastic responses and immunomodulatory counterbalancing responses^[23,24]. The role of cytokines such as IFN- γ is essential to prevent primary tumor development and growth^[25,26]. Besides the activity of adaptive immunity (T and B cell-receptor mediated), NK cells, derived from innate lymphoid cells, constitute a primary line of defense against tumor cells by both direct cytotoxicity and IFN- γ production^[27,28]. Evidently the immune system is unable to completely clear cancer cells in some instances. Moreover, in a process called immunoediting, tumor cell growth is actually promoted by the immune system^[29]. The immunosuppressive effect of surgery and anesthesia depends on a fine balance between activation/inhibition of pro-inflammatory and anti-inflammatory pathways.

Effects of surgery: During the last few years, it has been recognized that even though surgery is the mainstay for cancer treatment in many patients, surgical intervention may accelerate tumor progression and micrometastasis development^[10,30,31]. Right after surgical removal of the primary tumor, an array of local and systemic consequences ensues. First, due to mechanical manipulation of the tumor, malignant cells can get access to blood vessels and lymphatics^[32-34]. In addition, important humoral factors related to angiogenesis and cell proliferation, such as VEGF, are released from the primary source of cancerous cells during surgery^[35-37]. Conversely, with tumor removal, local production of antiangiogenic factors such as angiostatin and endostatin^[38,39] is markedly reduced. Taken together, the combination of the aforementioned factors creates a favorable *milieu* for neoplastic cell proliferation and metastasis development.

CMI is assumed to be important to control residual tumor activity once the primary tumor is resected; however, because of a variety of mechanisms, many perioperative factors tend to suppress CMI. Stress associated with surgery activates the sympathetic nervous system and neurohumoral pathways, resulting in high concentration of mediators that affect CMI at different levels.

The stress response includes the massive release of multiple mediators including glucocorticoids, endogenous

opioids, catecholamines, angiogenic factors, and cytokines. Special interest has been focused on the role of catecholamines and prostaglandins and their secondary effect on other mediator production. Tissue concentration of cyclooxygenase-2 (COX-2), an enzyme necessary for prostaglandin E2 synthesis, is low under normal circumstances^[40]; however, in malignant tumors, its production is abnormally high^[41]. Inhibition of COX-2 activity has been shown to decrease neoplastic invasive potential and tumor angiogenesis in animals and humans^[42,43]. On the other hand, some clinical studies have shown an inhibitory effect of β -adrenergic blockade on stress induced tumor progression^[44], whereas *in vitro* studies have evidenced the ability of β -adrenergic agonists to stimulate malignant cell proliferation even in absence of stress^[45,46]. Several mechanisms have been implicated in adrenergic enhancement of disease progression, including IL-6 and IL-8 overproduction by both the immune system and the tumor, apoptosis resistance^[44,47-50], suppression of NK cell cytotoxic activity^[51], angiogenic stimulation^[52], increased tissue invasion and increased arachidonic acid signaling^[53-55].

Acute pain: Studies in animals have shown that acute pain inhibits NK cell activity^[56-58] and tumor progression^[59,60], whereas other experiments have demonstrated enhanced NK cytotoxicity and increased lymphocyte proliferation^[61]. On the other hand, treatment of postoperative pain with opioids has been able to reduce cancer recurrence, despite their potential “prometastatic” effect^[62] (see opioid section below). It is difficult to ascertain the independent effect of acute postoperative pain on tumor progression, as it overlaps with the bimodal effect of opioids. It is likely that the stimulating effect of opioids on tumor cells is only evident in the absence of acute pain^[63]. Finally, there are no studies evaluating the impact of chronic pain on cancer recurrence.

Volatile anesthetics: The association between volatile anesthetics and cancer progression was observed more than four decades ago. Lundy *et al.*^[64] proposed that the combination of halothane, surgery and immunosuppression increased pulmonary metastases in mice inoculated with tumor cells. Shapiro *et al.*^[65] found that lung tumor progression was accelerated in mouse models when exposed to halothane and nitrous oxide. There are no human studies on the isolated effect of volatile anesthetics on tumor spread and metastasis, due probably to the multifactorial nature of immune system and tumor cell biology during the perioperative period. However, since inhaled anesthetics have direct and indirect effects on different aspects of the immune response, it could be hypothesized that they are important factors in postoperative immunosuppression and residual malignant cell invasion and migration.

Extensive experimental work has been carried out to elucidate the mechanisms underlying the immunosuppression induced by volatile anesthetics. Immunomodulatory

properties have been attributed to these agents^[66], including their effect on neutrophil function; reactive oxygen species production; and macrophage, lymphocyte and NK cell physiology^[67]. As neutrophils are a primary line of host defense, it is speculated that as halothane, isoflurane, and sevoflurane are able to blunt either neutrophil adhesion to endothelium *via* intercellular adhesion molecule-1 (ICAM-1), and superoxide production *in vitro*^[68-71], early phases of immunity might be compromised.

The role of the interaction between inhaled anesthetics and Hypoxia Inducible Factors (HIF) has received special attention in the last few years^[72]. These transcription factors are involved in organ protection in hypoxic situations^[73-75]. Isoflurane, desflurane and xenon have been shown to stimulate the expression of HIF in pharmacologic preconditioning, analogous to the one occurring under hypoxic conditions^[76-79]. There is an association between high levels of HIF and clinical prognosis in cancer, colorectal and breast cancer. It is speculated then that tumor cells could also benefit from pharmacologic preconditioning induced by volatile agents.

The effect of volatile anesthetics on neutrophils and HIF, as mentioned above, tends to favor tumor progression *via* pharmacologic preconditioning and depression of primary immunity. However, the depressant effect of these agents on the immune system might turn out to be beneficial in some instances. For example, sevoflurane and desflurane have been shown to reduce invasion of colorectal cancer cells through down-regulation of matrix metalloproteinases^[80].

In regard to lymphocyte function, sevoflurane and isoflurane are able to interfere with integrin-mediated lymphocyte adhesion by means of an allosteric block^[81,82]. In addition, volatile agents are able to induce caspase-dependent apoptosis in T-lymphocytes^[83]. These qualitative abnormalities added to lymphocytopenia induced by agents such as halothane and nitrous oxide, lead to depression of CMI and potential tumor progression in the perioperative period^[84].

Since NK cells represent a key element in the immune response against malignant cell progression and growth, many studies have focused on the effect of inhaled agents on this cell line^[85]. *In vitro* studies have shown that halothane and enflurane reversibly depress NK cell cytotoxicity elicited by IFN^[86,87]. The underlying mechanism for this effect is poorly understood but might be related to cortisol-mediated inhibition^[88] or CD8 T lymphocyte stimulation^[89].

Finally, although most studies linking volatile anesthesia to cancer progression show the immune system as the target for their facilitating actions on tumor cells, recent evidence shows oxidative DNA damage induced by isoflurane in elective surgery^[90]. Furthermore, Musak *et al*^[91] showed that healthcare personnel exposed to volatile anesthetics exhibit higher frequency of chromosomal damage. These findings open a window for possible direct carcinogenic effects of inhaled anesthetic agents, making the issue of perioperative tumor progression an even more complex matter.

Intravenous anesthetics: Intravenous (IV) anesthetics are used to induce hypnosis during anesthesia. As is the case for volatile anesthetics, special interest in IV agents has developed in the last decades in relation to neoplastic tissue growth and propagation in the perioperative period. Propofol, a non-barbiturate induction agent used in anesthesia and critical care (and its lipid carrier vehicle) has anti-inflammatory properties by a direct effect on innate immunity^[92]; however, it appears to lack effect on NK cell and lymphocyte function^[93]. Furthermore, the Th1/Th2 ratio was increased by propofol^[94]. Th1 cytokines activate CMI whereas Th2 cytokines stimulate B cells. Also relevant to antineoplastic immune response, is the fact that propofol impairs monocyte and macrophage function, including phagocytosis and cytokine production^[95-97], in addition to its ability to induce apoptosis in these cellular groups^[97].

Etomidate is a hypnotic agent used in cases where hemodynamic stability is a concern. It has the ability to suppress cortisol production; however, there are no reports linking this effect to tumor progression. Peripheral-type benzodiazepine receptors and gamma aminobutyric acid (GABA) are expressed in breast cancer cells^[98]. Since both receptors are targeted by etomidate, Garib studied the effect of the anesthetic agent in breast cancer cell migration *in vitro*, finding that it has no significant effect^[99]. Ketamine is a dissociative anesthetic agent, widely used in cancer with analgesic purposes. Ketamine significantly decreases NK cell cytotoxicity^[93,100], but at lower preincisional doses has shown to control pain with minimal effect on NK-cell in oral maxillofacial surgery^[101].

Opioids: Opioid derivatives are widely used in anesthesia and pain management. There is growing evidence suggesting a role of these medications in cancer progression and metastasis. The effect of opioids on tumor progression could be related to their ability to interfere with the barrier integrity against tumor propagation^[102], the angiogenic potential of the tumor, a direct immunosuppressive effect, or a combination of factors^[103].

Although the mechanisms underlying opioid-induced immunosuppression are not yet fully understood, it is recognized that μ -receptors^[104] and neuroendocrine mechanisms may play a role^[105-107]. The activation of opioid receptors elicits the stimulation of adrenocorticotrophic hormone production with its consequent cortisol release, which suppresses immune responses^[108,109]. Natural and synthetic opioids are potent activators of the sympathetic nervous system to produce high concentrations of catecholamines^[110], which are involved in tumor progression (see above).

Fentanyl has a dose-dependent depressant effect on T lymphocyte function and NK cell cytotoxicity that parallels lung tumor progression in animals. Remifentanyl has not been widely studied in reference to its effects on malignancies, however there is a single study evaluating its effect on neutrophil function, showing that neither fentanyl nor remifentanyl suppress neutrophil respiratory burst *in vitro*^[111]. Tramadol limits NK cell suppression

caused by surgery in rats^[112,113] and preserves immune function in cancer patients^[114]. There is a lack of evidence linking alfentanil, hydromorphone, and oxycodone to cancer metastasis.

Morphine is the opioid most widely studied in association to cancer recurrence. Peripheral opioid receptors are involved in modulation of cell proliferation^[115] and apoptosis^[116]. *In vitro* studies have shown the pro-apoptotic action of morphine on cancer cells by different mechanisms including inhibition of NF κ B *via* nitric oxide^[117,118], whereas other studies have shown inhibition of apoptotic processes *via* p53^[119-121], a key factor in programmed cell death. In general, most studies report the ability of morphine to inhibit tumor cell proliferation *in vitro*^[122-124].

Although the immunosuppressive effect of opioids has been widely documented, some reports describe opioids' immunomodulatory properties that might prove beneficial in the context of malignant disease^[125-127]. It is reasonable to conclude that the effects of opioids on the cancer immunity depend on the extent of their analgesic action, counterbalancing their primary protumoral effect.

An additional potential confounder here would be psychological symptoms such as depression and its linkages with cancer pain and that those patients with depression are usually on a higher dose of opioids to treat this cancer pain. Cancer chemotherapy in more metastatic and advanced tumors (and those that potentially cause more pain and depression and need more opioids) with pharmacological agents that induce immunosuppression has depression as one of its side effects as well^[128]. Specifically, IFN- α has been seen to decrease serum activity of prolyl endopeptidase (PEP). This enzyme is a cytosolic peptidase that is widely distributed in human tissues and body fluids. By playing an important role in intracellular protein turnover PEP is indirectly involved in the pathophysiology of psychiatric dysfunction in relation to mood disorder. High-risk melanoma patients receiving IFN- α were seen to have a clear decrease in PEP activity in the first four weeks of therapy^[129]. Van Gool *et al.*^[130] also investigated the levels of PEP in patients with metastatic renal cell carcinoma receiving immunotherapy and concluded that a role for PEP in the pathophysiology of IFN- α induced mood disturbance can neither be confirmed nor excluded.

The complex interplay of opioids, cancer pain, immunotherapy, depression and immunomodulation means that clearly the effect of opioids themselves on cancer recurrence and metastases cannot be clearly elucidated and there is much more associated with this cause and effect relationship than what is plainly evident based on current literature.

Local anesthetics: Amide-type but not ester-type local anesthetics possess anti-inflammatory properties^[131]. In addition, local anesthetics have antimicrobial properties^[132]. Taken together, these effects of local anesthetics have led some to hypothesize that they may have a potential role to deter tumor progression after surgery. Some *in vitro* studies have tested the ability of ropivacaine^[133], lido-

caine^[134], and procaine^[135]. Both lidocaine and ropivacaine inhibit TNF- α driven *Srv* activation and ICAM-1 phosphorylation in lung cancer tumor cells *in vitro* through a sodium-channel-blockade independent mechanism^[136]. Procaine has DNA-demethylating properties^[135] that potentiate antineoplastic action of cis-platin^[137,138]. There are no clinical studies evaluating the isolated effect of local anesthetics on cancer recurrence and metastases, so that the contribution of the direct effect of these agents to the beneficial effect of regional anesthesia in cancer patients is for now speculative.

Regional anesthesia effects: *In vitro* and experimental data in animals

The association between pain and immunosuppression has been documented for a long time in animals. Intermittent footshock in rats elicits immune dysfunction including NK cell hypoactivity^[57,58,139,140]. On the other hand, Page *et al.*^[141] demonstrated that postoperative pain is directly involved in surgery-related tumor progression. After these findings, different authors have documented beneficial effects of regional anesthetic techniques on immune function. Wada *et al.*^[142] demonstrated the preservation of the cytokine balance between TH1 and TH2 lymphocytes as the factor involved on attenuation of liver metastasis by combined regional and general anesthesia in mice. Bar-Yosef *et al.*^[59] used a rat model to show that spinal anesthesia preserved NK cell cytotoxicity and attenuated metastasis progression after inoculation of adenocarcinoma cells. Finally, Deegan *et al.*^[143] demonstrated that serum from patients with breast cancer who underwent general anesthesia with paravertebral block inhibited proliferation but not migration of malignant ER-MDA-MB-231 cells *in vitro*.

Regional anesthesia effects: Observational studies

Evidence regarding the facilitation of tumor progression induced by surgery and enhanced by some general anesthetics, has led researchers to postulate that regional anesthetic techniques might ameliorate those deleterious pro-metastatic effects, which could translate into better overall survival rates and recurrence-free survival in cancer patients. One landmark study that opened the window to explore the field of the effect of regional anesthesia on cancer progression was published by Exadaktylos *et al.*^[144] in 2006. They retrospectively studied 129 patients with breast cancer who underwent mastectomy with axillary clearance, with a follow-up time of 32 ± 5 mo. This cohort retrospective study showed that recurrence and metastasis-free survival was 94% (95%CI: 87%-100%) and 82% (95%CI: 74%-91%) at 24 mo and 94% (95%CI: 87%-100%) and 77% (95%CI: 68%-87%) at 36 mo in the paravertebral and general anesthesia patients respectively ($P = 0.012$). The study has limitations inherent to its retrospective nature, including selection bias and biological plausibility^[145]. With the sample size in a retrospective study like the one of Exadaktylos, it is possible that the association is the result of uneven distribution of risk factors between the groups. For instance,

it is likely that the severity of disease had been the cause of the anesthetic technique decision rather than the consequence. Additionally, the author used the Nottingham Prognostic Score to determine propensity to cancer recurrence, when this scale has not been validated for that purpose^[146]. Despite its limitations, this study stands as a landmark publication because it generated the hypothesis of a true association between anesthetic technique and cancer progression, which has led to development of other observational and new experimental studies on the subject.

In 2008, Biki *et al*^[147] addressed the issue of the effect of epidural anesthesia/analgesia on cancer recurrence after radical prostatectomy. This retrospective review showed that the epidural plus general anesthesia group had a 57% (95%CI: 17%-78%) lower risk of recurrence compared with the general anesthesia plus opioid group. Limitations of the study that could limit its validity include incomplete information about the protocol used^[148]. There is no mention of the quantitative postoperative opioid requirement, which might prove important as there is a relationship between opioids and immune depression/cell proliferation. In addition, no power analysis was performed and there are no data about the number of individuals who had surgery and were not included in the review as well as the number of patients dropped because of inadequate information. The evidence provided by Biki is not enough to change practice; nonetheless, it remains as an important study as it encouraged other authors to design prospective studies to clarify the cause-effect relationship between anesthetic technique and cancer recurrence. A potential pathophysiological mechanism to explain the results of Biki could be the higher Th1/Th2 lymphocyte ratio with regional anesthesia compared with general anesthesia^[149]. In contrast to the study of Biki, in 2013 Wuethrich *et al*^[150] published a retrospective study of 148 patients with prostate cancer, concluding that general anesthesia combined with epidural analgesia did not reduce the risk of cancer progression or improve survival after radical prostatectomy after 14 years of observation. The main strength of this study was the prolonged follow-up time. However, as no differences were detected, the study might be underpowered. As in any retrospective study, selection bias cannot be excluded. Finally, the general anesthesia group included ketorolac in the analgesic regimen. It has been shown that ketorolac, by its action on the enzyme COX-2, may suppress cancer relapse^[151]. It is possible that this effect could have influenced the results. By the same token, Tsui *et al*^[152] performed a secondary analysis on 99 patients undergoing radical prostatectomy, who had participated in a previous randomized controlled trial evaluating pain control, blood loss, and transfusion. They found no difference between epidural and control groups in terms of disease free survival after a follow-up time of 4.5 years. Among the 99 patients, 22 were lost to follow-up. Biochemical recurrence was detected in 31% of epidural patients compared to 40% of general anesthesia patients, with a hazard ratio of 1.3 slightly favoring general anesthesia, but with a

95%CI of 0.6-2.7. Despite randomization, the fact that the study was originally designed for different endpoints, renders the study underpowered for evaluating cancer recurrence^[153]. Again, the authors call for design of larger prospective trials.

Cummings *et al*^[154] in 2012 conducted a retrospective cohort study with 42151 patients who underwent surgery for colon cancer. The results are ambiguous, showing that the patients in the epidural group had a 5-year survival of 61% compared to 55% in the non-epidural group, whereas no significant reduction in cancer recurrence in the epidural group could be demonstrated. In spite of the limitations of a retrospective study including, selection bias despite propensity score use and information bias related to the administrative claims source for procedures; this large population-based study is robust enough to suggest a beneficial effect of epidural anesthesia/analgesia on survival after resection of nonmetastatic colon cancer, although no effect of epidural anesthesia/analgesia on cancer recurrence could be demonstrated. In a retrospective analysis, by means of a multiple regression analysis, Gupta *et al*^[155] showed a higher risk of death associated with patient-controlled analgesia (PCA) but not with epidural analgesia in rectal but not colon cancer surgery. This study included 655 patients in Sweden. The inherent limitations of a retrospective study were addressed by the authors; however there might be bias related to group allocation. There is a marked difference in group size (epidural group $n = 562$, PCA group $n = 93$), with no apparent cause, which raises the possibility of selection bias. Some confounding variables such as use of steroids and fluid therapy used were not addressed. Finally, the authors stated that the cause of death in both group was not validated. Taken together, the validity of the results from the study by Gupta *et al*^[155] is questionable. The results of Christopherson *et al*^[156], in a retrospective analysis, also demonstrated a survival benefit of epidural analgesia on survival at 1.46 years in non-metastatic colon cancer surgery. Conversely, Gottschalk *et al*^[157] did not find an association between epidural analgesia and cancer recurrence after colorectal surgery; however, a post-hoc analysis suggested some benefit in older patients. This is also a retrospective study that included 509 patients with colorectal cancer. The epidural group had more patients with rectal cancer, higher histologic grade, more adjuvant therapy and fluid loss. Additionally, there is no clear definition of rectal cancer recurrence, and the use of non-steroidal antiinflammatory medications was not adequately reported. These limitations make the results of Forget *et al*^[158] inconclusive.

Merquiol *et al*^[159] in 2013 published a retrospective study with propensity-based matching of patients with laryngeal and hypopharyngeal cancer surgery under general anesthesia with morphine or cervical epidural analgesia. The epidural group exhibited higher 5-year cancer-free survival (68%; 95%CI: 57%-82%) compared to the non-epidural group (37%; 95%CI: 25%-54%), and increased overall survival. Despite the use of propensity scores, selection bias and influence of confounding factors cannot

be ruled out; nevertheless, this study suggested a possible beneficial effect of neuraxial analgesia in neck cancer. Schlagenhauff *et al.*^[160] conducted a retrospective analysis of cancer registry data using matched pair analysis investigating survival after malignant melanoma. They found that patients who experienced local anesthesia had higher 10-year survival rates. This effect was visible after 3 years.

Conflicting reports in ovarian cancer have been published recently. Lacassie *et al.*^[161] found no benefit in overall survival or time to recurrence in patients with advanced stages of ovarian cancer with epidural analgesia/anesthesia. They retrospectively studied 89 patients with propensity score matching and weighting. Again, the limitations of retrospective studies are observed with this study and the exclusion of 9 patients due to incomplete documentation might affect the validity of the results. Binczak *et al.*^[162] failed to demonstrate a statistically significant association between the perioperative analgesia and recurrence-free survival after abdominal surgery for cancer. This study is a retrospective analysis of patients randomized for a prospective study with different endpoints, and as such is underpowered to detect a difference between analgesic regimens in terms of cancer recurrence and survival. Finally, in a meta-analysis of retrospective and prospective studies on the effect of anesthetic technique on survival in cancer, Chen *et al.*^[163] suggest that, especially in colorectal cancer, epidural anesthesia and/or analgesia might be associated with improved overall survival in cancer undergoing surgery; however, their results do not support an association between epidural anesthesia and cancer control.

In conclusion, the possible association between regional anesthesia and cancer survival and recurrence, yet intriguing, has emerged mainly from experimental animal studies and retrospective human analysis. Prospective studies, ideally randomized clinical trials are needed to establish causation.

CLINICAL TRIALS OF THE EFFECT OF ANESTHESIA ON CANCER RECURRENCE

It is challenging to design a study with sufficient power and robustness to clearly prove the idea that a specific type of anesthesia can reduce the occurrence of cancer, as long-term follow-up is required. Anesthetic effects must be clearly discernible from a multitude of other factors related to the neoplasm propagation. Interindividual variability in immune system performance as well response to anesthesia further complicates the issue. This also means that large studies are needed to understand the difficult-to-single-out effects of anesthesia on tumor propagation.

The review of clinical trials should be started from animal studies. Bar-Yosef *et al.*^[59] conducted an interesting study in which rats were subjected to a laparotomy during general halothane anesthesia alone or combined with either systemic morphine or spinal block using bupivacaine with morphine. Control groups were either anes-

thetized or undisturbed. The animals were subjected to a standard load of adenocarcinoma cells, and the “clinical outcome” was measured by change in tumor load and activity of NK cells. Strikingly, spinal anesthesia significantly reduced tumor load that was initially elevated after surgery. More specifically, laparotomy conducted during general anesthesia alone increased lung tumor retention up to 17-fold. The addition of spinal block reduced this effect by 70%. The number of metastases increased from 16.7 ± 10.5 (mean \pm SD) in the control group to 37.2 ± 24.4 after surgery and was reduced to 10.5 ± 4.7 during spinal block. This study is seminal and many follow-up clinical trials used the results generated by Bar-Yosef *et al.*^[59] to calculate power of their randomized clinical trials even though they did not use any clinical metrics of tumor progression. Further support to this study was brought by Wade *et al.*^[142]. This group inoculated mice with liver tumor cells *via* laparotomy while the mice were under general anesthesia alone or combined with spinal block. They concurred that spinal anesthesia significantly reduces tumor load. However, both studies are problematic because injecting the cells into the bloodstream and measuring the tumor load later may have little clinical relevance to human patients.

Currently, there is not a finished randomized clinical trial investigating the relationship between type of anesthesia and neoplastic growth. Some studies were terminated without enrolling patients while several other studies are underway but have not yet reported the results.

Study NCT00418457 will investigate the relationship between the addition of regional anesthesia to the general surgery regimen and recurrence of breast cancer. This study is planning to enroll 1100 patients and to investigate the effect of a paravertebral block. Using data from animal experiments, investigators predict such a sample size over 5 years will provide 85% power for detecting a 30% treatment effect at an alpha of 0.05 with a total of four potential stopping points^[59,142]. Follow-up is planned for 10 years.

Exadaktylos *et al.*^[144] have previously shown that the use of regional anesthesia in cancer surgery reduced the risk of recurrence and metastases of breast cancer by four fold. In a recent analysis of a previously conducted study of paravertebral blocks for breast cancer surgery, oppfeldt and carlson evaluated the effects of regional anesthesia on cancer recurrence^[164]. Eighty-eight patients having breast cancer surgery were enrolled in this study. The patients received 4-6 paravertebral injections from level C7 through T5 on the side of surgery. The treatment group received a total of 30 mL of ropivacaine 0.5% and the placebo group received placebo injections of isotonic saline in an equivalent volume. Both groups had a standardized anesthesia consisting of propofol, fentanyl and ventilation *via* a laryngeal mask.

Six years or more after surgery the investigators found that local or metastatic recurrence of the cancer in five patients (13%) in the ropivacaine group and in fourteen (37%) patients in the saline group, RR = 0.35 (95%CI: 0.14-0.87). In addition, the mortality related to

the breast cancer was significantly lower in the ropivacaine group (ropivacaine 4, saline 12), RR = 0.32 (95%CI: 0.11-0.92). Also, patients without recurrence of cancer consumed significantly lesser opioids (45 mg morphine equipotent doses) compared to patients with recurrence of cancer (58 mg morphine equipotent doses), $P = 0.016$. The authors concluded that attenuation of surgical stress and reduced opioid consumption reduces the risk of developing metastases^[164].

A very similar design is being tested in NCT00684229. In this multicenter clinical trial a comparison of colorectal cancer recurrence will be measured between patients randomly assigned to epidural anesthesia combined with general versus general anesthesia only. Follow-up is planned for 5 years.

In NCT01588847 the investigators hypothesize that patients suffering from malignant melanoma who undergo radical inguinal lymph node dissection will demonstrate less immune function compromise and superior long-term survival when spinal anesthesia is used, compared to general anesthesia. The time frame for this study is 5 years. Investigators will be evaluating in the short term some aspects of immune system performance.

NCT01179308 is focusing on patients undergoing lung resection. Again, investigators propose to evaluate the effect of combined epidural-general anesthesia compared to general anesthesia on cancer recurrence semi-annually over a period of 5 years.

The National Science Council of Taiwan will co-sponsor a study looking into the effect of local infiltration anesthesia with lidocaine and bupivacaine on the recurrence of breast cancer while patients are rendered unconscious with propofol (NCT015332233). A second avenue of this study involves standard general inhalational anesthesia with opioids. Estimated enrollment is scheduled for 40, which seems to be too small to achieve significant power. This number of enrollment is in clear contrast to other the target number of other studies.

The EPICOL study (NCT01318161) enrolls patients after undergoing surgery for colorectal cancer in Sweden. Regional anesthesia in the form of epidural anesthesia will be contrasted to oral narcotics. The follow-up is planned for total of 7 years and the enrollment goal is 400 patients. Additionally, authors of the study plan to conduct large-scale measurements of cytokine and angiogenesis factors in the patient population. No effect of epidural or spinal blockade will be examined. Researchers plan to enroll 60 subjects and measure only immune system functions in the short-term after surgery.

Similarly, NCT01902849 focuses on the modulation of immune aspects after surgery. The investigators will analyze IL-6 and IL-10 levels until 24 h post-op.

In the interesting spin CTC study (NCT01716065), researchers will look at the circulating tumor load in subjects undergoing surgery for primary nonmetastatic cancer. Though this study parallels aforementioned studies in animals, the target goal is 20 subjects.

These clinical trials and the planned studies going forward if properly powered and statistically robust will go a long way in answering the as yet unanswered question of

modifying the anesthetic plan to provide a better cancer related outcome for the patient in question.

OTHER POTENTIALLY IMPORTANT FACTORS

Blood transfusion

It is now a well know theoretical fact that transfusion-associated immunomodulation (TRIM) is the driving force behind allogeneic blood transfusion related tumor recurrence. This is related to the immunosuppressive effects of the allogeneic blood^[165,166].

Patients undergoing surgery for colorectal cancer have experienced a significant decline in immune function as measured by a reduction in T-helper and NK cell lines. The roles of these cells in the immunopathology of cell defense and tumor immunity have been highlighted in the earlier text^[167-170].

So what really is the biggest villain within a unit of allogeneic blood transfusion itself? Much needs to done to reach a precise answer. The current evidence points towards white blood cells^[169]. A study investigating patients undergoing resection of gastric cancer randomized patients to allogeneic or autologous transfusion. IFN- γ , T-helper cell, and T-helper/cytotoxic T-cell ratio were reduced in both groups after operation. The reduction was greater in the allogeneic transfusion group. Five days after the operation, levels had returned to baseline for patients receiving autologous transfusions but remained suppressed in the allogeneic group^[171]. Literature has not clearly supported TRIM as an effector of cancer recurrence. As might be expected, several potential confounders such as severity or stage of the cancer, and or co-morbid conditions, have emerged and are difficult to control for while designing studies^[172]. Other observational studies (esophageal cancer) and randomized control trials (colorectal cancer) have not reported leukocyte depletion or allogeneic white blood cells to affect cancer outcome^[173-176]. The clinical evidence of whether TRIM is associated with a worse oncologic outcome, and of whether leukodepletion reduces TRIM, remains unanswered.

Immunotherapy

Opioids have been known to suppress immune response, specifically NK cell activity. It has been seen that in rats that pretreatment with an IFN inducer increases NK cell activity to above baseline in rats and attenuates the fentanyl-induced suppression to above baseline levels^[177].

Similarly, when IFN- α and IFN- β are used before surgery in rats, they may offset some of the inhibition of NK cell cytotoxicity associated with surgery and anesthesia^[178]. Going forward the use of immunotherapy for cancer in humans during the perioperative period has been proposed, though present literature has not reported significant success^[179].

Beta-blockers

A large body of recent data supports the use of beta-blockers in cancer patients. The proposed mechanisms

revolve around the attenuation of the anxiety driven intense sympathetic drive and related IL release during the initial phase of cancer seeding. The growing evidence that norepinephrine and epinephrine affect some types of cancer backs this. The body's "fight or flight" response related to psychological stressors may release these hormones and affect cancer by interacting with molecular pathways already implicated in abnormal cellular replication, such as the P38/MAPK pathway, or *via* oxidative stress. Various studies have shown less distant metastases in patients with prostate^[180] and lung cancer^[181]. The strongest evidence probably comes from the breast cancer subgroup wherein there is a favorable benefit for cancer recurrence in particular^[182,183]. An important consideration with these studies is that all of them are retrospective in nature. Stronger evidence with blinded randomized trials is probably needed before we can think of specifically initiating beta-blockers in the perioperative period to decrease cancer recurrence.

Hypothermia

Based on the premise that hypothermia excites a stress response and glucocorticoid release that in turn increases immunosuppressive effects, hypothermia has a mechanistic linkage to cancer recurrence. In animal studies, a temperature of 30.8 °C has been shown to suppress NK cell activity and also suppress resistance to metastasis using a specific tumor model^[184]. In humans, mild hypothermia to 35.5 °C exacerbates the immunosuppressive effects of abdominal surgery^[185].

Stress response

In humans as well as in animals, stress responses have been linked to NK cell suppression, perioperative immunosuppression and increase tumor retention^[17,186].

The stress level in cancer patients is associated with the degree of postoperative immunosuppression and has been shown to predict NK cell toxicity and T-cell responses. This may be the reason for success with beta blocker therapy as highlighted in the section above and an area of interest for anesthesiologists.

Future directions

Though much has been said and done about anesthetic technique and cancer recurrence, the question very much remains unanswered. Multiple high quality, well-designed and validated studies are needed before a strong statement can be made one way or the other about the influence of an anesthetic technique on the recurrence and behavior of certain cancer types. The currently available data do favor regional anesthesia as a sole vehicle or in combination with general anesthesia, in addition to an increasing trend to autologous blood transfusion and attenuation of stress responses in the perioperative period. Areas of future interest could be related to some of the other anti-inflammatory and immunomodulatory drugs that we use in the perioperative period. These include a better categorization of various types of opioids, NSAIDs and other analgesics. A greater focus needs to

be on longer follow-up of patients in these observational studies and long term outcomes related to the anesthetic technique and perioperative interventions.

As an anesthesiologist and a perioperative physician these variables are important and while we wait for better clinical studies in humans, we have to move to shaping these perioperative factors for better outcomes in surgical cancer patients.

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Complex regional pain syndrome: From diagnosis to rehabilitation

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of CRPS is not fully understood, it is recognised that inflammatory processes and autonomic dysfunction are involved. These processes are associated with peripheral and central sensitisation as well as changes in brain structure and function, and are reflected in the clinical presentation of CRPS. CRPS management requires an interdisciplinary team and requires the therapeutic approach to be individualised. With regard to pharmacological treatment, bisphosphonates, corticosteroids, ketamine and anticonvulsants have been demonstrated to be effective for CRPS management. Psychotherapy, including cognitive-behavioural therapy, has produced promising results but more studies are needed to confirm its efficacy. Among rehabilitation interventions, there is evidence of the efficacy of physiotherapy and occupational therapy in diminishing CRPS symptoms and achieving a higher level of functioning. In this regard, the rehabilitation modality that seems the most promising according to the actual literature is graded motor imagery, which can help to reverse the maladaptive neuroplasticity occurring in CRPS.

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Key words: Complex regional pain syndrome; Autonomic; Inflammation; Plasticity; Rehabilitation

Core tip: Complex regional pain syndrome (CRPS) involves a complex pathophysiology including sensory, motor and autonomic disturbances that causes functional disability and reduced quality of life. The management of CRPS remains challenging for health care professionals. This review provides a summary of the recent literature on CRPS pathophysiology and management. The potential mechanisms of effective interventions are also discussed.

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Abstract

Complex regional pain syndrome (CRPS) is a debilitating pathology characterised by intense chronic pain associated with vasomotor, sensory and motor dysfunction of the affected limb. Although the pathophysiology

INTRODUCTION

Initially known as causalgia, complex regional pain syndrome (CRPS) was reported for the first time in 1865 during the American Civil War in soldiers who were affected by neurologic injuries^[1]. In the early 20th century, CRPS was known as Sudeck's atrophy, after the German surgeon Sudeck^[2], who observed similar clinical features among patients who suffered from orthopaedic injuries without neurologic disorders. Later, CRPS was described as reflex sympathetic dystrophy because it was believed to be caused by an overactive sympathetic nervous system (SNS). The progressive advancement of the knowledge on CRPS pathophysiology led to several additional terminology changes over the years, during which CRPS was referred to as algodystrophy, algoneurodystrophy, neurodystrophy or shoulder-hand syndrome (because of distal symptoms expanding proximally)^[3]. The current term, CRPS, was adopted in 1994 by the International Association for the Study of Pain (IASP)^[4].

CRPS is a pathological condition characterised by chronic pain for which the duration and intensity are disproportional relative to the trigger event, which is frequently a trauma to the upper or lower limb^[5]. This painful disorder includes sensory, autonomic and motor disturbances^[6], which cause functional disability and a reduced quality of life^[7-9]. The literature reports two types of CRPS, depending on whether it is associated with nerve damage or not; CRPS-1: no nerve damage, formerly known as reflex sympathetic dystrophy, and CRPS-2: with nerve damage, formerly known as causalgia^[4,10]. However, it should be noted that there is no evidence supporting that the physiopathology, the therapeutic response, or the clinical presentation differ between both types of CRPS^[11]. Accordingly, a bone fracture or a surgery often causes damage to small nerve fibres, but most CRPS diagnosed after a fracture are classified as CRPS-1^[12,13]. Nevertheless, the distinction between CRPS-1 and CRPS-2 will be made in this review, when possible, in accordance with the IASP guidelines^[4]. Because our understanding of CRPS pathophysiology and the therapeutic approaches to treat CRPS have changed considerably over the past few years, this review will summarise the available literature on the pathophysiology, diagnostic criteria and the evidence-based approach to treat CRPS.

DIAGNOSIS AND PATHOPHYSIOLOGY

Diagnostic criteria

The diagnosis of CRPS is based on the clinical examination with the observation of physical signs and symptoms. To date, there is no biomarker or "gold standard" to confirm CRPS^[14-16]. The first diagnostic criteria for CRPS were established by the IASP in 1994. Table 1

Table 1 Orlando (International Association for the Study of Pain) criteria for complex regional pain syndrome

Criteria 1	The presence of an initiating noxious event or a cause of immobilisation
Criteria 2	Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event
Criteria 3	Evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain (can be sign or symptom)
Criteria 4	This diagnosis is excluded by the existence of other conditions that would otherwise account for the degree of pain and dysfunction

Table adapted from Merksey *et al*^[158].

Table 2 Budapest clinical diagnostic criteria for complex regional pain syndrome

Criteria 1	Continuing pain, which is disproportionate to any inciting event
Criteria 2	Must report at least one symptom in three of the four following categories: Sensory: reports of hyperesthesia and/or allodynia Vasomotor: reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry Sudomotor/oedema: reports of oedema and/or sweating changes and/or sweating asymmetry Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
Criteria 3	Must display at least one sign at time of evaluation in two or more of the following categories: Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement) Vasomotor: evidence of temperature asymmetry and/or skin colour changes and/or asymmetry Sudomotor/oedema: evidence of oedema and/or sweating changes and/or sweating asymmetry Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
Criteria 4	There is no other diagnostic that better explains the signs and symptoms

Table adapted from Harden *et al*^[158].

describes these criteria, which are referred to as the Orlando criteria. Although their sensitivity was high (98%), their specificity was poor (36%), resulting in a fairly small number of correct diagnoses^[17].

More recently, a modified version of these criteria has been proposed to achieve a better specificity and to improve the efficacy of CRPS diagnosis, by adding more features of CRPS. Table 2 describes the Budapest Criteria, which have been validated^[18]. The use of different criteria across studies leads to variable results and makes the between-study comparisons difficult^[9]. The Budapest criteria are used for both CRPS-1 and CRPS-2. The method used to distinguish CRPS-1 from CRPS-2 is the absence (CRPS-1) or the presence (CRPS-2) of nerve damage. To date however, there is no standardised procedure to detect the presence or absence of nerve

damage^[4,19]. Thus, the distinction relies on clinical judgment that may be supported by diagnostic examinations such as electromyography with nerve conduction tests or surgical exploration.

EPIDEMIOLOGY

Although epidemiological studies on CRPS are scarce and limited, this is not surprising given that CRPS is reported to be a relatively rare disease. According to a population-based study conducted in the Olmsted County of Minnesota, the incidence of CRPS-1 has been estimated to be 5.46 cases/100000 per year in the United States^[20]. The results from another study conducted more recently in the Netherlands estimated the incidence of CRPS to be approximately 26.2 cases/100000 per year^[21]. This discrepancy has been attributed to differences in population characteristics, such as ethnicity and socio-economic factors, as well as methodological differences (inclusion criteria based on the retrospective use of the IASP criteria only^[20] vs the use of the IASP criteria or the opinion of a general practitioner^[21]). In addition, the authors of the study conducted on the Netherlands population did not clearly state if they included only CRPS-1 or both types of CRPS patients, which may also contribute to the higher incidence reported in that study. The prevalence of CRPS-1 has been estimated to be 20.57 cases/100000 in the United States^[20] and the number of new cases per year is expected to range between 20000 and 80000^[12]. To date, no other large population-based study is available. Nevertheless, it is generally accepted that CRPS-1 is more common than CRPS-2^[20].

Previous studies suggest the existence of risk factors for developing CRPS. In terms of demographic characteristics of the most commonly affected patients, women are two to three times more likely to develop CRPS than men and most CRPS cases among women occur after menopause^[21]. Accordingly, some authors have suggested that hormonal factors may be involved in the pathophysiology of the disease^[21,22]. Women with menstrual cycle-related problems and osteoporosis would be more likely to develop CRPS after a trauma^[23]. However, results of a population-based case-control study including 53 CRPS patients and 58 controls did not find any association between the development of CRPS and oestrogen exposure, but this finding may be related to the low statistical power of the study^[24]. Although it can affect people of all ages, CRPS is more likely to develop between 40 and 60 years old^[25] with a mean age of 53 years old at the time of the diagnosis^[26]. This finding is consistent with the prevalence of chronic pain in general, which peaks in middle age^[27,28]. Suffering from migraine is also considered a risk factor to developing CRPS, in accordance with the similar physiopathological processes between the conditions, such as neurogenic inflammation^[29].

The development of CRPS follows a minor injury to the upper limb twice as frequently compared with a lower limb injury^[20,21,30]. The most common triggering event is a distal radius fracture including Colles fracture^[20,21,31]. A

recent prospective multicentre cohort study conducted on 596 patients estimated the incidence of CRPS-1 after a distal radius fracture to be approximately 14%^[9]. Based on the Budapest CRPS criteria^[18], the general incidence rate for developing CRPS-1 after a fracture would be 7%^[9]. However, depending on the diagnostic criteria and the CRPS features (CRPS-1 vs CRPS-2, upper limb vs lower limb, surgical complications, association with another diagnosis, *etc.*), the incidence rate of CRPS after a fracture ranges from 0.9% to 51%, regardless of the location^[9,22,32-39]. Immobilisation of the hand or the upper extremity after any trauma is considered an important risk factor for the development of CRPS^[12,40]. To a lesser extent, other types of injury may also be a trigger event for developing CRPS. CRPS can occur after a central lesion such as stroke or can develop spontaneously in a small proportion of cases (less than 5%)^[10,20,21,30,41]. It has been suggested that psychological factors may constitute risk factors for the development of CRPS^[42-45], but this theory is no longer supported^[12,23,46,47]. For instance, a group of authors conducted a multicentre prospective study including 596 patients with an upper limb fracture, in which they examined the relationship between the development of CRPS-1 and several psychological factors, such as agoraphobia, depression, somatisation, interpersonal sensitivity and insomnia. The study revealed that none of these factors was significantly associated with the development of CRPS^[46]. The lack of association between psychological factors and CRPS is also corroborated by the results of a systematic review including 31 articles^[45] and also by previous prospective studies^[48-50] and a large retrospective case-control study including 186 CRPS patients and 697 controls matched for age, sex and trauma^[23]. Thus, the psychological symptoms reported by CRPS patients are thought to be a consequence of disability and chronic pain itself, rather than being a predisposing factor^[36,46,48,49]. Otherwise, some authors suggest a genetic predisposition to developing CRPS^[51], but larger studies are required to establish clearer patterns of inheritance. Finally, the severity of the triggering event is not considered as a risk factor in the development of CRPS^[10,12].

PATHOPHYSIOLOGY

Although the pathophysiology of CRPS is not completely understood at this time, it is generally accepted that it involves several mechanisms^[11], including an alteration of the central nervous system (CNS)^[25,31]. According to the authors of a recent review, physiological reactions to the initiating injury would lead to disturbances of inflammatory processes and autonomic function^[12]. These pathological processes would, in turn, lead to maladaptive neuroplasticity^[12], such as peripheral and central sensitisation. Each of these processes may appear concurrently or sequentially and is related to specific signs and symptoms observable during the evolution of the disease, which will be described below. There is also some evidence that the relative contribution of each mechanism to CRPS differs from one patient to another and also differs at different

time points in the course of the disease^[52].

Inflammatory component

Relatively recent theories suggest that the pathophysiology of CRPS is linked to disturbances of neurogenic inflammatory processes^[12,53], including higher plasma levels of bradykinin^[54], increased systemic levels of neuropeptides^[41,55], such as calcitonin gene-related peptides, and the release of pro-inflammatory cytokines such as tumour necrosis factor- α ^[56] or interleukin-6^[57]. It has also been found that patients with chronic pain may have lower endogenous anti-inflammatory activity^[58]. Accordingly, a recent meta-analysis conducted on 15 studies revealed that CRPS is associated with a predominantly pro-inflammatory state, with different inflammatory profiles in the acute vs the chronic stage of the disease^[53]. These findings are consistent with the vasodilation, oedema, increased sweating^[41,55] and the hyperalgesia observed in the acute stage of CRPS^[41,59]. These findings are also in agreement with a recent systematic review showing that corticosteroids improve the signs and symptoms of CRPS-1^[60]. Proinflammatory cytokines and neuropeptides may also be involved in peripheral sensitisation^[11,57]. Therefore, there is clear evidence that disturbances in neurogenic inflammatory processes are implicated in the pathophysiology of CRPS.

Involvement of the SNS

In addition to the inflammatory processes, alteration of the SNS has been proposed to contribute to the pathophysiology of CRPS. To explain the autonomic features, such as a cool and bluish limb, it was thought that CRPS was caused by a reflex vasoconstriction, reflecting post-traumatic SNS hyperactivity^[5,61]. However, this hypothesis is no longer supported, in spite of the involvement of the SNS in CRPS^[62,63]. It is now recognised that SNS activity is reduced in the first stages of the disease, which manifests as decreased reflex vasoconstriction in the affected area^[64,65]. This symptom is associated with the vasodilatation of the peripheral vessels and may explain the warming of the affected region^[11]. Changes in the pattern of clinical features as CRPS evolves from an acute to a chronic state may be related to circulating catecholamines^[11]. As an adaptive mechanism, the SNS hypoactivity seems to progressively increase the sensitivity of peripheral adrenergic receptors to circulating catecholamines that are released in response to psychological stress or pain itself^[11]. This phenomenon may contribute to the exaggerated vasoconstriction in later stages of the disease^[11,66]. Thus, the affected limb changes from a warm, swollen and reddish state to become cold and bluish^[64]. It is also known that a chronic dysregulation of the SNS may lead to sympathetically maintained pain in 10% of CRPS patients^[4].

Contribution of the oxidative stress in the pathophysiology of CRPS: Long-term sympathetic disturbances result in the redistribution of blood flow in micro-circulatory vessels. This process impairs their nourishment^[67], the

endothelial function, and reduces acetylcholine-induced vasodilatation^[68]. These alterations have been suggested to lead to hypoxemia and acidosis, which may produce free radicals and oxidative stress^[69]. A previous study proposed that free radicals are the result of mitochondrial dysfunction in the respiratory chain^[25]. Accordingly, free radicals have been detected in the saliva and the serum of the affected limb in CRPS-1 patients^[70], as well as in two animal models of CRPS^[71,72]. Furthermore, a multicentre randomised controlled trial (RCT) demonstrated the protective effect of vitamin C, a well-known antioxidant, on the development of CRPS after a wrist fracture treated with a plaster cast^[73] or by surgery^[74]. Therefore, oxidative stress may be involved in the pathophysiology of CRPS, but it is still not clear if it is a cause or a consequence of the disease^[25]. More prospective studies are needed to better understand the potential role of oxidative stress in the pathophysiology of CRPS, but it may constitute a biomarker of and a therapeutic target for CRPS.

Plasticity of the peripheral and CNS

Changes in the peripheral and CNS: Peripheral sensitisation is thought to play a role in CRPS pathophysiology^[75]. It is a form of neuroplasticity relying on the capacity of neurons to change their function, chemical profile or structure in response to a specific situation^[76]. Peripheral sensitisation results in a continuous release of catecholamines by the nociceptive fibres of the affected area^[77] and brings sustained nociceptive input to the spinal cord. This causes activity-dependant changes in the spinal cord and central sensitisation, resulting in enhanced central responsiveness to nociceptive inputs^[76]. This enhanced nociceptive transmission may induce a pain sensation that outlasts the initiating input or that requires lower level of peripheral drive to maintain it^[76].

Altered cortical representation of the affected limb:

In CRPS, motor and sensory deficits that are not limited to the area of injury have been suggested to be related to maladaptive neuroplasticity in the brain. For instance, the representation of the affected hand in the primary somatosensory cortex is significantly shrunk and shifted toward the lip compared with the unaffected hand^[78-81]. These changes in the hand primary somatosensory cortex representation are correlated with the amount of pain^[81] and mechanical hyperalgesia in CRPS^[79]. With rehabilitation, the cortical organisation is progressively re-established and correlates with the decrease in pain and the diminishing extent of mechanical hyperalgesia^[80]. The results of a follow-up study revealed a reversal of cortical reorganisation in agreement with clinical improvement at least 1 year after therapy^[80]. Thus, chronic CRPS pain seems to correlate well with the cortical representation of the affected limb, which may contribute to the persistence of pain^[80,81].

It has also been reported that the representation of the affected and unaffected hand muscles is asymmetrical in the motor cortex of patients with CRPS-1^[82]. In that study, the cortical representation (size, motor evoked po-

tentials, and calculated volumes) was significantly larger for the unaffected hand than for the affected hand and this asymmetry was not found in the control group of healthy subjects. An fMRI study also demonstrated sub-spatial adaptive changes in the CNS of CRPS patients by investigating cerebral activation during a finger tapping task^[83]. The authors found significantly larger brain activations compared with healthy controls and also compared with the unaffected side of the CRPS patients. This finding may be explained by defective inhibitory mechanisms in the motor cortex that were previously demonstrated^[84-86]. Besides, a transcranial magnetic stimulation study found a hyperactivity of the contralateral motor cortex in CRPS patients^[84]. The authors hypothesised that this hyperexcitability may be linked to an adaptive process related to the decreased mobility of the affected limb and not necessarily to the painful sensations^[84], but further studies are still required to fully understand this phenomenon^[6]. Alterations of the premotor cortex have also been observed in a study including eight chronic CRPS-1 patients with dystonia (mean duration of disease of 11 years)^[87]. Their results revealed that less cerebral activation was present in both the ipsi- and contralateral hemispheres when imagining movements, compared with the activation patterns of age-matched healthy controls^[87].

Results of a recent imaging study including voxel-based morphometry and DTI analyses revealed gray matter atrophy in the right hemisphere, especially in the right insula, right ventromedial prefrontal cortex (VMPFC), and right nucleus accumbens in 28 CRPS patients^[88]. Interestingly, gray matter atrophy in the VMPFC correlated with the interaction between pain intensity and duration in CRPS patients, while right anterior insula gray matter atrophy correlated with pain duration^[88]. In addition, the gray matter atrophy in the right anterior insula was associated with reduced autonomic responses^[89], consistent with the autonomic dysregulation in CRPS and the role of the insula in autonomic regulation^[88]. Furthermore, the gray matter atrophy observed in the VMPFC was associated with poor performance in an emotional decision-making task^[88,90], congruent with the clinical features of CRPS.

In summary, the literature exposes evidence about the pathophysiology of CRPS, but several questions on the mechanisms of the disease remain, especially in relation to the specific role of oxidative stress^[25] and the patterns of cortical reorganisation during the onset and the course of the disease^[6]. Further studies are also required to better understand the links between physiopathological processes and clinical features, to improve treatment modalities offered to CRPS patients.

CLINICAL PICTURE

Physical features

Nearly 100% of patients with CRPS report hyperalgesia, that is, an increased pain sensation to a normally painful stimulus^[91]. Allodynia, or a painful sensation elicited by a stimulus that usually does not elicit pain, is also com-

mon, affecting one third of patients with CRPS^[91]. These sensory disturbances are not limited to a single peripheral nerve territory but rather follow a glove distribution^[16], and may be linked with the sensitisation processes implied in the CRPS pathophysiology described above. It is recognised that CRPS patients may have impaired processing of proprioceptive or tactile input, but higher multisensory integration systems seem unaffected^[92]. Accordingly, the results of a recent study conducted on 24 CRPS patients and 24 controls revealed that CRPS patients had an intact perception of illusory ownership, which suggests unaffected functions of multisensory cortical areas^[92].

Autonomic disturbances resulting in distal oedema are present in 81% of patients^[91]. Skin changes in colour and temperature are also common symptoms of CRPS^[91]. Disorders of sweating can also be noted^[31] in 55% of patients, with hyperhidrosis being more frequent than hypohidrosis^[93]. Finally, trophic changes such as the increased growth of hair and nails of the affected limb are some of the physical symptoms related to CRPS^[91], in addition to bone demineralisation^[94]. All of these autonomic disturbances are related to the dysregulation of the SNS described above. Principal physical features induced by CRPS, such as oedema, skin colour changes and muscle atrophy, are illustrated in Figure 1.

In terms of motor function, 77% of patients present with weakness of the affected limb and 45% have exaggerated deep tendon reflexes^[91]. A recent kinematic study including 80 CRPS patients also suggests that voluntary motor control may be impaired, causing bradykinesia and akinesia in both the affected and the unaffected upper limb^[95].

Psychological features

The psychological factor most reportedly associated with CRPS is the fear of pain^[96]. In accordance with the fear-avoidance model of chronic pain^[97], the fear of pain may have a significant impact on global functioning. For instance, CRPS patients avoid certain activities fearing that they will trigger pain. This avoidance contributes to isolation and higher levels of anxiety^[98]. In addition, a large proportion of CRPS patients present symptoms of depression, such as mood or sleep disturbances, as the prevalence of depression in CRPS is estimated to range from 31% to 96%^[45]. Psychological factors, such as anxiety, stress or inconsistent emotional states may have an impact on catecholamines neurotransmission and may play a role in the pathophysiology of CRPS, including the dysregulation of the SNS and sensitisation^[11,98,99]. Psychological stress also seems to be related to the development or maintenance of CRPS-1^[45], which may results in repeated sympathetic activation and locally altered catecholamine responsiveness^[45,98,99].

In summary, stress or anxiety may have an impact in the maintenance of CRPS in relation with their influence on catecholamine activity^[99]. However, as mentioned previously, other psychological factors such as depression or somatisation seem to be consequences of the disability



Figure 1 Clinical signs of complex regional pain syndrome. A: Oedema and colouration changes around the metacarpophalangeal joints of a 42-year-old woman with bilateral upper limb complex regional pain syndrome (CRPS) in the acute phase (around six months); B: Thenar muscle atrophy and slick skin aspect of a 22-year-old woman with left upper limb CRPS for a duration of 3 yr; C: Significant knee oedema in a 46-year-old woman with right lower limb CRPS lasting 2 yr; D: Blue coloured left lower limb CRPS in the cold phase (3 yr) of a 23-year-old woman.

and chronic pain itself, rather than being predisposing factors^[36,46,48,49].

Cognitive and perceptual features

Recent studies revealed cognitive impairments in CRPS patients. In a neuropsychological study including 137 CRPS patients, significant neuropsychological deficits were present in 65% of patients, presenting with impairments in executive functions^[100]. Among the perceptual features, patients with CRPS may suffer from physical and spatial hemineglect^[16,101,102] as a result of a disturbed body schema induced by the changes in the cortical representation of the affected limb^[101,103-106]. Indeed, CRPS patients perceive their affected limb as bigger than it really is^[106] by more than 8%^[107] and have difficulty recognising their own limb^[108] and estimating its position^[104]. Moseley *et al.*^[102] found that when they receive concurrent vibrotactile stimulations at 140% of their tactile threshold to both limbs without the contribution of vision, CRPS patients tend to neglect stimulations of the affected limb. This finding suggests a complex alteration of the representation of the bodily space. A recent study including a group of 20 CRPS patients and two age- and gender-matched control groups (healthy volunteers and patients with chronic pain other than CRPS) revealed that CRPS patients show a slower reaction time in response to a visual stimulus presented in the visual field corresponding to the side of the affected limb^[101]. In that study, CRPS patients also had a significantly lower score in the clock-drawing test than the healthy controls, which is also consistent with spatial hemineglect.

In summary, CRPS can affect many aspects of daily life. It may have a devastating effect on the quality of life and productivity. A large proportion of patients (81%) have to quit their jobs at the peak of the disease and only 27% can return to a productive life after the crisis^[109].

This decrease in productivity generates significant costs for the society. Therefore, it is important to deal quickly and appropriately with CRPS. The next section will present the main treatment modalities currently used with this population.

CRPS MANAGEMENT

In this section, the most common treatments for CRPS will be presented. However, it should be emphasised that CRPS is a complex pathology, including both central and peripheral abnormalities, and it is sometimes associated with psychosocial components. Therefore, CRPS should be treated using an interdisciplinary approach^[19].

Pharmacology

Similar to other chronic pain syndromes, pharmacological treatments are widely used for the treatment of CRPS. However, drug therapy works best if prescribed in combination with other management modalities, such as rehabilitation^[19]. Various types of drugs such as opioids, calcitonin, bisphosphonates and antidepressants or anticonvulsants may be taken orally^[31,94,110]. Essentially, the strategies and drug combinations are the same as for neuropathic pain management. The goal in using pharmacological agents is to act on the pathophysiological processes generating pain, *i.e.*, inflammation or sympathetic dysfunction^[31]. However, scientific evidence supporting pharmacotherapy in CRPS remains limited^[94,110].

Opioids: According to the results of a study conducted on 102 CRPS patients, 21% of CRPS patients are treated with opioids^[111] and this type of drug is mostly used in the early stages of the disease^[111]. However, only one placebo-controlled RCT studied the use of oral sustained-release morphine in CRPS-1 patients who were previ-

ously treated with spinal cord stimulation ($n = 43$)^[112]. No significant effect on pain reduction has been found with the use of morphine compared with placebo^[112]. Additionally, the morphine group reported 20 side-effects a day compared with 2 a day for the placebo group^[112]. Accordingly, authors of the evidence-based guidelines in CRPS treatments stated that there is insufficient evidence regarding the efficacy of opioids in reducing CRPS pain^[110]. To our knowledge, no study has been conducted on opioids other than morphine for the treatment of CRPS. Even if opioids are well-known to inhibit nociceptive processes in the CNS, addiction may potentially develop in a small subset of patients^[113]. Because of their serious adverse effects, opioids should be prescribed with caution in the treatment of CRPS^[113].

Calcitonin: Calcitonin is of great interest in the treatment of CRPS for its analgesic properties, by producing the release of β -endorphins, and for its action in preventing bone resorption^[50]. In spite of these promising theoretical effects, however, results of recent systematic reviews demonstrated conflicting evidence of calcitonin's efficacy in the treatment of CRPS-1^[110] or in the treatment of both types of CRPS^[94], according to the outcomes of pain reduction, functional outcome, clinical features or bone mineralisation. The authors of a systematic review based on 41 articles related to CRPS treatment stated that to date, the beneficial effects of calcitonin on CRPS patients have not been demonstrated^[94]; further studies are required to establish a clear recommendation regarding the use of calcitonin in CRPS management.

Bisphosphonates: Bisphosphonates are effective in reducing the signs of inflammation associated with CRPS^[94,110]. In three placebo-controlled studies, bisphosphonates were significantly more effective than placebo for upper limb CRPS-1 patients ($n = 20$, $n = 39$ and $n = 32$) in decreasing inflammation signs, including pain and oedema, and improving mobility^[114-116]. These positive effects have been found among both early and long-standing CRPS patients^[117]. However, despite this significant beneficial effect on CRPS inflammation signs, evidence is lacking about the optimum dosage, frequency and duration of treatment^[110].

Antidepressants: There are published reports that support the use of tricyclic antidepressants for the management of neuropathic pain^[113,118-120]. Their analgesic effects are presumably due, in part, to their action on serotonergic and noradrenergic descending inhibitory pathways^[113,120]. Tricyclic antidepressants are reported to be part of pharmacotherapy for 19% of CRPS patients^[111]. There is also some evidence that serotonin and noradrenaline reuptake inhibitors, but not selective serotonin reuptake inhibitors, are efficient in the treatment of chronic pain^[113,120]. However, based on systematic reviews on CRPS management, no study has yet examined the efficacy of antidepressants for the treatment of CRPS spe-

cifically^[110,113]. Therefore, there is currently no evidence of the efficacy of antidepressants for the treatment of CRPS.

Corticosteroids: There are a few trials that studied the benefits of corticosteroids in CRPS management and the results of these studies are clinically positive with regard to pain, oedema and sweating^[94,110,121-123]. Most of these studies were conducted with patients presenting an acute CRPS with inflammation signs and it is actually unknown if corticosteroids offer similar benefits for chronic CRPS, when pro-inflammatory cytokines are at a lower level^[19,124]. However, because of their potentially severe adverse effects, corticosteroids should not be taken for a long period of time^[113] and appear to be rarely prescribed in clinical practice^[111]. Further studies should be conducted to establish guidelines on the duration and dosage before corticosteroids can safely be prescribed for CRPS^[110,113].

Anticonvulsants: Anticonvulsants, such as gabapentin, are one of the most effective and most commonly prescribed pain medication for neuropathic pain in general^[125,126], and are also prescribed for CRPS^[113]. It is reported that 12% of CRPS patients are treated with anticonvulsants^[111]. The benefits of gabapentin for CRPS has been studied in two RCTs^[127,128]. There is evidence that gabapentin has a small to moderate effect in reducing CRPS pain eight weeks after the beginning of the treatment^[127]. However, patients taking gabapentin feel more side effects, such as fatigue, sleepiness or dizziness, than patients taking a placebo^[128]. Another anticonvulsant, carbamazepine, has been studied in a RCT of CRPS patients and it has been found to significantly diminish pain compared to placebo^[112]. Even if other types of anticonvulsants, such as pregabalin, seem to have some effects on pain, no other type of anticonvulsants has been studied for the treatment of CRPS^[19]. Even if beneficial effects have been demonstrated for pain reduction in CRPS patients, the pros and cons should be weighed when adding anticonvulsants to the CRPS treatment plan because of the potential adverse side effects and the unknown long-term effects^[110].

Muscle relaxants: Muscle relaxants, such as baclofen, is used by 3% of CRPS patients^[111] and may be helpful for the treatment of CRPS^[129]. However, because of the small samples (less than 10 patients) included in studies conducted on the efficacy of muscle relaxants for CRPS, authors of recent evidence-based guidelines on CRPS management report that the evidence is insufficient to claim their efficacy^[110].

Ketamine: Even if large and well-designed RCTs need to be conducted, the intravenous administration of ketamine in sub-anaesthetic doses significantly reduces pain among CRPS patients, as revealed by both prospective and retrospective studies^[75,110]. As an NMDA receptor

antagonist, ketamine is of particular interest because of its potential ability to reverse central sensitisation^[75]. Although a promising effect has been demonstrated, larger studies are required to validate the routine use of ketamine in CRPS^[75,112,113].

Topical agents: Topical medications, such as lidocaine patches, are used by 79% of CRPS patients^[31,111]. In this drug category, dimethylsulphoxide cream seems to be more efficient in reducing CRPS symptoms in the early stages while inflammatory signs are present^[75,130]. When symptoms of cold temperature or bluish skin are present, N-acetylcysteine has been found to be the most effective, based on a randomised double-blind study including 146 CRPS patients^[131]. The efficacy of these two types of drugs that are free radical scavengers support the involvement of oxidative stress in the pathophysiology of CRPS.

Local and regional sympathetic blockade: Local sympathetic blockade (*e.g.*, with lidocaine or guanethidine) such as stellate ganglion blockade or lumbar sympathetic blockade are widely reported in the literature^[31,94] and aim to modify the activity of the SNS locally. The therapeutic response to sympathetic blockade is inconsistent and may only be more effective than placebo at reducing the duration but not the magnitude of pain^[94,132]. A Cochrane review also indicate that there is low quality evidence that local anaesthetic sympathetic blockade is not effective at reducing pain in CRPS^[133]. Intravenous regional blockade using a wide variety of pharmacological agents has also been described for the treatment of pain in CRPS^[133]. According to this Cochrane review, there is very low to moderate evidence that intravenous regional blockade with atropine, droperidol and guanethidine is not effective to reduce pain in CRPS, while there is very low evidence that ketanserin and bretylium plus lidocaine may be effective. Because sympathetic blockade is a relatively invasive modality, it is suggested that it should be used when other modalities do not bring positive changes in the patient's condition^[19]. In addition, it should be stressed that these interventions may have positive effects for a limited number of patients only, because it is known that pain in CRPS is sympathetically maintained for about 10% of patients^[4]. The other 90% patients, with sympathetically independent pain, should benefit from other types of treatment. Because there is no standardised method to determine if CRPS pain is sympathetically maintained or sympathetically independent^[113], sympathetic blockade remains a controversial modality.

In summary, among the pharmacological treatments for CRPS, strong evidence is available for bisphosphonates^[94,110,114,116], corticosteroids^[94,110,120,123], ketamine injections^[75,110] and anticonvulsants^[127], but further studies are required to establish the guidelines for well-validated routine administration. There is actually insufficient or conflicting evidence to recommend the use of opioids^[110,112,113], calcitonin^[94,110] or antidepressants^[110,113]. Because of the limited proportion of patients who may benefit from sympathetic blockade, this intervention also

remains controversial^[94,110].

Other medical treatments

Most surgical treatments reported in the literature refer to sympathectomy or more recently, intracranial neurostimulation^[31], and represent the most invasive treatment modalities to be used as a last resort because of the quite minimal evidence for their efficacy^[110,134]. Surgical treatments will not be discussed in more detail because they have been reviewed elsewhere^[135].

Recently, repetitive transcranial magnetic stimulation (rTMS) was shown as a potential therapeutic option for CRPS, when used in combination with pharmacotherapy and physiotherapy^[136]. The results of a double-blind, placebo-controlled randomised trial conducted with 23 patients with upper limb CRPS-1 revealed a significant reduction of pain and improvement of the emotional state with 10 daily sessions of rTMS applied on the primary motor cortex^[136]. However, these beneficial effects did not continue after the treatment period ended^[136]. Similar results had previously been found in a study conducted on 10 CRPS patients^[137].

Psychotherapy

The rationale of psychological interventions for CRPS management derives from the recognised benefits of these approaches in management of other chronic pain syndromes^[19]. In addition, psychological and behavioural factors are thought to interact with pathological processes involved in the physiopathology of CRPS, including changes in catecholamine levels, as discussed earlier^[11,19,99].

Randomised control trials on psychological interventions for CRPS are scarce. In most studies, the experimental design only allows limited conclusions^[11]. The available clinical studies show some benefits in the treatment of CRPS using cognitive-behavioural therapy^[98,138], operant conditioning, pain management techniques, relaxation training^[31] with biofeedback^[19] and family education^[98]. Regarding other chronic pain syndromes, one goal of psychotherapy is to develop abilities to control pain, to play an active role in pain management and rehabilitation^[98]. Psychotherapy can also have a beneficial effect on comorbidities related to CRPS, such as depression. Authors of recent clinical guidelines in CRPS management recommend that education about the condition should be a low cost psychological approach to be used for all acute and chronic CRPS^[19]. Specifically, information about negative effects of disuse, the importance of reactivation and the importance for the patient to take an active part in CRPS management should be provided to the patient and its family^[19]. Because some cases of CRPS may resolve spontaneously, individualised psychotherapy is mostly recommended for chronic CRPS and should begin 6-8 wk after the onset of the disease^[98]. These psychotherapy sessions should focus on empowerment, which is defined as the ability to gain control over the condition, diminish catastrophic thoughts and reactivate the affected limb^[19]. An in vivo graded exposure approach, which consists of gradually exposing patients to situations that they think

may trigger pain (associated with the fear avoidance theories^[97]) seems to have promising results in diminishing pain intensity and the fear of pain, as well as improving global functioning^[139]. However, results from this study need to be replicated with a larger sample (only eight female CRPS-1 patients were included) to determine the efficacy of this approach. Noteworthy, the implication of family members is found to be important in the rehabilitation process in order to maintain good patterns of thoughts and reactivation of the affected family member at home^[19].

In line with the interdisciplinary approach for CRPS management, psychotherapy should be considered among the possible treatment modalities, although the evidence remains mixed regarding the benefits of these approaches and further controlled studies are required to confirm their efficacy^[98]. However, because psychological approaches are effective for other chronic pain syndromes, it is plausible that they are also useful for CRPS management, according to authors of recent clinical guidelines in CRPS management^[11].

Rehabilitation

Functional restoration is found to be the key objective of rehabilitation for CRPS patients, according to authors of a recent systematic review^[19]. The principle of functional restoration is to obtain a gradual progression of the movement, beginning with an activation of pre-sensorimotor cortices, followed by very gentle active movements and eventually, gradual weight bearing^[19]. Although rehabilitation is typically part of the CRPS management, RCTs to assess rehabilitation strategies are lacking because of the various clinical presentations and evolution of CRPS, necessitating the development of personalised intervention.

Occupational therapy: Occupational therapists (OTs) are recognised to be ideal therapeutic leaders in functional restoration processes because they are trained with biopsychosocial principles and work primarily with functional assessments and treatments^[19,140,141]. Emerging research has made OT interventions to work towards earlier stages of movements, using graded motor imagery (GMI)^[19]. The use of GMI^[105,142-144] has attracted the attention of researchers in recent years (a video illustrating GMI is presented at the following web address: <http://www.youtube.com/watch?v=hMBA15Hu35M> and the steps are fully described in a 2011 article^[145]) because these modalities may have an effect on cortical reorganisation, which seems to be involved in CRPS. Only a few studies have been conducted on the use of GMI in the treatment of CRPS^[105,142,143,146,147] but strong evidence of effectiveness has been demonstrated^[117]. In general, the use of GMI would reduce pain, normalise autonomic signs, improve lateralisation and improve functioning in both the short- and long-term. GMI may also be helpful in normalising movements for CRPS patients^[19]. FMRI studies support the cortical activation sequence induced by GMI in healthy subjects, but no such studies have

been conducted with CRPS patients^[148]. Further studies with larger samples are required to generalise the effect of GMI to the entire population of CRPS patients^[145,148].

Following GMI, the objectives are to minimise oedema, normalise sensation, promote normal positioning/decrease muscle guarding and increase functional use of the affected limb in order to promote independence in all areas, such as work, leisure and personal cares^[149]. OT using various modalities, such as desensitisation^[150] or sensory discrimination training, splinting^[19] and adapting activities, is also effective in decreasing functional limitations and improving activity levels^[140,141]. Stress loading, including the two phases of scrubbing and carrying, is also a technique used by OTs in order to initiate active motion and compression of the affected joints^[151]. However, most of the studies that focused on OT interventions did not standardise the treatment modalities, which makes the replication of the results difficult.

Physical therapy: Physical therapy (PT) plays an important role in CRPS management by increasing the range of motion, flexibility and strength by gentle progressive exercise programs^[19]. The use of physiotherapy is documented in the literature^[110,140,152], but the efficacy of the interventions remains mixed. Used alone or in combination, treatment modalities such as heat/cold therapy, electrotherapy, manual therapy, exercises or simulation of occupations have been described^[31,138]. It is also common that some aspects of psychotherapy, such as pain management techniques or relaxation techniques, are included in rehabilitation^[153]. A recent meta-analysis suggests that physiotherapy has a beneficial effect on pain reduction, oedema, mobility and skin temperature and would be effective in acute and chronic CRPS^[110,154].

It is generally accepted that PT interventions must be executed within the limits of pain tolerance^[155]. A relatively new and controversial rehabilitation approach for CRPS treatment is the “pain exposure” treatment^[152,156,157]. Groups of researchers found that rehabilitation therapy focused on functional improvement based on rehabilitation time having regular PT interventions while avoiding pain (*i.e.*, following rehabilitation objectives while not considering pain severity as a guideline) could permit the safe improvement of the function of the affected arm, reduce pain, improve walking speed and improve muscle strength^[152,156,157]. Because of the ethical implication of this type of therapy and the rationale that is still not well described, there is actually no evidence supporting the efficacy of this rehabilitation modality in CRPS treatment.

In summary, most modalities (*e.g.*, manual therapy, electrotherapy, desensitisation, activity modification and adaptation, *etc.*) used in PT and OT, except for the “pain exposure treatment”, have been demonstrated to be effective in diminishing CRPS symptoms and improving the level of functioning and should play an important part in CRPS management. Although rigorous studies using standardised rehabilitation modalities are required to raise the level of evidence of rehabilitation strategies, GMI is a very promising avenue.

CONCLUSION

This review aimed at gathering evidence regarding the pathophysiology, clinical features and interventions in the management of CRPS. Even if future studies are necessary to achieve a better understanding of the disease, the literature supports the involvement of neurogenic inflammatory processes, autonomic dysfunction and maladaptive neuroplasticity, such as peripheral and central sensitisation, in CRPS pathophysiology. The potential involvement of oxidative stress in the pathophysiology of CRPS also opens the door to a secondary prevention treatment in prescribing vitamin C to people with a hand trauma. CRPS has a negative impact in physical, psychological, cognitive and perceptual aspects and that a multidisciplinary approach is required to treat these patients. Among the pharmacological approaches, little evidence supports the use of several drugs, except for bisphosphonates, corticosteroids, ketamine or anticonvulsants that have demonstrated positive effects on CRPS symptoms. With regard to rehabilitation, positive effects have been found in diminishing the patients' signs and symptoms and improving global functioning, but evidence remains mixed because of a lack of standardised procedures. However, GMI seems to be the most promising treatment for CRPS.

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Opioid misuse in Canada and critical appraisal of aberrant behavior screening tools

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Abstract

The incidence of prescription opioid misuse in Canada is increasing. Initiatives for safe prescribing practices for opioid medications include risk assessment for current and future opioid misuse. A clinical screening tool that can be universally applied to all patient populations is currently not available. Our objective was to provide a brief narrative review on opioid misuse from a Canadian perspective as well as a critical appraisal of the available clinical screening tools for detecting aberrant behaviors associated with opioid misuse. The Drug Abuse Screening Test, Addiction Behaviors Checklist, Diagnosis, Intractability, Risk and Efficacy Inventory, Pain Assessment and Documentation Tool, Prescription Drug Use Questionnaire, Prescription Opioid therapy Questionnaire, Screener and Opioid Assessment for Patients with Pain (SOAPP), Revised SOAPP, Pain Medication Questionnaire, Opioid Risk Tool and Current Opioid Misuse Measure were included in the following review. Overall, a wide variability in quality, sensitivity and specificity was observed between screening tools. There is an overall lack of applicability to diverse patient populations as the majority of screening tools have been validated in pain clinic populations only. To conclude, there is a great need for a validated and convenient aberrant behaviors risk assessment tool that can be applied to a diverse patient population in a clinical setting.

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Key words: Opioid analgesics; Opioid-related disorders; Prescription drug misuse; Risk assessment; Drug-seeking behavior; Canada

Core tip: With the increase in opioid prescribing in Canada, prescription opioid misuse is a growing concern from a health care, financial and safety standpoint. Definitions regarding opioid misuse and covariate risk factors predictive of opioid misuse are controversial. The currently available risk assessment tools used to predict or detect opioid misuse vary in terms of sensitivity, specificity, quality, reproducibility and have been validated in very limited patient populations. There is a clear need for the development of a generalizable risk assessment tool to assess for prescription opioid misuse.

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INTRODUCTION

The prevalence of prescription drug abuse in Canada is on the rise, with opioids leading as the most abused class of medications. Next to the United States, Canada has the second-highest level of prescription opioid use globally. Over a 10 year period (2000-2010), the total number of opioid medications consumed in Canada rose by greater than 200%^[1]. Of this increase in opioid consumption, an analysis by Fischer and colleagues determined a higher prescribing prevalence of "strong opioids" such as oxycodone, hydromorphone, fentanyl, meperidine, meth-

adone and morphine, whereas weak opioids such as codeine were prescribed less frequently over the 2005-2010 period^[2].

With increased opioid prescribing, misuse leading to addiction, overdose and death is a growing health issue. A population-based study in Ontario over a two-year period (2006-2008) showed 58% of drug-related deaths were attributed to opioid toxicity with oxycodone accounting for one-third of opioid-related deaths^[3]. From this same study, 7% of those who died used opioids prescribed for friends/family, 19% manipulated the dosage form (injections, inhalation, chewing), and 5% had been switched from another opioid near the time of death. Other behaviors such as diversion of opioids from health care facilities (0.6%), intentional double doctoring (2.1%) and purchasing opioids from street sources (2%) existed. From a national perspective, the 2009 Canadian Alcohol and Drug Use Monitoring Survey (CADUMS) showed a prevalence of nonmedical prescription opioid analgesic use of 4.8% and 0.4% for those trying to “get high”^[4]. Finally, a meta-analysis estimated that 3.3% of chronic non-cancer pain patients taking opioid medications were addicted and 11.5% displayed aberrant behaviors^[5].

Currently, there exists an initiative towards the promotion of safe prescribing practices in Canada, particularly concerning the prescribing and monitoring of opioid medications. In March 2013 a report published by the Canadian Centre on Substance Abuse^[6] acknowledged the increase in non-medical use of prescription drugs as well as the increase in criminal activity surrounding diversion. This document outlines strategies such as provincial monitoring programs, stricter legal implications for possession/diversion of prescription medications as well as risk-reducing strategies such as controlling/restricting prescribing practices. Several provinces have already implemented provincial drug monitoring programs in the form of provincial databases as a tool to assist healthcare professionals in identifying/discouraging double-doctoring, refuse early fills, avoid harmful drug interactions/overdose and identify patients who misuse prescription opioids^[7].

An intuitive strategy to promote safe prescribing practices for opioid medications would entail the identification of patients at highest risk for misuse coupled with appropriate intervention. Risk stratification would directly influence pain treatment considerations as well as intensity of patient monitoring required if considering initiation of opioid therapy. Several screening tools to identify aberrant behaviors have been proposed in the literature. However, the validity and generalizability of these tools are often questionable due to several factors, as will be discussed. It has been demonstrated that no one risk factor can predict drug abuse in a given individual, but particular combinations of risk factors are more predictive than others^[8]. There is a clear need for the development and validation of a robust clinical risk assessment tool that both identifies aberrant behaviors and weights them appropriately. There are very few well-designed clinical trials of adequate duration, ideally long-term studies,

which fulfil these requirements^[9].

The purpose of the following article is to provide a brief background on definitions and methods of opioid misuse, review covariate risk factors associated with opioid misuse as well as explore the available risk assessment tools for aberrant behaviors in terms of their practicality and generalizability to various practice settings.

DEFINITIONS, METHODS AND CONSEQUENCES OF OPIOID MISUSE

Prescription opioid misuse is considered a form of substance abuse. Table 1 provides an overview of definitions to differentiate clinical aspects of substance abuse^[8,10-13]. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders^[14,15] has revised its criteria for substance abuse by merging “substance abuse” and “substance dependence” into one category entitled “substance use disorder”. The severity of the disorder is rated on a continuum from mild to severe depending on the number of symptoms present (see Table 1 for details). One of the main reasons for the revision was the diagnosis of drug dependence was often confused with addiction. Patients on long-term opioid medications are considered physically dependent and/or tolerant but may not be addicted to the medication. It has been argued that these two criteria should not be used when assessing for a substance use disorder in patients on opioids, but this practice has not been validated by clinical studies^[8].

The 2009 CADMUS estimated that approximately 19% of Canadians are using prescription opioid medications and 4.8% are using for non-medicinal purposes. In other words, approximately 1 in 20 patients prescribed opioid medications are not using them as prescribed^[4]. As this was a self-reported telephone survey, the prevalence of opioid misuse might be underreported. Some examples of opioid misuse include altering the dosage form (crushing, biting/chewing tablets, opening capsules, chewing fentanyl patches, crushing and injecting, cold water extractions/purifications of combination products), obtaining opioids in another manner (stealing/borrowing from friends/family members, purchasing off the street/internet, using another person’s identity to obtain a prescription, obtaining black market opioid sample cards, “double doctoring”), taking more opioid than prescribed or taking opioid medications in conjunction with alcohol or other sedating medications^[6,8].

Opioid misuse has several serious consequences (Table 2). First and most concerning, is mortality related to impaired functioning/motor-vehicle collisions, accidental overdoses and suicide. From 2006-2008, 58% of 2330 drug-related deaths in Ontario were related to opioid use^[3]. The addition of long-acting oxycodone to the Ontario drug formulary was associated with a 5-fold increase in oxycodone-related mortality and a 41% increase in overall opioid-related mortality from 1991-2007^[16]. Second, burden of disease and overall harm of opioid medication misuse exceeds illicit drug use and is second to to-

Table 1 Definitions^[8,10-13]

Tolerance	A state of adaptation where fixed doses of opioids over time results in the need for increasing doses to maintain the same effect
Physical dependence	A state of adaptation manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist
Dependence (DSM-V criteria) ^[14]	A substance use disorder as a maladaptive pattern leading to clinically significant impairment or distress for at least 12 mo and meet ≥ 2 of the following: Recurring opioid use leading to a failure to fulfill role obligations Societal and interpersonal problems Using opioids in situations that are physically hazardous Tolerance Withdrawal Taking opioid in larger amounts and for longer periods than intended Unsuccessful at cutting down Spending time to obtain or use the opioid Giving up activities due to opioid use Continuing use despite physical or psychological problems Craving or strong urge to use the opioid
Aberrant behavior	Behaviours that may cause suspicion about addiction in opioid-treated pain patients or a behavior outside the boundaries of the agreed-on treatment plan which is established as early as possible in the doctor-patient relationship
Misuse	Use of a medication for non-medical use or for reasons other than prescribed. Wilful or unintentional use of a substance in a manner not consistent with legal or medical guidelines such as altering dosage forms, sharing medications with the potential for harmful consequences.
Abuse	Misuse with consequences. The use of a substance to modify/control mood or state of mind (to obtain a "high") in a manner that is illegal or harmful to oneself or others. Examples of potential consequences include accident, injuries, blackouts, legal issues, and sexual behavior increasing the risk of sexually-transmitted diseases
Addiction	A primary, chronic, neurobiological disease with genetic, psychosocial and environmental factors influencing its development and manifestations. It is characterized by compulsive use, continued use despite harm and craving
Diversion	The unintentional transfer of a controlled substance from legitimate distribution and dispensing channels into illegal channels or obtaining a substance by an illegal method

DSM-V: The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders.

Table 2 Consequences of opioid misuse^[1,3,8,17,18,21]

Overdose-related death
Deteriorating social relationships
Reduced productivity/increased disability
Increased morbidity (opioid related side-effects/withdrawal symptoms, hyperalgesia)
Increased healthcare utilization/increased healthcare costs
Increased risk of blood-borne diseases (associated with injection drug use)
Malpractice claims
Increased drug diversion
Legal repercussions

bacco and alcohol^[1]. In 1999, projected health and social costs for each person addicted to opioids approximated \$44000/year^[17]. In 2002, a survey regarding the costs of substance abuse in Canada reported opiates as the second leading contributor to hospital admissions/hospital days and admission for psychiatric reasons^[18]. Unfortunately, the report did not specifically address the proportion of admissions due to prescription opioids. A study on emergency room visits demonstrated a 250% increase in number of visits related to narcotic withdrawal, overdose, intoxication, psychosis and harmful use between 2005-2011^[17]. In addition, the number of detoxification admissions related to controlled-release oxycodone to the Centre of Addiction and Mental Health in Toronto demonstrated an increase from 3.8% to 55.4% over a 5-year period^[19]. Information on job status/productivity losses

related to opioid misuse is currently unavailable from a Canadian perspective. Overall, there is a trend towards increased hospitalizations and increased enrollment into detoxification programs demonstrating an increase in health-care associated costs^[17]. Third, physicians have expressed concerns about prescribing opioid medications due to increased liability risks as well as increased potential for patient harm. It has been shown that family physicians prescribing opioid medications more frequently to their patients have resulted in increased contributions to opioid-related mortality. In one study, physicians in the uppermost quintile who prescribed opioids most frequently wrote the final prescription for 62.7% of patients whose death was related to opioids^[20]. Family physicians have voiced their concerns regarding the misuse/addiction potential of opioids, lack of specialized pain management knowledge as well as awareness of increasing government restrictions and investigations into opioid prescribing practices^[21]. Referral programs to specialized pain clinics have either long wait times (median of 6 mo for most pain clinics, 12 times longer than private multidisciplinary pain treatment facilities) or limited access with no specialist care available (*i.e.*, Prince Edward Island and the Territories)^[22]. As a result, over 95% of general practitioners have an active role in prescribing pain medications for their patients^[1,21]. Finally, the legal aspects of opioid misuse including diversion, robbery/theft and associated consequences such as increased crime rates and increased incarceration are a concerning aspect of

Table 3 Risk factors associated with opioid misuse^[8,23,24,26,27,37]

Non-modifiable risk factors	Age: Younger age (inverse risk relationship) Gender: Males (caucasian) Women misuse due to emotional issues versus men who misuse due to legal/behavioral issues Genetics: Family history of substance use disorder(s) Variations in <i>OPRM1</i> <i>PENK</i> gene polymorphisms
Reported pain severity/type of pain	Multiple pain complaints Chronic back pain Report greater degree of pain-related limitations
Comorbid psychological factors	History of substance use (cannabis, alcohol and other illicit drugs especially) Concomitant mood disorder, depression and/or anxiety Multiple psychosocial stressors Interpersonal problems with coworkers/family/friends History of risk-taking or thrill-seeking behavior Frequent contact with high-risk individuals or environments
Drug-related factors	Self-reported craving High daily doses (≥ 120 mg morphine equivalents per day) Use of short-acting opioids

OPRM1: μ -opioid receptor gene 1; PENK: Pre-proenkephalin.

opioid misuse. Data from Health Canada indicated that thefts/drug diversion from licenced dealers and Canadian pharmacies are a progressing issue. Oxycodone is of particular concern, with 340328 doses missing in 2010 from pharmacies, 168420 doses lost from licenced dealers, and over 300000 doses lost due to armed robbery or break-and-entry, representing a substantial increase since 2005^[1].

RISK FACTORS FOR OPIOID MISUSE

A comprehensive review of the literature on identification of covariate risk factors for opioid misuse has been established^[8,23-25]. A summary of risk factors can be found in Table 3. It has been suggested that solitary risk factors are poorly predictive of opioid misuse. Having a combination of one risk factor from each domain of (1) psychosocial issues; (2) drug-related factors; and (3) genetic factors most strongly predicts future likelihood of substance use^[8]. Rice and colleagues conducted a retrospective study with a primary objective of identifying patient characteristics and behaviors associated with a diagnosis of opioid abuse ($n = 6380$) versus those not diagnosed with opioid abuse ($n = 815536$)^[26]. The authors identified several “key characteristics” (defined as an OR of > 2) contributing to increased risk of opioid abuse which included; prior opioid prescriptions, a larger number of prior opioid prescriptions (1-5 prescriptions or 6 or more prescriptions), prior prescription of buprenorphine or methadone, past history of non-opioid drug abuse, comorbid mental illness, comorbid hepatitis and having a family history of opioid abuse. Other factors such as younger age (OR = 1.11) and male gender (OR =

1.35) also showed to increase risk, which is a consistent finding from other studies^[23,24]. Perhaps most concerning is the fact that adolescents are especially at risk of opioid misuse. An Ontario study conducted in 2010-2011 reported a non-medical prescription opioid use prevalence of nearly 1 in 5 (20%) secondary students (grades 9-12) compared with 5.9% in the adult population^[25]. Considering previous drug use is a very strong predictor of future substance use, a high prevalence of non-medical use of prescription opioids in young individuals will likely influence their drug use habits in their adult years.

The presence of comorbid psychiatric conditions is a strong predictor of opioid misuse. Coexisting depression and/or anxiety has been shown to increase risk^[8,27]. Chronic pain patients report a greater frequency of depression and anxiety than patients with other medical conditions. Some studies have reported a 50%-85% prevalence of concomitant psychiatric conditions in patients with chronic pain^[24]. One study demonstrated that patients with a high psychiatric morbidity defined as ≥ 2 positive responses on the Prescription Drug Use Questionnaire (PDUQ) were associated with younger age, longer duration on opioids, higher Screener and Opioid Assessment for Patients with Pain (SOAPP) and Current Medication Misuse Measure scores, greater incidence of abnormal urine drug screens and higher scores on the drug misuse index, indicating an overall increased risk for opioid misuse^[27]. To prevent future opioid misuse, treatment of the underlying mood disorder should be addressed prior to the initiation of opioid therapy.

Other predictors of future opioid misuse include drug related factors such as the use of immediate release opioid formulations, high daily doses of opioids and self-reported craving of opioid medication^[8]. Use of immediate release opioid medications (verses sustained release formulations) may increase risk of misuse due to the quick release of medication and capability of inducing a “high”. This theory is controversial as one prospective, comparative study found no difference in misuse between methadone and immediate release hydromorphone in 200 pain clinic patients^[28]. Wasan *et al*^[29] found that patients who reported craving opioids on the PDUQ were more likely to misuse their medication.

The overall purpose of risk factor identification is to stratify patients into “low” and “high” risk groups in order to formulate an individualistic follow-up plan. The categorization of the patient will determine the vigilance and intensity in which monitoring and follow-up should occur.

ABERRANT DRUG BEHAVIORS: PREDICTING MISUSE AND CRITICAL APPRAISAL OF AVAILABLE SCREENING TOOLS

As defined in Table 1, aberrant behaviors include “behaviours that may cause suspicion about addiction in opioid-treated pain patients or behaviors outside the boundaries

Table 4 Aberrant drug-behaviors^[5,9,38]

Indicator	Examples
Altering route of delivery ¹	Injecting, biting, crushing, separating oral formulations
Accessing opioids from other sources ¹	Obtaining the drug from friends/relatives Selling/purchasing from the "street" Double-doctoring Altering or creating fraudulent prescriptions Drug hoarding/trading Multiple emergency room visits
Unsanctioned use	Unauthorized dose escalations Binge use
Drug seeking behavior	Repeat prescription losses ¹ Aggressive requesting of higher doses Harassing staff for faxed prescriptions or "emergency" fit-in appointments Manipulation of the prescribing physician Claiming nothing else "works"/requesting specific opioid ¹
Repeated withdrawal symptoms	Dysphoria, myalgias ¹ , GI symptoms, cravings, nausea/vomiting etc.
Co-morbid conditions	Addicted to illicit drug, alcohol, cannabis and/or sedatives/hypnotics Underlying mood/anxiety disorders unresponsive to treatment
Social irregularity	Deteriorating/poor social function Concern expressed by family members
Views on opioid medication	Sometimes acknowledges being addicted Strong resistance to tapering or switching opioids Admits to mood-levelling effects Acknowledges distressing withdrawal symptoms

¹Associated with higher risk of addiction than others. GI: Gastrointestinal.

of the agreed-on treatment plan which is established as early as possible in the doctor-patient relationship". Table 4 contains a descriptive list of potential aberrant behaviors. The Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain suggest that behaviors such as altering the route of delivery and/or obtaining opioids from other sources are highly indicative of addictive behavior, more so than other behaviors^[9].

To identify behaviors associated with opioid misuse, several screening tools have been developed. Table 5 provides an overview of commonly used screening tools for aberrant behaviors. A universally accepted or "gold standard" screening tool for detecting aberrant behaviors in primary care patients on long-term opioid therapy for non-cancer pain management currently does not exist for several reasons^[30]. Validation studies for predictive value and sensitivity/specificity of the questionnaires are limited. Sensitivity of the questionnaire evaluates the ability of the screening tool to identify patients who would later display aberrant behaviors whereas specificity measures the ability of the tool to identify patients who will not show aberrant behaviors. The development of aberrant behavior risk assessment tools stemmed from specialty clinics for pain management, where opioid prescribing is high. Validation studies often had very small sample sizes and/or were targeting very specific patient populations (*i.e.*, veterans). Banta-Green and colleagues investigated the applicability of the PDUQ to a general medical

population and found a very poor internal reliability compared with the index study involving pain centre patients (0.56 *vs* 0.81 respectively)^[31]. Therefore, the overall generalizability of the questionnaires to diverse patient populations is poor^[32]. Further, the limitations of written screening tools in patients who are not able to understand the assessment questions (*i.e.*, brain damage, illiterate, blindness, language barriers) create selection bias as these patients may not be evaluated correctly due to lack of response or incomplete understanding. One study reported that 15% of patients were unable to complete ≥ 1 of the risk assessment measures^[33]. The survey items and tested domains vary considerably from tool to tool. Some tools are specific to outpatient prescription opioid therapy whereas others are designed to screen for overall substance abuse risk. Standardization of screening tools is therefore not present. One of the largest criticisms of the validation studies for aberrant behavior risk assessment tools is the fact that baseline aberrant behaviors are often used to compare predictive validity. Aberrant behaviors documented at the index clinic visit are used as a baseline to compare future incidence of aberrant behaviors. Intuitively, patients with baseline aberrant behaviors are more likely to exhibit behaviors in the future, therefore biasing the predictive ability of the tool towards a more positive result (producing a false increase in predictive reliability). In an attempt to eliminate this criticism, the investigators of the SOAPP screening tool revised and retested their tool (SOAPP-R)^[34]. Finally, many of the validation studies for aberrant behaviors risk assessment tools did not incorporate pain monitoring tools such as the Brief Pain Inventory to monitor the control of patients' pain. Uncontrolled pain may be misinterpreted as drug-seeking behavior, therefore confounding the predictive ability of the screening tool.

A comparison of screening tools for aberrant behaviors has been conducted in an attempt to identify the most reliable tool. Moore and colleagues compared the predictive ability of a clinical interview, the Screener and Opioid Assessment for Patients with Pain (SOAPP), Opioid Risk Tool (ORT) and Diagnosis, Intractability, Risk and Efficacy Inventory (DIRE) screening tools in a group of 48 patients discharged from a pain management clinic to detect likelihood of aberrant behaviors^[35]. The authors found the sensitivity was highest for the clinical interview (0.77), followed by SOAPP (0.72), ORT (0.45) and DIRE (0.17). Combining the clinical interview with the SOAPP assessment tool increased sensitivity to 0.90. In another study, Jones *et al.*^[33] compared the ORT, Pain Medication Questionnaire (PMQ), the Revised SOAPP (SOAPP-R) and a detailed psychologist interview for sensitivity and specificity in chronic pain patients followed for 6 mo. The clinical psychologist had highest sensitivity, identifying 71% of the discharged patients for aberrant behavior. The 3 written measures had lower sensitivities; SOAPP-R (39%), PMQ (34%) and ORT (20%). For specificity, the ORT was most successful (88%), followed by PMQ (77%), SOAPP-R (69%) and clinical psychologist (60%). In 2009, the American Pain Society and American Acad-

Table 5 Overview of Aberrant drug-related behaviors risk assessment tools

Name of assessment tool and type of study	Description	Who administers and time to administer	Interpretation of results	Validated	Sensitivity/specificity	Limitations	Intended use	Quality score ^[36]
Substance abuse assessment tools								
Drug abuse screening test ^[39]	28-item yes/no questionnaire to assess drug dependence or abuse (shorter versions of 10 or 20 items also available)	Patient; 5-10 min	A score of 6 or more indicates a drug abuse or dependence problem	Yes	0.81-0.96/0.71-0.94	Test and retest were only a few weeks apart (psychometrics may be falsely better), susceptible to patient deception. Also hasn't been extensively tested in pain patients, therefore not specific to opioid use	For the initial assessment of drug abuse or dependence	N/A
Prospective multiple studies								
Risk assessment tools								
Opioid risk tool ^[40]	A 5-domain checklist (family history of substance abuse, personal history of substance abuse, age, history of sexual abuse and psychological disease) gender stratified and weighted	Patient; < 2 min	Low risk 0-3 points Moderate risk 4-7 points High risk ≥ 8 points	Yes	<i>c</i> statistic for male model = 0.82 and female = 0.85 (both excellent discrimination) Sensitivity to detect discontinuance of opioids due to ADRB = 0.45 ^[35]	Has only been validated in a pain clinic, therefore applicability outside this population is limited	To be used as a risk assessment tool for aberrant behaviors prior to initial opioid prescription	4/9
Prospective								
Diagnosis, intractability, risk and efficacy inventory ^[41]	7 item questionnaire-4 domains (diagnosis, intractability, risk and efficacy) with the domain of risk divided into 4 subcategories (psychological, chemical health, reliability and social support) to determine if a patient is suitable for maintenance opioid therapy	Physician; < 2 min	Each question is scored from 1 (least compelling/favorable) to 3 (most compelling/favorable) A score of ≤ 13 indicates an unsuitable candidate for maintenance opioid therapy A score of ≥ 14 indicates a good candidate with higher scores with a greater likelihood of successful prescription	Yes	Sensitivity to detect discontinuance of opioids due to ADRB = 0.45 ^[35] Sensitivity to detect discontinuance of opioids due to ADRB = 0.17 ^[35] To predict patient compliance = 0.94/0.87	Used primary care vignettes versus real-time patients, small sample size (<i>n</i> = 61), drew upon patient cases in a referral centre (may not be generalizable), prospective validation needed	A decision tool to assess reliability of patients prescribed high risk therapy (opioids) in a primary care setting	N/A
Retrospective								
Screener and opioid assessment for patients with pain ^[36,42,43]								
Prospective	14-item questionnaire with answers scored on a likert 5-point scale of 0 (never) to 4 (very often) regarding drug history and other aberrant behaviors	Patient; < 5 min	A score of ≥ 8 indicates "high risk" of future aberrant drug related behaviors	Yes	Original Validation study 0.86/0.73 Sensitivity to detect likelihood of discontinuance of opioids due to ADRB = 0.72 ^[35]	Predictive validity questionable as self-reported aberrant behaviors at baseline were compared to those at follow-up; also used PDUQ to identify/include higher-risk pain clinic participants (<i>n</i> = 175)	For the initial assessment of aberrant behaviors prior to initiating opioid therapy	5/9
Screener and opioid assessment for patients with pain- revised ^[134]								
Prospective	24-item questionnaire with answers scored on a likert 5-point scale of 0 (never) to 4 (very often) regarding drug history and other aberrant behaviors	Patient; 2-5 min	Scores range from 0-96 Low risk < 18 points High risk ≥ 18 points	Yes	Original validation study 0.81/0.68 Ability to predict discharge from opioid treatment 0.39/0.69 ^[33] Ability to predict presence of aberrant behaviors 0.41/0.71 ^[33]	Has only been validated in a pain management clinic setting, less sensitive and specific than original SOAPP tool	For the initial assessment of aberrant behaviors prior to initiating opioid therapy	6/9
Ongoing assessment tools (monitoring)								
Addition behaviors checklist ^[144]	20-item yes/no questionnaire evaluating aberrant behaviors since last clinic visit and within current clinic visit	Physician; 5-10 min	A score of ≥ 3 "yes" answers indicates possible inappropriate opioid use and should alert physician to investigate further	Yes	0.88/0.86	Validation study conducted in predominantly male veterans and some high risk patients were excluded	A tool to assess previous and current/ongoing aberrant behaviors of patients on opioids	4/9
Prospective cohort								

Current opioid misuse measure ^[16] Cross-sectional	17-item questionnaire with answers scored on a Likert scale from 0 (never) to 4 (very often) assessing the frequency of aberrant behaviors in the previous 30 d	Patient; < 10 min	A cut-off score of ≥ 10 weakly increases the risk for ADRB	Yes	0.74/0.73	Has only been validated in a pain management centre, small follow-up sample size ($n = 87$), cross-validation studies are pending, limited evidence	To be used as a monitoring tool for aberrant behaviors in chronic pain patients	5/9
Pain medication questionnaire ^[46,47] Cross-sectional Prospective cohort (long-term evaluation)	26-item self-assessment questionnaire with answers scored on a Likert 5-point scale of 0 (disagree) to 4 (agree)	Patient; 5-10 min	Low risk 0-34 points High risk: 70-104 points High risk patients are associated with history of substance abuse, higher psychosocial distress and poorer functioning	Yes	None available	Has only been validated in a pain management clinic setting	An assessment tool for ongoing aberrant behaviors	6/9 4/9 (long-term)
Prescription drug use questionnaire ^[31,48] Cross-sectional	42-item yes/no questionnaire evaluating 6 domains: evaluation of pain condition, opioid use patterns, social/family factors, family history, history of substance abuse and psychiatric history	Physician; 15 min	Each "yes" answer counts as one point. A score of 15 or greater indicates a substance use disorder	Yes, but poor results	Cronbach's coefficient for reliability $\alpha = 0.81$ in original study with pain clinic patients but decreased to $\alpha = 0.56$ in a general medical setting	Evaluates risk at a single time point, very lengthy/time consuming. Pain behaviors to be used in conjunction with other clinical criteria administered by a mental health care practitioner. Performed poorly in a general medical population for the presence of addictive disease	A tool for addictive behaviors to be used in conjunction with other clinical criteria	6-7/9
Prescription opioid therapy questionnaire ^[10] Retrospective	Substance Abuse History Interview (3 questions) plus checklist of 6 aberrant behaviors	Physician; 2-5 min	Each item checked on substance abuse history equals one point 0-1 low risk 2-3 high risk	Yes	Sensitivity and specificity for each of the 6 aberrant behaviors determined ^[36] but some inconsistencies with original study	Limited to a pain clinic population, developed using retrospective chart review	A screening tool to identify substance abuse history and ongoing aberrant behaviors	7/9 ²
Documentation tools Patient assessment and documentation tool ^[50] Cross-sectional (field tested)	A 41-item clinician-directed interview chart note tool divided into 4 domains (4 A's): analgesia, activities of daily living, adverse events and aberrant drug-related behaviors	Physician; 10-15 min	A descriptive tool to aid in documentation (chart note)	Field-tested, but not validated	N/A	Descriptive tool; validation needed (no sensitivity or specificity data available)	A documentation tool to organize chart note information related to opioid use	N/A

¹Recommended for use in the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain Practice Toolkit^[9]; ²method of quality determination not consistent with original study design therefore questionable interpretation. ADRB: Aberrant drug-related behaviors; N: Sample size; N/A: Not assessed; PDUQ: Prescription drug use questionnaire; SOAPP: Screener and opioid assessment for patients with pain; DSM: Diagnostic and statistical manual of mental disorders.

emy of Pain Medicine published a clinical practice guideline attempting to evaluate the ability of available screening tools to predict future aberrant behaviors^[36]. The authors gave a quality score (maximum of nine points) to each of the assessment tools with one point awarded for a "yes" answer for the following domains: (1) Evaluates population other than the one used to derive the instrument; (2) Consecutive series of patients or a random subset; (3) Describes severity of symptoms, opioid dose/duration and underlying conditions; (4) Adequate description of screening instrument; (5) Appropriate criteria included in screening instrument; (6) Adequate description of method for identifying aberrant drug-related behaviors; (7) Appropriate criteria used to identify aberrant drug-related behaviors; (8) Aberrant drug-related behaviors assessed in all enrollees; and (9) Blinded assessment of aberrant drug-related behaviors.

Quality scores for the screening tools included in the analysis can be found in Table 5. The SOAPP-R assessment tool scored highest (6/9) amongst the initial screening tools with a prospective study design. Although the Prescription Opioid therapy Questionnaire scored highest amongst the retrospective or cross-sectional studies (7/9), the criteria used to evaluate the quality of the screening tool was unclear in comparison to the original study design and therefore may not reflect a true quality rating.

DISCUSSION AND CONCLUSION

The clinical/psychological interview remains the optimal strategy to identify opioid misuse, likely due to its in-depth nature. The SOAPP-R tool has decent overall quality, predictability of discontinuation of opioids due to aberrant drug behaviors as well as sensitivity and specificity. In addition, it has been cross-validated in over 600 patients and has been found to identify approximately 80%-90% of patients who will eventually misuse opioids^[24]. These are likely the tools of choice, especially for initial clinic visits when the decision to initiate or continue opioids is being considered. As stated above, combining risk assessment tools with a clinical interview strengthens predictive ability. However, both the limitations and intended patient population of each tool should be considered when choosing a risk assessment tool for a particular clinic. Overall, the available screening tools are preliminary at best.

Another major gap in clinical knowledge is the degree of impact these screening tools have on clinical outcomes^[36]. To date, there is a paucity of evidence to suggest that more frequent follow up and stricter prescribing practices diminish the incidence of opioid misuse for “high risk” patients on opioids.

An ideal opioid risk assessment tool to detect aberrant behaviors should be both sensitive and specific, maintain internal and external validity, have a robust population base (ideally for primary care or a general outpatient clinic setting) written in uncomplicated, patient-friendly language and be concise/efficient to administer. An ongoing clinical study at Health Sciences Centre Pain Clinic in Winnipeg, Manitoba, Canada is currently investigating a new aberrant behaviors checklist in chronic pain patients. The purpose of this study is to prospectively follow 150 patients on prescription opioid medications and trial an aberrant behaviors checklist for predictive validity and to assign weights to certain behaviors indicating greater or lesser predictability for opioid misuse. The results of this study could potentially add new data on specific aberrant behaviors that are most predictive of opioid misuse, leading to the development of a tool that could be subsequently validated for primary care use.

In conclusion, prescription opioid misuse in Canada is a serious public health issue that is increasing in prevalence and contributing significantly to patient morbidity and mortality. Chronic pain management goals include risk-assessment strategies to strive for optimal pain management while minimizing risk of opioid misuse. Identification of risk factors associated with opioid misuse can be a challenge due to variability between available risk assessment tools. A universal screening tool identifying aberrant behaviors would be the ideal standard of practice, similar to other chronic disease states that employ standard screening recommendations. Additional long-term validation studies in diverse patient populations are needed to improve and expand the current knowledge base. In addition, assessment of clinical relevance and impact of interventions for opioid misuse on patient

outcomes are required. Strategies to curb opioid misuse should be a top priority from a governmental, financial and public health standpoint.

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Molecular mechanism of inflammatory pain

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Abstract

Chronic inflammatory pain resulting from arthritis, nerve injury and tumor growth is a serious public health issue. One of the major challenges in chronic inflammatory pain research is to develop new pharmacologic treatments with long-term efficacy and few side effects. The mediators released from inflamed sites induce complex changes in peripheral and central processing by directly acting on transducer receptors located on primary sensory neurons to transmit pain signals or indirectly modulating pain signals by activating receptors coupled with G-proteins and second messengers. High local proton concentration (acidosis) is thought to be a decisive factor in inflammatory pain and other mediators such as prostaglandin, bradykinin, and serotonin enhance proton-induced pain. Proton-sensing ion channels [transient receptor potential V1 (TRPV1) and the acid-sensing ion channel (ASIC) family] are major receptors for direct excitation of nociceptive sensory neurons in response to acidosis or inflammation.

G-protein-coupled receptors activated by prostaglandin, bradykinin, serotonin, and proton modulate functions of TRPV1, ASICs or other ion channels, thus leading to inflammation- or acidosis-linked hyperalgesia. Although detailed mechanisms remain unsolved, clearly different types of pain or hyperalgesia could be due to complex interactions between a distinct subset of inflammatory mediator receptors expressed in a subset of nociceptors. This review describes new directions for the development of novel therapeutic treatments in pain.

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Key words: Acid-sensing ion channel; Acidosis; G-protein-coupled receptor; Inflammation; Proton-sensing ion channel; Transient receptor potential V1

Core tip: Tissue acidosis that occurs during inflammation is central to the development and maintenance of chronic pain. Recent studies have revealed a variety of proton-sensing ion channels (*e.g.*, acid-sensing ion channels, transient receptor potential V1) and G-protein-coupled receptors (*e.g.*, G2 accumulation 2A, G-protein-coupled receptor 4, ovarian cancer G-protein-coupled receptor, T-cell death-associated gene 8) responsible for acid-induced pain. These cell-surface membrane proteins are promising therapeutic targets for the development of new analgesic drugs for chronic inflammatory pain.

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INTRODUCTION

Cancer, nerve injury, and arthritis often cause chronic inflammatory pain^[1]. Chronic pain may have a profound

effect on a person's life and society when not effectively treated. Although a variety of pharmacologic treatments are available, they are limited by unacceptable side effects or short-term efficacy. The development of long-acting pharmacologic therapies requires knowledge of how chronic inflammatory pain signals are initially interpreted and subsequently transmitted and perpetuated. This review focuses on recent findings from studies of the molecular mechanisms of inflammatory pain transmission and modulation, especially the roles of mediator-gated ion channels and G-protein-coupled receptors (GPCRs).

INFLAMMATORY PAIN

When our body senses noxious stimuli (such as a cut from a sharp knife, burn from an open flame, or contact with burning or erosive chemicals), the signal quickly activates primary sensory afferents (nociceptors) and delivers a message to the brain to elicit the pain feeling. When stimuli are absent, the painful experience disappears. The situation is called acute pain because the pain signal is transient^[2]. Noxious stimuli activate transducer receptors located on medium myelinated (A δ) and small unmyelinated (C) nociceptors to induce the receptor potential. The receptor potential activates a variety of voltage-gated ion channels to transmit pain signals to secondary nociceptors in the dorsal horn of the spinal cord, then to the brain^[3].

If the tissues are damaged mechanically or by pathogen infection, autoimmune disease, or tumor growth, the sites of the damaged or infected tissues usually show inflammatory responses such as redness, swelling and heat accompanied by persistent pain; endogenous mediators released from the damaged or infected tissues increase the extravasation of the vessels and attract the immune cells, including mast cells, macrophages, neutrophils, and platelets, to the injured site for the inflammatory response^[1]. The "inflammatory soup" is rich in purines, amines, cytokines, protons, ions and growth factors. These mediators can directly activate the nociceptors, evoking pain or modulating the sensitivity of the primary nociceptors, thus causing a hyperreactive reaction to stimuli. As a result, normal stimuli such as a light touch or a brush are perceived as painful (allodynia), or normally painful stimuli cause pain of greater intensity (hyperalgesia)^[4]. In the periphery, inflammatory mediators bind to GPCRs to activate protein kinases A and C (PKA and PKC) to phosphorylate receptors or increase receptor expression, which enhances the sensitivity of primary nociceptors, called peripheral sensitization. Primary nociceptor-driven transmitter release activates intracellular kinases to phosphorylate receptors. This situation leads to an immediate and activity-dependent increase in the excitability and responsiveness of dorsal horn neurons, called central sensitization. Central sensitization could be sustained for some time because of transcriptional changes^[2,4].

INFLAMMATORY MEDIATORS OF PAIN

The endogenous mediators, such as prostaglandin E₂

(PGE₂), bradykinin (BK), serotonin [5-hydroxytryptamine (5-HT)], proton, histamine, and ATP, are released from the damaged site of the tissue and immune cells to induce inflammation and nociception^[2]. These mediators act on transducer receptors situated on sensory neurons to induce complex changes in peripheral and central signal processing. Although some mediators can act directly on ion channels to induce receptor potential, for the most part these chemical interactions occur through the activation of receptors coupled with G-proteins and second messengers, thus activating protein kinases. Such activated kinases phosphorylate ion channels to alter ion permeability or phosphorylate cellular proteins to increase gene expression.

Earlier studies of single mediators demonstrated that BK, PGE₂, 5-HT, and proton have excitatory action on cutaneous nociceptors and induces transient pain^[5-8]. More sustained effects are achieved only in a high-concentration (10^{-5} mol/L) combination of inflammatory mediators (BK, 5-HT, PGE₂, and histamine)^[9]. Steen *et al.*^[10] proposed that the combination of inflammatory mediators plays a role in sensitizing the low pH effect. The acidosis in inflamed tissues is the decisive factor for ongoing nociceptor excitation and sustained pain. However, the interaction between various mediators remains unclear.

TISSUE ACIDOSIS AND ACID-SENSING RECEPTORS

Tissue acidosis is a common phenomenon found in inflammation (reduced to pH 5.4)^[11], in lesions or incisions (reduced to pH 6.5)^[12], in ischemic heart or muscle (pH 5.7-7.0)^[13,14], and even in malignant tumors (pH 5.8-7.4)^[15]. High local proton concentrations in inflamed tissues can excite and sensitize rat skin nociceptors and can cause sustained pain in human skin^[7,16,17]. As well, the combination of inflammatory mediators (BK, 5-HT, PGE₂, and histamine) in acid solution (pH 6.1) can excite and sensitize rat skin nociceptors^[18]. Injections of the inflammatory mediator combination in neutral solution in human skin induces dose-dependent, transient, burning pain, but the effects become more intense and prolonged when the mediator combination is in acidic solution^[19]. Studies of rat dorsal root ganglion (DRG) neurons revealed that acidic solutions induced a cation conductance in a subset of neurons^[19], and a proton-activated sustained current is potentiated more by the mediator combination than each mediator alone^[20]. Proton-activated currents found in the sensory neurons are due to direct activation of the non-selective cation channels and indirect modulation of ion channels^[21]. Proton-gated ion channels and proton-sensing GPCRs expressed on nociceptors are potential candidates responsible for acidosis-induced pain.

PROTON-GATED ION CHANNELS: ACID-SENSING ION CHANNELS

Acid-sensing ion channels (ASICs), which belong to

the family of degenerin/epithelial amiloride-sensitive Na^+ channels, are voltage-insensitive cationic channels activated by extracellular protons^[22-25]. The ASIC family, comprising ASIC1a, ASIC1b, ASIC2a, ASIC2b, ASIC3, ASIC4 and ASIC5, is expressed in the peripheral and central nervous systems^[26-28].

Among ASICs, ASIC3 is the most sensitive receptor to protons, with pH 0.5 for activation around 6.7, and is expressed in both small- and large-diameter DRG neurons^[29-31]. The expression of ASIC3 in DRG is increased with hind paw inflammation in rats^[32,33]. As well, ASIC3 channel activity is enhanced by several components of the inflammatory soup, such as BK, 5-HT, hypertonicity, arachidonic acid, and nitric oxide^[34-38]. Thus, ASIC3 is considered a sensor of acidic and primary inflammatory pain^[34]. Study of skin nerves revealed that loss of ASIC3 increases the sensitivity of mechanoreceptors to light touch but decreases that of mechanoreceptors to a noxious pinch^[39,40]. Surprisingly, mice lacking the ASIC3 gene still respond to acid stimuli and have acid-induced pain or primary inflammatory pain^[39,41-43]. However, inhibiting ASIC3 function with a specific peptide or small interfering RNA significantly reduces cutaneous acidic pain under normal or inflammatory conditions and postoperative pain^[34,44].

Given that ASIC3 is predominantly expressed in muscle nociceptors rather than in cutaneous nociceptors^[45], ASIC3 should be required for development of secondary mechanical hyperalgesia induced by acid injection in skeletal muscle or by muscle inflammation^[46-48]. Although the ASIC3 requirement for development and maintenance of muscle inflammatory pain is argued, selective microRNA-targeted ASIC3 inhibits primary and secondary hyperalgesia induced by muscle inflammation^[49]. Interestingly, a recent study by Lin *et al.*^[50] suggested that ASIC3-mediated muscle pain is negatively modulated by substance P *via* regulation of the M channel in a G-protein-independent pathway.

ASIC1a is predominantly expressed in small-diameter DRG neurons^[23,51] and is less sensitive than ASIC3 with pH 0.5 for activation around 6.5^[29,30]. Mice lacking ASIC1a show normal mechanical sensitivity in cutaneous afferents but enhanced mechanically evoked firing rate in gastrointestinal afferents^[52,53]. In contrast to the ASIC3 role in secondary hyperalgesia, ASIC1a-deficient mice do not develop primary hyperalgesia induced by muscle inflammation, so ASIC1a and ASIC3 may play distinct roles in the development and maintenance of hyperalgesia, respectively^[43]. Downregulation of ASIC1a expression in spinal dorsal horn neurons by using selective inhibitor or antisense oligonucleotides reduces complete Freund's adjuvant (CFA)-induced thermal and mechanical hypersensitivity, which suggests that ASIC1a contributes to central sensitization in inflammatory pain^[54]. A recent study provides a new view for ASIC1a and ASIC3 roles in inflammatory pain in that acidosis may induce endocytosis and maturation of macrophages through ASIC1a and ASIC3^[55]. Mice lacking ASIC1a, ASIC2 and ASIC3 genes lost acid-induced transient currents, but their be-

havioral sensitivity to mechanical stimuli was increased, so ASICs indeed contribute cutaneous mechanosensation but in complex behavioral changes^[56].

PROTON-GATED ION CHANNELS: TRPV1

Transient receptor potential/vanilloid receptor subtype 1 (TRPV1/VR1) is a 6-transmembrane domain, non-selective cation channel and activated by vanilloid, heat, capsaicin, and proton^[57,58]. TRPV1 is predominantly expressed in small-diameter DRG neurons in rats and mice^[57]. Disruption of the TRPV1 gene in mice reduces responses of DRG neurons to acid and thermal stimuli and eliminates carrageenan-induced thermal hyperalgesia, so TRPV1 may be involved in acid-induced pain and inflammation-induced thermal hyperalgesia^[59,60]. However, surprisingly, blockage of the TRPV1 function in peripheral or spinal loci by selective antagonists inhibits mechanical hyperalgesia induced by CFA, capsaicin, or bone cancer^[61-64]. Although TRPV1 participates in both mechanical allodynia and thermal hyperalgesia induced by cutaneous inflammation, it does not participate in muscle inflammation^[65]. TRPV1 mediates the development of heat but not mechanical hypersensitivity after muscle inflammation^[66]. With peripheral inflammation, the mRNA TRPV1 expression is increased and the channel function enhanced in DRG neurons^[67-69]. Interestingly, DRG neurons with increased TRPV1 expression and function are mainly non-peptidergic rather than peptidergic neurons^[69]. Since most non-peptidergic neurons project to skin targets, TRPV1 would mainly participate in cutaneous inflammatory pain^[70,71]. Okun *et al.*^[72] suggested that CFA-induced ongoing pain is transient and depends on TRPV1-positive afferents but cannot be blocked by TRPV1 antagonism. TRPV1 may be responsive to noxious stimuli while nociceptors are sensitized (inflammation). Its function could be sensitized by inflammatory mediators such as BK^[73,74], chemokines (CCL3)^[75], 5-HT^[76], PGE₂^[77,78], proton^[79] or by protease-activated receptor 2^[80,81]. A recent study suggested that TRPV1 and TRPA1 are involved in the transition of acute to chronic pain in a chronic pancreatitis model^[82].

PROTON-SENSING G-PROTEIN-COUPLED RECEPTORS: OGR1 FAMILY

In 2003, Ludwig *et al.*^[83] found two GPCRs, ovarian cancer GPR 1 (OGR1) and G protein-coupled receptor 4 (GPR4), fully responsive to protons at pH 6.8 and stimulating inositol triphosphate and cAMP formation, respectively. Later, the 2 other family members, G2 accumulation (G2A) and T-cell death-associated gene 8 (TDAG8) were identified as proton receptors, with full activation at pH 6.4-6.8^[84-86]. OGR1, GPR4, and G2A were previously identified as receptors for sphingosylphosphorylcholine (SPC) or lysophosphatidylcholine (LPC), but the original publications have now been retracted^[87-89]. Whether OGR1, GPR4, and G2A are SPC or LPC receptors

remains unclear. In addition to responding to protons, TDAG8 also responds to psychosine^[85,89]. Although G2A was considered a proton-sensing receptor, Radu *et al*^[90] suggested that G2A is less likely to be a pH sensor because it does not generate a significant response after acid stimulation. G2A shows conservation of only 1 of 5 critical histidine residues that are involved in pH-sensing of OGR1, so G2A may be less sensitive to protons^[83]. Later, Obinata *et al*^[91] found that G2A can respond to oxidized free fatty acid (9-hydroxyoctadecadienoic acid, 9-HODE). Recent studies with gene-knockout techniques have revealed the absence of some but not all pH-induced cellular effects in OGR1-, TDAG8- or GPR4-deficient mice or cells, so OGR1 family members are indeed involved in proton sensing, and the pH-dependent activities could be highly cell-type- or signaling-pathway-specific^[90,92-94]. Interestingly, mice lacking G2A show some deficiencies in LPC- or acid-related cellular effects^[90,95-97]. Whether G2A is a proton, LPC or fatty acid receptor remains debated.

Proton-sensing GPCRs are widely expressed in non-neuronal and neuronal tissues^[98]. Approximately 75% to 82% of OGR1 family members are found in small-diameter DRG neurons responsible for nociception and 61% to 74% are present in isolectin B(4) (IB4)-positive neurons, so they may be involved in chronic pain^[79,98]. Indeed, one of the members, TDAG8, showed increased expression after CFA-induced inflammation, and its activation sensitizes TRPV1 function^[79]. TDAG8 is involved in CFA-induced inflammatory pain by modulating TRPV1 function. Later, knockdown of spinal TDAG8 expression was found to reduce bone cancer pain^[99]. Thus, TDAG8 could have pro-nociceptive roles in the peripheral and central nervous system. Although a recent study suggested that TDAG8 is a negative regulator in inflammation because of exacerbation of arthritis induced by anti-type II collagen antibody in TDAG8-deficient mice, whether TDAG8 has an anti-nociceptive role in inflammatory pain remains unclear^[100].

In endothelial cells, G2A expression blocks NF- κ B activation and chemokine expression, thus inhibiting macrophage accumulation, which suggests that G2A expression may have a protective role in preventing early events of inflammation^[96]. This situation could explain why G2A expression is downregulated in capsaicin- and CFA-induced inflammatory pain, so G2A could have an anti-nociceptive role in inflammatory pain^[79]. GPR4 is present in endothelial cells of blood vessels, and mice lacking GPR4 show vascular abnormalities, which suggests that GPR4 has a role in vascular growth and vascular stability^[93]. Vascular stability is important for leukocyte adhesion and function^[101]. GPR4 antagonism attenuates acidosis-induced inflammation and modulate a wide range of inflammatory genes in endothelial cells^[102].

SEROTONIN AND SEROTONIN RECEPTORS

In the periphery, serotonin (5-HT) released from plate-

lets, mast cells, and endothelial cells into the inflamed site is pro-inflammatory and pro-nociceptive, exciting nociceptive afferents and inducing hyperalgesia^[9,103-106]. In central loci, the descending pathway on serotonergic neurons from the rostral ventromedial medulla to the spinal cord has facilitatory or inhibitory effects on DRG neurons depending on the activation of 5-HT receptor subtypes^[107]. Seven subgroups of serotonin receptors (5-HT₁₋₇) have been identified, and some subtypes have more than one receptor (*e.g.*, 5-HT₁ has 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}; and 5-HT₂ has 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C})^[108]. Although Sufka *et al*^[103] (1992) suggested that all of the 5-HT_{1A}, 5-HT_{2A}, and 5-HT₃ subtypes participate in 5-HT-induced pain, the presence of multiple 5-HT receptors on afferent nociceptors reflects distinct pain models or mechanisms.

Taiwo *et al*^[104] reported that only the 5-HT_{1A} agonist mimics the 5-HT effect to induce hyperalgesia and 5-HT_{1A} antagonists block mechanical hyperalgesia induced by 5-HT. Nevertheless, Kayser *et al*^[109] suggested that mice lacking 5-HT_{1A} show increased sensitivity to noxious heat but not mechanical pain stimuli. The other study of formalin testing also suggested that 5-HT_{1A} mediates antinociception^[110]. In addition to 5-HT_{1A}, the receptors 5-HT_{1B}, 5-HT_{1D} and 5-HT_{1F} also have anti-nociceptive effects in heat-evoked or formalin-induced nociceptive responses^[109,110]. Later, 5-HT_{2B/2C} but not 5-HT_{1A} was found to mediate 5-HT-induced mechanical hyperalgesia^[111]. Spinal and peripheral injection of a specific antagonist (RS127445) of 5-HT_{2B} reduced formalin-induced flinching behavior, which suggests that 5-HT_{2B} has a pro-nociceptive role in peripheral as well as spinal loci^[112]. However, Urtikova *et al*^[113] suggested that blockage of peripheral or spinal 5-HT_{2B} by a specific antagonist (RS127445) could enhance hyperalgesia induced by chronic constriction nerve injury. 5-HT_{2B} may have distinct roles in different pain models.

Ionotropic 5-HT₃ is directly responsible for inflammatory pain^[109,114,115]. Lack of the 5-HT₃ gene in mice or blocking with the 5-HT₃ antagonist granisetron elicited normal acute pain responses but reduced persistent pain responses^[109,115]. Giordano *et al*^[116] showed that 5-HT₃ contributes to chemical but not thermal and mechanical nociceptive pain. 5-HT_{2A} potentiates the effects of other inflammatory mediators^[117]. In the study by Tokunaga *et al*^[118], only the 5-HT_{2A} agonist but not 5-HT_{1A} and 5-HT_{3A} agonists mimicked 5-HT-induced thermal hyperalgesia, which was blocked by the 5-HT_{2A} antagonist ketanserin. However, Loyd *et al*^[119] suggested that both 5-HT-induced and 5-HT-enhanced capsaicin-evoked thermal hyperalgesia require 5-HT_{2A} and 5-HT₃. Likely, 5-HT_{2A} potentiates 5-HT₃-mediated nociceptive responses to thermal stimuli. Recent studies show that 5-HT_{2A} has a pronociceptive role in spinal nociceptive transmission and seems to be involved in both mechanical and thermal hyperalgesia in the spinal nerve ligation model^[120,121].

In addition, 5-HT₄ enhances the inflammatory pain signal^[122]. 5-HT₇ inhibits capsaicin-induced mechanical

sensitivity^[123]. Intrathecal injection of 5-HT_{2A}, 5-HT₃ and 5-HT₄ antagonists significantly reduced spinal cord stimulation-induced long-lasting pain in rat models, with no effect by administration of 5-HT_{1,6,7} antagonists^[124]. 5-HT₂ and 5-HT₇ are major receptors to potentiate TRPV1 function in inflammatory pain^[76].

PROSTAGLANDIN E2

Prostaglandin E2 (PGE₂), derived from an arachidonic acid by the cyclooxygenase (COX) pathway, is released from damaged cells and contributes to inflammatory pain^[125]. Non-steroidal anti-inflammatory drugs are the commonly used analgesics that reduce prostaglandin synthesis by inhibiting COX-1 and COX-2^[126]. Four subtypes of PGE₂ receptors (EP₁, EP₂, EP₃ and EP₄) belong to GPCRs^[125,127]. The roles of PGE₂ receptor subtypes in pain are undefined because of inconsistent results from studies involving gene targeting techniques, but are better resolved in combined studies with pharmacological approaches^[126]. PGE₂-induced thermal hyperalgesia is mediated by EP₁ predominantly through a PKC-dependent pathway and is due to potentiation or sensitization of TRPV1^[77]. Wang and colleagues showed that PGE₂-induced pain is mediated by EP₃ through PKA and Epac/PKC pathways to sensitize purinergic P2X₃ receptors^[78,128]. Several lines of evidence also support the roles of PGE₂ in modulating pain transduction. PGE₂ potentiates the TRPV1 function in response to capsaicin^[78]. Repeated administration of PGE₂ sensitizes T-type calcium channels, thus resulting in mechanical hyperalgesia^[129]. PGE₂ potentiates the voltage-gated tetrodotoxin-resistant sodium channels (Nav1.5, Nav1.8 and Nav1.9) by a cAMP-PKA signaling pathway^[130,131].

TRANSITION FROM ACUTE TO CHRONIC PAIN

The possible mechanisms of chronic inflammatory pain could be that continuous sensitization induced by inflammatory mediators in primary afferent nociceptors results in persistent and long-lasting pain or neuroplastic changes in primary afferent nociceptors after initiating insults lead to enhanced and prolonged sensitization of nociceptors even with low-level exposure of pro-nociceptive inflammatory mediators. The mechanisms of chronic pain and the regulation of the transition from short-term to long-lasting pain have become clearer from studies with the PGE₂ priming model.

Administration of PGE₂ in rat induces short-term hyperalgesia that depends on PKA activity^[132]. With carageenan pre-injection, rats display long-lasting hyperalgesia induced by PGE₂, and the prolonged effect can be inhibited by PKC ϵ blocker or attenuated by antisense oligonucleotides for PKC ϵ ^[133,134]. Therefore, PKC ϵ may be necessary to maintain hyperalgesic priming. Indeed, a highly selective PKC agonist can induce hyperalgesic priming in rat^[134]. In contrast, the study by Ferrari *et*

al^[135] proposed that a transient decrease in GRK2 levels leads to increased nociceptor response to inflammatory mediators, and the reduced GRK2 levels are PKA- but not PKC-dependent. Ferrari *et al*^[136] later proposed that the prolongation of PGE₂-induced hyperalgesia is mediated by an autocrine mechanism. PGE₂ activates EP receptors followed by cAMP production, which in turn activates PKA and induces hyperalgesia. The increase in intracellular cAMP level triggers the transporter to transport cAMP outside the cell. The extracellular cAMP is metabolized to AMP and adenosine, thus activating the Gi-coupled A₁ adenosine receptor. The Gi pathway stimulates PKC ϵ , which is responsible for the late phase of PGE₂-induced hyperalgesia, although evidence has shown that after injury, the inflammatory mediators may release and reach the effective concentration in a different time course. Each mediator activates its own receptor subtypes, thus contributing to the development of hyperalgesia. However, which receptor is the major receptor causing the acute to chronic pain remains unclear.

ESTABLISHMENT AND MAINTENANCE OF CHRONIC PAIN: THE ROLE OF AN EXCITATORY AMINO ACID IN CENTRAL SENSITIZATION

The establishment and maintenance of chronic pain is not simply a reflection of peripheral inputs or abnormality but is also a dynamic reflection of central neuronal plasticity. Once the central sensitization occurs, painful sensations are generated even in the absence of the noxious stimulus^[137]. Several lines of evidence implicate the contribution of excitatory amino acids in neuroplasticity and central sensitization in the spinal cord. Noxious stimulation or peripheral inflammation causes the release of an excitatory amino acid, glutamate, in the spinal dorsal horn^[138,139]. Dorsal horn neurons that are sensitized with peripheral inflammation show increased responsiveness to the iontophoretic application of the excitatory amino acid^[139,140], and such responsiveness or sensitization is reduced after the administration of glutamate receptor antagonists^[141,142].

Glutamate receptors include ionotropic amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), N-methyl-D-aspartate (NMDA), kainate receptors and metabotropic G-protein-coupled glutamate receptors (mGluRs). The contribution of ionotropic glutamate receptors to the central sensitization are considered the ability of AMPA and NMDA receptor antagonists to reduce the responsiveness of dorsal horn neurons and in producing analgesic effects^[142]. Intrathecal injection of NMDA leads to hyperalgesia, which can be reversed by application of an NMDA antagonist^[143]. The NMDA antagonist MK-801 reduces the hyperalgesia that develops in rats with adjuvant-induced inflammation^[144] or reduces the inflammation-induced expansion of the receptive field of spinal nociceptive neurons^[145].

Peripheral inflammation elevates levels of phosphorylated NMDA receptors in the spinal dorsal horn^[146,147]. The sustained release of the neuropeptides (such as substance P and CGRP) and glutamate causes PKC activation and Ca²⁺ influxes through NMDA receptors. With Ca²⁺ influx, several intracellular signal pathways, including the phospholipase C-PKC pathway, phosphatidylinositol-3-kinase (PI3K) pathway, and mitogen-activated protein kinase (MAPK) pathway, are activated. Activated intracellular signaling pathways result in phosphorylation of spinal NMDA receptors, enhancing Ca²⁺ currents at NMDA receptors. Activated intracellular signaling pathways also phosphorylate AMPA receptors, thus increasing the density of AMPA receptors on the membrane^[148]. These mechanisms create a positive feedback loop for glutamate transmission and alter the neuronal plasticity in the dorsal horn. In the formalin-induced inflammatory pain model, intrathecal injection of the MEK inhibitor PD98059 can reduce the second phase of the licking/lifting behavior and attenuate extracellular signal-regulated kinase activity, so some intracellular signaling pathways may also be involved in central sensitization^[149].

CONCLUSION

At the inflamed site of the tissue, endogenous mediators (5-HT, PGE₂, BK, and proton) are released from damaged cells and accumulate. Nociceptors innervating the skin, muscle and organs detect the noxious stimuli and express one or more cell-surface receptors to respond to these inflammatory mediators. The mediators can directly or indirectly alter the sensitivity of the receptors on nociceptors. ASIC3, ASIC1a and TRPV1 seem to be important transducer receptors contributing to hyperalgesia induced by inflammation. ASIC1a participates in primary mechanical hyperalgesia induced by muscle inflammation, but ASIC3 may have a predominant role in secondary mechanical hyperalgesia. TRPV1 could be responsible for mechanical and thermal hyperalgesia induced by cutaneous inflammation. Inflammatory mediators such as 5-HT, PGE₂, BK, and proton sensitize TRPV1 or ASIC3 to prolong the hyperalgesia. PGE₂ acts on EP₁ to sensitize TRPV1 or on EP₃ to sensitize P2X₃. Proton and BK sensitize TRPV1 through TDAG8 and B₂, respectively. 5-HT potentiates TRPV1 function, possibly through 5-HT₂ and 5-HT₇. Although each mediator receptor has its own dominant second-messenger signaling cascade, each could also be coupled in part to other second-messenger pathways. For short-term hyperalgesia, the cAMP-PKA pathway is dominant, but prolonged hyperalgesia is regulated by PKC ϵ -dependent or -independent pathway.

The signal of a stimulus is triggered by a peripheral nociceptor, followed by conduction to central neurons. In acute pain, the signal is mediated by glutamate acting on AMPA and kainate subtypes of ionotropic glutamate receptors of postsynaptic neurons and generating the excitatory postsynaptic potential. If the signal is generated by intense or persistent noxious stimuli, the depolarization of the postsynaptic neurons will activate NMDA re-

ceptors. NMDA receptor activation induces Ca²⁺ influx, which activates intracellular signaling pathways to further enhance Ca²⁺ influx through NMDA receptors. NMDA receptors can also be modulated by GPCRs such as NK1, EP or mGlu receptors that are also expressed on the superficial dorsal horn of nociceptor terminals^[150]. All these NMDA-receptor-mediated mechanisms contribute to central sensitization, which is important for establishing and maintaining chronic pain^[151].

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Regional anesthesia for acute pain management in elderly patients

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Abstract

Normal aging is a process that involves loss of functional reserve of most organ systems of the human body, most significantly: cardiovascular, pulmonary, renal and nervous systems. Advancements in both surgery and anesthesia have made it possible to operate more safely on the elderly population and those older patients with multiple severe co-morbidities that were not routinely possible in the recent past. Regional anesthesiologists have proven to be instrumental in this regard as regional anesthetic/analgesic techniques may now permit surgeons to operate on the elderly who were not ideal surgical candidates or unable to tolerate general anesthesia. In addition, regional techniques provide alternatives that may optimize acute pain control and reduce the incidence of devastating side effects during the perioperative period such as: myocardial infarction, pulmonary embolism, pneumonia, and also increases the opportunity to allow for early ambulation and shorter hospital stays. These anesthetic options now provide the elderly patient with better medical care alternatives, but also can show a significant financial impact on health care system resources. Further understanding on aging molecular biology, physiology and pathophysiology, together with technical improvements

of regional anesthetic techniques will continue to make it safer and more efficacious to operate on the elderly population with evidence of reduced morbidity and mortality. Although there is only anecdotal evidence that regional anesthesia (RA) improves survival, there is little doubt that RA plays an important role in perioperative optimization of pain control and decreases pain management complications as well as a reduction in healthcare costs. Beyond traditional operating rooms, elderly patients may increasingly benefit from RA and acute pain management in Emergency Rooms, medical clinics and even within a patient's home. Therefore, the focus of this review is directed toward geriatric patients and beneficial effects of RA on outcomes in the elderly.

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Key words: Regional anesthesia; Elderly patients; Pain management; Local anesthetics; Opioid analgesics; Multi-modal; Cognitive impairment; Organ systems; Procedure- and patient-specific

Core tip: Perioperative advancements has made operating on the elderly more safe, however, aging involves functional reserve loss and older patients often present with co-morbidities. Regional may prove instrumental and permit operations on those who are not ideal candidates, reduce incidence of adverse effects, optimize pain control, provide medical care alternatives and may reduce financial impact on healthcare systems (early ambulation, shorter hospital stay). Understanding of aging, together with improvements in regional will make it safe to operate on the elderly with reduced morbidity and mortality. Regional plays an important role in pain control, decreases management complications and can reduce healthcare costs.

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INTRODUCTION

The diversity, amount of known consequences and abundant number of theories describing the aging progression demonstrate the multidimensionality and complexity associated with understanding mechanisms of aging. Despite advances in anesthesia, analgesia and drug delivery systems, debate continues as to whether regional anesthesia (RA) is more efficacious and safer in elderly and cognitively impaired patients. However, there is some demonstration and evidence-based outcomes to suggest that RA may be an optimal anesthetic for elderly patients in specific clinical scenarios^[1]. One approach to planning perioperative pain management in geriatric patients is to consider possible postoperative complications associated with commonly performed surgical procedures in order to assess benefits of RA.

Common morbidity complications of the elderly include: neurological, pulmonary, and cardiovascular events^[2]. The most routinely performed surgical interventions are: orthopedic and general surgery (aside from ophthalmologic procedures). Definition and descriptions of RA are variable as are the various techniques of RA anesthesia and analgesia (Figure 1). Investigations on RA are inclusive of different regimens and regional techniques including: RA alone versus combined RA and general anesthesia (GA), RA only versus combined RA and regional analgesia, thoracic versus lumbar RA, for example. Lack of consistency within RA studies and protocols has inhibited the ability to portray firm indications, suggestions, guidelines, and recommendations about any advantageous or optimal anesthetic/analgesic technique for a particular surgical intervention in the geriatric population. With the ever-increasing diversity of available procedures, it has become increasingly complex to make clear-cut recommendations or suggest guidelines that suit all clinical situations. Geriatric surgical patients have unique age-related changes in physiology and several altered reactions to pharmacology^[3] and some examples are identified in Table 1^[6].

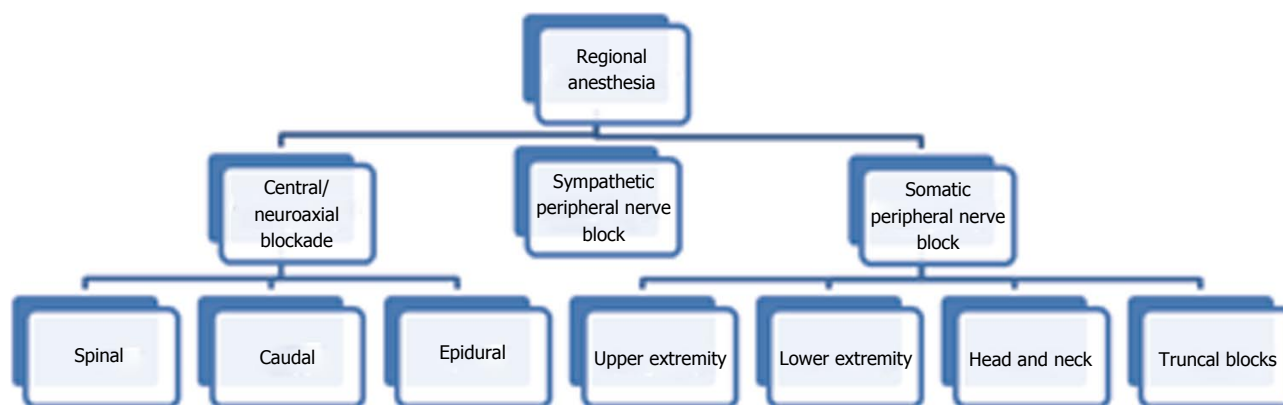
Several age-associated physiological events will also affect pharmacodynamics such as changes in the sensitivity to a specific drug, either up or down, as well as changes in the susceptibility of the elderly to certain drugs. The above-mentioned potential interaction between aging and pharmacodynamics, pharmacokinetics, and polypharmacy, introduces additional concerns when treating the elderly and increases opportunity of exposing older patients to adverse drug reactions. As a result, RA and analgesic options using local anesthetics may provide for a more attractive and safer alternative to avoid systemic administration of various narcotic drugs in addition to other adjunctive analgesic medications.

Many elderly patients have co-morbid disease(s),

varying degrees of physical de-conditioning (especially prior to lower extremity orthopedic procedures), poor perioperative health status and compromised organ reserve capacity. Therefore, alternatives to traditional anesthetic/analgesic options, such as local anesthetic drugs, may prove more efficacious to avoid further compromise in older medical and surgical patients. Established and theoretical indications for RA being a competent and safe technique in the elderly and cognitively impaired patients includes profiles from such methods currently being performed in traditional ORs and Emergency Rooms for both diagnostic and therapeutic interventions. Additionally more and more centers are sending patients, even polypharmacy elderly patients, home with continuous peripheral nerve catheters for prolonged benefits of pain management from RA^[1,8,9].

Perioperative clinical outcomes associated with RA effectiveness that may result in reduced morbidity (traditional and nontraditional complications)^[10] and mortality include: optimal pain management, improved functional and economical outcomes, reduced compromise of functional health status, increased quality of life measurements, along with reduced effects on: cognition, central nervous system (CNS), cardiovascular, pulmonary, gastrointestinal (GI), immune, endocrine, and coagulation systems. Therefore, it is important to consider and recognize patient age, anticipated surgical procedure, patient co-morbidity(s), and potential postoperative pain management requirements when deciding upon an appropriate choice of anesthetic technique and perioperative pain management strategy in the elderly. As an example, although recent studies have shown that exercise and nutrition may slow down protein synthesis impairment and sarcopenia^[11] in general the aging body has a skeleton composed of components with significant bone loss and aging skeletal muscles with progressive muscle mass loss along with a decrease in strength and aging joints. Such age-induced pathology (present in up to 80% of the elderly over 65 years) predisposes the elderly to a higher risk of falls and dis-coordination along with an increased incidence of orthopedic injuries^[12]. Therefore, a thorough approach to perioperative pain management should consider these influences when selecting an optimal pain therapy protocol.

Anesthesiologists' responsibilities for patient medical care is no longer limited to traditional operating room (OR) environments. Outside OR treatment and therapy is needed and the acute pain control expertise of regional anesthesiologists is becoming more in demand. In the emergency room (ER), in medical wards and intensive care unit settings, physicians are in search of alternatives to provide therapeutic intervention(s) without transporting sick patients to the OR. For example, a lateral femoral cutaneous nerve block can be used as a diagnostic option as well as therapeutic treatment for meralgia paresthetica. Management of elderly orthopedic trauma patients in the ER can involve many regional anesthetic options. In shoulder and upper extremity injuries, an interscalene, supracl-

Figure 1 Regional anesthesia options^[3,4].Table 1 Pharmacokinetics alterations with aging^[5,7]

Organ system	Deficits with aging
Liver	Decrease in hepatic blood flow will result in reduction of first pass elimination, phase I metabolism affected earlier than phase II
Kidneys	Reduction in renal blood flow cause decrease in both creatinine clearance, glomerular filtration rate and tubular secretion activities
Plasma drug-binding proteins	Decrease in albumin or other binding proteins will result in higher fraction of plasma free drug
Fluid distribution	Decrease in total body water and muscle, and increase in total body fat may results in smaller effective dose and longer duration of drug effect, especially for lipophilic drugs

vicular, infraclavicular, axillary, and individual nerve blocks could be effective interventions associated with low risk of complications for older patients. Lumbar plexus block, fascia iliaca compartment block and femoral nerve block have been used successfully in elderly hip fracture patients. Hip fractures are one of the most common injuries with the elderly in a traumatic fall and one of the most common orthopedic trauma injuries associated with poor outcomes in the elderly population. Other lower extremity injuries such as ankle fractures can be effectively managed with a distal sciatic nerve block in addition to a femoral/saphenous block. The most common truncal injury, often associated with devastating outcomes in the elderly, are rib fractures (often multiple). Here is another example where such an injury can be managed by a variety of RA techniques such as thoracic epidural, paravertebral, intercostal and intrapleural blocks^[1]. In addition, outside of hospitals and surgical center environments, anesthesiologists are treating patients and sending them home with continuous peripheral nerve blockade catheters to continue management of acute pain in surroundings much more familiar to older patients who may be at risk of anxiety and/or depression under prolonged exposure to unfamiliar settings. This beneficial value is in addition to the many known (gastrointestinal dysfunction) and possible (cognitive dysfunction) negative effects from traditional opioid analgesics for dependence of pain management. Some specific indications and contraindications for RA in the elderly, both inside and outside of the operating room arena are included in Table 2^[1].

NERVOUS SYSTEM IN THE ELDERLY

Normal aging results in several biochemical and anatomical

changes of the brain and spinal cord along with qualitative and quantitative effects on the nervous system (Table 3). Age-related changes in the peripheral nervous system (PNS) and CNS may affect functional outcomes during the perioperative period and should be considered in a patient's preoperative evaluation. Effect of aging on functional reserves of CNS and PNS along with potential surgical and anesthetic ramifications must also be considered.

Aging central nervous system

Anatomical and biochemical changes of the CNS < brain and spinal cord associated with normal aging include: (1) volume of brain mass, number of synapses, and neurotransmitter concentrations; (2) cerebral electrical and metabolic activity; (3) changes in brain nerve fibers; (4) changes within the spinal cord (cervical spinal cord maintains its shape, but decreases in size); and (5) modification of the bony spinal canal (shape and area of spinal cord are independent of spinal canal diameter). Reductions of brain reserve are portrayed as symptoms and signs of neurological dysfunction, decreases in functional activities of daily living, increased risk of postoperative cognitive dysfunction (POCD), and increased sensitivity to anesthetic medications. The major signs, symptoms and changes include altered reflexes, deteriorations of gait and mobility, altered sleep patterns, impairment of memory and intellect, and decrements of the senses (vision, hearing).

Aging somatic peripheral nervous system

Changes that occur in the somatic nervous system of the PNS with aging include: (1) peripheral nerve deterioration; (2) dysfunction of genes responsible for myelin sheath protein components; (3) decreased myelinated nerve

Table 2 List of older patient considerations related to regional anesthesia/analgesia

Indications	Contraindications
Poor cardiac reserve in patients who may not tolerate general anesthesia	Patient refusal
Poor pulmonary reserve: general anesthesia may result in prolonged mechanical ventilation	Sepsis, systemic infection and local infection are relative contraindications, and need to be assessed individually
Known history of adverse cognitive effects due to opioids and/or general anesthesia	Sedation and agitation may place patients at risk during PNB procedures
Severe hepatic insufficiency	Coagulopathy; relative contraindication with superficial PNB where bleeding can be easily controlled by compression
Severe renal insufficiency	Pre-existing neurological disease needs to be documented well and assess risk/benefit ratio
Difficult airway such as in elderly with cervical disk injury/pathology	Hypovolemia and severe aortic stenosis are relative contraindications for neuroaxial blocks, but not for PNBs
Chronic pain patients	Concern that PNB may mask compartment syndrome (controversial), however, collaboration between anesthesiologist and surgeon is necessary
Multiple rib fractures	Allergy to local anesthetics (rare)

PNB: Percutaneous needle biopsy.

Table 3 Nervous system changes in the elderly^[11,13-15]

Structural changes: gross and molecular level	Neuronal axon loss and pathology (more than seen with glial cells) Neural cytoskeleton changes resulting in neurofibrillary tangles and neuritic plaques (induces glial cell-mediated inflammation) Loss of dendrite components and decrease in neural synaptic activity Amyloidoses due to amyloid protein accumulation
Biochemical changes	Neurotransmitter imbalance: mostly involves changes in serotonin, dopamine, norepinephrine, acetylcholine Circulatory changes: multi-infarct senile dementia; increased BBB permeability Metabolic disturbances: atherosclerosis and associated blood flow and O ₂ consumption decreases
Functional sequelae	Gait changes Sleep and wakefulness alterations and EEG changes Cognitive impairment Decreased balance stability/physical equilibrium

BBB: Blood-brain barrier; EEG: Electroencephalograph.

fiber conduction velocity; (4) mild motor and sensory discriminatory changes of the feet; and (5) changes of the senses (*e.g.*, pain, touch, proprioception). Aging is associated with deterioration and decreases in the number of myelinated peripheral nerves for all mammals, particularly large myelinated fibers, resulting in atrophy along with degenerative changes of the myelin. The aging process affects levels of expression for key genes encoding major protein components of the myelin sheath such as proteolipid protein and myelin basic protein. Maintenance of myelin sheath integrity involves continued expression of genes specifically associated with myelin sheath protein production. Restoration of myelin sheaths to demyelinated axons (remyelination) is a spontaneous process of the nervous system, but aging has a detrimental effect. Spontaneous remyelination efforts are slowed as is evident by rate (slowing) of reappearance of transcripts of major myelin proteins (proteolipid and myelin basic proteins) and dysfunction of regulatory factors. Oligodendrocyte progenitor recruitment and differentiation are impaired by age-related decline in remyelination. Alterations of inflammatory responses by macrophages also contribute to a decline in remyelination secondary to aging. Aging induces functional changes by decreasing peripheral myelinated nerve conduction velocity as older adults have a 10%-30% decrease of efferent motor fiber conduction

velocity. Normal manifestations in patients older than 65 years include some degree of absent ankle reflexes along with mild abnormal sensory and motor symptoms of the feet (absent vibratory sensation of the big toe).

Aging autonomic nervous system

The autonomic division of the PNS also experiences alterations secondary to aging. Autonomic nervous system (comprised of nerves, ganglion and plexus) dictates most of the involuntary physiological functions of the body through parasympathetic and sympathetic divisions. Aging of the autonomic nervous system is characterized by: (1) limited adaptability to stress; (2) net activation of the sympathetic nervous system; (3) decreased basal activity of parasympathetic nervous system; (4) decreased baroreflex sensitivity; and (5) slowing and weakening of homeostatic functions. The aging autonomic nervous system has reduced autonomic abilities that influence a patients' response to physiologic changes, stresses, surgery and anesthesia. Increases in sympathetic nervous system activity are organ-specific with the GI system and skeletal muscle as targets. Neuronal noradrenergic reuptake is reduced in the elderly resulting in an increased sympathetic tone of the heart and an increase in basal adrenal secretions along with attenuation of adrenal adrenergic secretion in response to stress. There is a loss

of beat-to-beat heart rate variability during respiration in the elderly due to reduced respiratory vagal modulation of the resting heart. Findings of decreased baroreflex sensitivity are due to a function of increased arterial stiffness versus aging associated alterations of the autonomic nervous system. The autonomic nervous system and its effectors play an important role in responses to hemodynamic challenges and advancing age could result in an imbalance of homeostatic mechanisms such that findings of orthostatic hypotension, exercise intolerance, increased upper body sweating, and temperature intolerance may be evident.

Aging nervous system and anesthetic considerations

There are a host of factors in older patients predisposing them for cognitive dysfunction. Memory deterioration can occur in > 40% of people older than 60 years of age, and progressive loss of intellectual activity along with mental deterioration (senile dementia) happens in 14% of the population aged ≥ 75 ^[16,17]. Daily living activities can be dramatically affected by age-related memory decline, but is not inevitable. Deficiencies of specific neurotransmitters (related to Parkinson's, Alzheimer's dementia, and other disorders) often occur in geriatric patients. Changes in neurotransmitter activity and amounts have also been implicated as a factor influencing anesthetic agent sensitivity. Cerebral metabolic activity is decreased in older subjects and may be a result of decreased neurotransmitter concentrations and synaptic activity. Degenerative changes of myelin sheaths in the CNS may lead to cognitive dysfunction through changes in nerve conduction velocity leading to disruption of normal timing of neuronal circuits. Further contributions to cognitive decline are due to loss of cerebral white matter nerve fibers resulting in decreased connections between neurons. Although these changes have been identified in the aging brain, the mechanism causing effects on functional activity reserve remain unclear.

Older patients' perioperative evaluation for any surgical procedure should be performed as a multidisciplinary team approach for optimal operative management, therapy and long-term follow-up, when indicated. Elderly patients often present with age-related changes of the nervous system, and whether these changes are normal or pathologic, they are to be considered in the anesthetic plan and during selection of appropriate postoperative pain management. Emphasis on a routine design of an anesthesia assessment plan should be established due to the influence of aging and decreases of functional reserve of both the CNS and PNS. Alterations of functional reserve in the elderly may be reflected as increased susceptibility to POCD, delirium, altered pharmacodynamics, and stroke. Definitions and conditions of the various cognitive changes and dysfunction can be found in Table 4 and partially assessed by Mini-mental-status-exam, but more accurately by a wide array of cognitive assessment tools. While the most common perioperative mental status change is acute delirium, many other deficits have been reported, such as deficits in memory/recall, orientation, attention, language, registration, an ability to follow

commands, as well as depression and anxiety.

Cognitive disorders can occur after surgery in which mental function reaches a nadir in the early postoperative period and returns to preoperative levels within one week following surgery. CNS dysfunction is common in elderly postoperative patients, but stroke occurs relatively infrequently^[18]. A more common occurrence is the incidence of postoperative delirium (POD; most common psychiatric condition of hospitalized patients) and POCD. Incidence of POD and POCD may exceed 50% in certain surgical settings such as cardiac and orthopedic (femoral neck fracture repairs) surgeries^[19,20]. POD and POCD are common complications in elderly surgical patients and the incidence is higher than other postoperative co-morbidities such as respiratory failure and myocardial infarction^[21]. Complications of POD and POCD are significant because such adverse outcomes can result in increased length of hospital stay, medical complications including death, and often require discharge to skilled care facilities^[22,23]. The economic impact of delirium is considerable, adds costs to hospitalization and is responsible for billions in additional Medicare charges. POD and POCD occur far more frequently in elderly than in younger patients and the elderly surgical population is increasing in number.

Geriatric patients undergoing certain high-risk types of surgery and patients with certain coexisting medical disease(s) (preoperative cognitive dysfunction along with adverse physiological parameters associated with advanced age) are at higher risk for development of postoperative cognitive disorders and long-term cognitive dysfunction. Research has indicated that cognitive disorders in high-risk elderly patients occurs far more frequently than anticipated. This is evident by one such early study that brought formal recognition of this issue in the elderly surgical population; revealing that patients ($n = 1200$) older than 60 years had a high incidence (25.8%) of cognition impairment postoperatively, lasting for one week that persisted in some patients (9.9%) to 3 mo following surgery^[24]. Functional status of elderly surgical patients may be more relevant than medical morbidity outcomes. Postoperative cognitive status relates directly to the patient's functional ability which is a determining factor in rehabilitation and whether or not a patient is discharged to home or will require a skilled care facility for recovery. In addition, functional status serves as a strong predictor of mortality as a result of hospitalization^[25,26]. Decreased neurocognitive function yields a decrease in health related quality of life along with adverse financial and social impact for patients and their care providers. Finally, cognitive dysfunction postoperatively serves as a surrogate for the quality and modalities of continued hospital care^[27].

RA ramifications and neurologic morbidity and mortality

There are many theories that RA effects in the elderly will reduce the incidence of POCD^[28]. Evidence has shown a decreased incidence in a host of morbidity factors and some mortality specific advantages when using RA in the elderly for certain surgical procedures^[29-33].

Table 4 Types of cognitive dysfunction

MCI (4 subtypes associated with causes of dementia)	<p>Concept to describe transitional level of neurocognitive impairment</p> <p>MCI is a predictor of future dementia</p> <p>Diagnosis by neuropsychological testing and clinical observation</p> <p>Divided into 4 subtypes (based on presence of: (1) memory impairment plus; (2) number of other cognitive domains affected)</p> <p>Preoperative MCI may result in postoperative delirium</p>
Delirium	<p>Fluctuating consciousness, develops over hour to days</p> <p>Altered perception and cognition (not associated with dementia)</p> <p>In hospital predictors of delirium include:</p> <ul style="list-style-type: none"> Bladder catheters ↓ Functional status Male gender Malnutrition Infection Depression 3 or more medications H2 antagonists Age Opioids Iatrogenic events Benzodiazepines Alcohol + drug abuse
POD ^[74]	<p>Develops on postoperative day 1-3, can be sustained > 1 wk</p> <p>Age associated central cholinergic deficiency as a positive predictor</p> <p>Two types of postoperative delirium:</p> <ul style="list-style-type: none"> Hypoactive form (more common and more commonly overlooked) Hyperactive type <p>Perioperative use of benzodiazepines are associated with POD</p> <p>Postoperative in-dwelling perineural catheters reduce incidence of POD</p>
Emergence Delirium	<p>Present upon regaining consciousness following general anesthesia</p> <p>Predicts postoperative delirium</p>
POCD	<p>Condition in which patients have difficulty in performing cognitive tasks following surgery that they could perform prior to surgery</p> <p>Occurs frequently in and following: carotid endarterectomy, hip fracture repair surgery and cardiac surgery patients (most frequent)</p> <p>ISPOCD: developed criteria of POCD based on pre- and post-operative neuropsychological testing scores</p> <p>Predictors of POCD 1 wk postoperatively include:</p> <ul style="list-style-type: none"> Duration of anaesthesia Age (predictor of POCD at 3 mo) Postoperative infection Low level of patient education Pulmonary complications Need for a second operation
Dementia Alzheimer's disease (most common form), vascular dementias, frontal lobe, reversible, senile, Lewy body, and Parkinson-associated	<p>Apathy and personality changes occur early</p> <p>Behavioral changes appear as the condition progresses</p> <p>Psychotic symptoms are late signs (typically difficult to control)</p> <p>Multiple cognitive deficits</p> <p>Clinical findings are associated with:</p> <ul style="list-style-type: none"> Problems with social activities Decline from a previous status Problems of occupational activities <p>Gradual and progressive loss of mental abilities</p> <p>Dementia often results in postoperative delirium</p>

POCD: Postoperative cognitive dysfunction; ISPOCD: International study of postoperative cognitive dysfunction; MCI: Mild cognitive impairment; POD: Postoperative delirium.

There is a reduced incidence of acute postoperative confusion in elderly patients following hip fracture surgery under RA^[34]. High delirium risk surgery (such as femoral neck fracture repair) performed under spinal anesthesia (without perioperative premedication or sedation) has reported no incidence of delirium in these elderly patients^[35]. Higher degrees of postoperative pain are associated with an increased incidence of cognitive dysfunction^[36], so it would seem prudent that control of postoperative pain would decrease the incidence of post-

operative cognitive impairment. Therefore, the implication is that different analgesic modalities, which provide different postoperative analgesic levels (and varying side effects), may result in a varying incidence of postoperative cognitive influence or level of cognitive dysfunction. This implication is important for RA techniques because analgesic regimens of local anesthetics were shown to provide superior pain control over systemic opioids^[29] and also reduces systemic side effects of opioids that have been associated with the occurrence of POCD^[37].

Table 5 Cardiovascular changes associated with the aging process^[12]

Cardiac changes	Coronary artery disease due to atherosclerosis
	Changes in CNS innervations of the cardiovascular system: increase in sympathetic and decrease in parasympathetic activity
	Diminished response to beta-receptor stimulation
	Increase in apoptosis resulting in muscle mass loss, compensatory hyperplasia of remaining cells, abnormal cardiac function that can eventually lead to diastolic and systolic heart failure
Vascular system changes	Increase in microtubule component of cytoskeleton of cardiocytes results in contraction dysfunction
	Decreased blood flow due to increased cell adherence, micro-thrombogenic events, atherosclerosis
	Increased vasoconstriction and vascular wall stiffening
	Impaired endothelium integrity and ability to repair

CNS: Central nervous system.

In addition, epidural analgesia can reduce the incidence of postoperative pulmonary complications that have shown to be connected with an increased occurrence of POCD^[24,38,39].

Numerous trials examining intraoperative neuraxial anesthesia compared to GA has not determined preservation of postoperative cognitive function and there is no conclusive evidence that RA and analgesia are associated with a lower incidence of POCD. The problems in evaluating studies addressing issues of cognitive preservation in elderly surgical patients are due to multiple design flaws and methodological variability contained in the literature. Attempts at interpreting past and current evidence provides conflicting results and even in the hierarchy of evidence (meta-analysis of randomly controlled trials and large randomized trials), there is lack of data to demonstrate preservation of cognition beyond the first few hours after surgery when selecting RA^[40,41]. However, results from meta-analysis may demonstrate significant improvement in mortality when neuraxial blockade is used without GA^[42], but until POCD predictors and consequences are determined, it remains difficult to make recommendations for appropriate treatment and prevention of POCD.

Pharmacokinetic changes that accompany aging can explain some components of the analgesic drug response(s) seen in the elderly. Brain sensitivity to anesthetic and analgesic agents increases with age and is unique to each drug. The mechanism(s) that define altered brain pharmacodynamics to anesthetics and analgesics in the elderly are unclear at the present, although altered brain kinetics may provide direction. Age-related altered brain sensitivity may result from changes in receptors, signal transduction, and homeostatic mechanisms of the CNS. Aging is associated with decreases in cholinergic and dopaminergic neurons and receptors along with decreasing numbers of nervous system synapses. In addition, alterations of brain phospholipid chemistry associated with changes in second messengers, such as diacylglycerol, remain evident^[43].

CARDIOVASCULAR SYSTEM IN THE ELDERLY

RA/analgesia and cardiovascular system in the elderly.

A variety of morphologic, and functional changes occur

within the cardiovascular system with aging and are identified in Table 5. Aging processes on the heart and vascular systems have important clinical implications in the treatment of elderly surgical patients and considerations of postoperative pain management, especially those receiving RA. Currently, there is little evidence to suggest differences in cardiovascular outcome, morbidity and mortality using RA in the elderly^[44,45], although there have been studies showing a significant benefit and influence on short-term survival^[30,31,46,47]. There is little suggestion to indicate statistically significant differences in anesthetic technique toward incidence of death or major complications, but analysis does show positive influence on pain management and better cumulative results when considerations are provided for and depending upon the type of surgery being performed. For example, when epidural anesthesia and analgesia are combined with GA for elective abdominal aortic aneurysm repair, there is a shorter duration of postoperative intubation required, reduced time within and resources of the intensive care unit, lower incidence of death and major complications, better postoperative pain relief, and improved overall outcome^[47]. In addition, early placement of continuous epidural analgesia in elderly patients for hip fracture surgery versus a regimen of systemic opioids has been associated with a reduced incidence of adverse cardiac events^[30].

RA ramifications and cardiovascular morbidity and mortality

Recent meta-analysis of randomly controlled trials ($n = 9559$) showed that patients undergoing various orthopedic procedures and receiving neuraxial blockade had a one-third reduction in overall mortality^[39]. Another meta-analysis ($n = 2427$) found that patients who received epidural anesthesia and analgesia (with or without GA) had a reduced incidence of perioperative myocardial infarction and in those instances when a thoracic epidural was maintained for analgesia longer than 24 h, results showed significantly fewer postoperative myocardial infarctions^[31,46]. Yet another meta-analysis ($n = 68723$) on Medicare patients found an association of significantly lower odds ratio of death at 7 and 30 d when postoperative epidural analgesia was used^[32].

Perioperative stresses of life-style disruption, anesthesia, surgery, postoperative pain, and convalescence will activate (to varying degree) the sympathetic nervous

Table 6 Pulmonary changes and the elderly patient^[6]

Structural aging	Increase of lung parenchymal compliance due to degeneration of elastic fibers Loss of respiratory muscle mass resulting in less endurance and less respiratory reserve Increased alveolar permeability, which results in bronchial fluid with increased neutrophils and increased ratio of CD4/CD8 cells Decreased surface area for oxygen exchange
Functional aging	Chest wall rigidity Reduced maximum breathing capacity A greater in difference between alveolar and arterial oxygen concentration Increase in closing capacity Less effective coughing Impaired swallowing with high risk of aspiration pneumonia

system of elderly surgical patients with mixed and potentially negative imbalances between myocardial oxygen supply and demand predisposing patients to myocardial ischemia and infarction. Perioperative myocardial infarction and other deleterious cardiovascular events such as congestive heart failure, sudden death, and cardiac arrhythmias typically occur with increased frequency within the first few days following a surgical intervention^[48-50]. In addition, patients with a reduced cardiovascular reserve or patients at risk of perioperative myocardial events have a higher incidence of myocardial ischemia and infarction. Another important factor to consider in geriatric surgical candidate that can influence development of perioperative myocardial ischemia and infarction is the negative contribution from hypercoagulation during the surgical perioperative period^[48].

Thoracic epidural analgesia may attenuate adverse cardiovascular pathophysiological events (hyper-coagulation) because epidural analgesia has demonstrated an effect of decreasing cardiac sympathetic outflow yielding more favorable balance between myocardial supply and demand. Reduced cardiac sympathetic activity results in decreased inotropy, eases negative hemodynamic effects related to heart rate and blood pressure, mitigates myocardial oxygen consumption, and produces a favorable myocardial balance by improving coronary blood flow to the subendocardial areas of the myocardium at risk for ischemia^[51]. There currently remains uncertainty to statistically proven beneficial influence from RA on the incidence of myocardial ischemia, myocardial infarction or myocardial malignant arrhythmias. However, use of thoracic epidural analgesia (not lumbar) has revealed statically significant reduction in ventricular malignant arrhythmias and a decreased incidence of postoperative myocardial infarction^[46]. Therefore, physiologic benefits of RA in appropriate surgical settings can decrease adverse cardiovascular pathophysiological events such as myocardial infarction in the older surgical candidate.

PULMONARY SYSTEM IN THE ELDERLY

RA/analgesia and the respiratory system in the elderly

Significant perioperative risk among elderly patients can often be attributable to respiratory compromise and complications. A substantial portion of risk is explained by both functional and structural changes within the pul-

monary system commonly associated with aging (Table 6). In addition, pathology and iatrogenic conditions can further create respiratory risk during the perioperative period. Therefore, clinicians should titrate analgesic medications carefully and assess patients frequently for evidence of analgesic drug adverse side effects and adequate pain control. Epidural analgesic techniques may benefit elderly patients undergoing thoracic and upper abdominal surgery because these techniques allow quick restoration of respiratory function with added benefits of decreasing morbidity, hospital stay and health care costs^[49,52].

RA ramifications and pulmonary morbidity and mortality

Although RA is commonly used for older patients, many studies have shown that the anesthetic choice has no significant effect on perioperative morbidity and mortality within any age group. Intuitively it makes reasonable judgment that elderly patients may benefit from RA because they can remain minimally sedated (preservation of pulmonary function), airway manipulation is avoided, postoperative pain control is provided, and recovery from any adverse respiratory influences may be minimized or reducing by eliminating the use of inhalation anesthetics/GA. However, a multitude of factors influence perioperative outcome and these often make it difficult to decide upon the most appropriate anesthetic technique. Therefore, the decision to perform RA must be determined and assessed on a case-by-case basis considering patient's pulmonary function, health status, anesthesiologist expertise, along with type and duration of planned surgery along with both patient- and procedure-specific regional techniques if chosen.

Structure and functional changes of the lungs that occur with aging act to decrease pulmonary reserve^[53]. Aging effects on respiratory parameters have minimal influence in unstressed individuals, but functional changes become evident with stress. For instance, age-related decreased respiratory muscle strength becomes relevant under stresses of left ventricular failure or pneumonia. In addition, elderly patients are less able to adequately meet respiratory demands induced by hypoxia and hypercarbia, a greater decrease in arterial oxygen tension is needed to increase minute ventilation in older patients, and the elderly may not increase their minute ventilation under stress of illness or injury with the increased production of carbon dioxide^[54].

Functional residual capacity (FRC) reduction is associated with ventilation-perfusion (V/Q) mismatching, an increased alveolar-to-arterial oxygen gradient, and decreased efficiency of gas exchange. Further reductions in FRC are created by assuming the supine position and under influence of GA. GA can reduce FRC by 15%-20% and last 7-10 d following surgery^[55]. Older patients undergoing GA are predisposed to atelectasis from a combination of reduced FRC and age associated increases in closing volume. Vital capacity (VC) can be reduced after upper abdominal incisions (25%-50%) and postoperative pain along with use of systemic opioid analgesics, which can contribute to a reduction in tidal volume and impair clearing of secretions (altered cough mechanics).

Hypoxic pulmonary vasoconstriction (HPV) is affected and maybe abolished during inhalation anesthesia. Blunting of HPV in the elderly during GA causes a greater incidence of intraoperative V/Q mismatch and increased alveolar-to-arterial oxygen gradient. Elderly patients have an increased sensitivity to ventilatory depression from opioids, benzodiazepines and inhalation anesthetics because their responses to hypoxia and hypercarbia are impaired. GA has major effects on the pulmonary system since inhalation anesthesia depresses respiratory responses to hypoxia and hypercarbia and these patients commonly require airway manipulation due to a high propensity of obstruction because of respiratory muscle (thoracic) relaxation. These above influences can compromise usual protective responses of the pulmonary system during the perioperative period and are to be considered in elderly surgical candidates. Therefore, negative effects on pulmonary function predispose these older patients to atelectasis, increased risk of hypoxemia and pneumonia, V/Q mismatch, and other postoperative pulmonary challenges^[56].

With RA, airway manipulation can be avoided and respiratory parameters of lung tidal volume, respiratory rate, respiratory drive (effort), and end-tidal carbon dioxide concentration can be preserved. Unchanged FRC, from baseline, has been observed during spinal and lumbar epidural anesthesia. However, intercostal blocks, thoracic paravertebrals, cervical or high thoracic epidural blockade can be associated with lung volume reduction secondary to intercostal muscle relaxation. Therefore, choice of anesthesia may affect degree of pulmonary dysfunction in older individuals. Studies have shown that elderly patients undergoing lower extremity orthopedic procedures have fewer hypoxic events with epidural anesthesia (using local anesthetics) compared to systemic opioids; GA in older patients results in lower PaO₂ levels (on post-op day 1) compared to epidural anesthesia; and respiratory complications are less frequent with combined epidural plus GA compared to GA with postoperative intravenous morphine analgesia for pain management^[33,57].

RA and analgesia with local anesthetics for postoperative pain may provide a greater safety margin for elderly patients compared to systemic or epidural opioids. Using RA and analgesia (without opioids) in the elderly population, especially patients with severe pulmonary dysfunction,

may be more appropriate for postoperative pain relief^[44,58]. Oxygen saturation in elderly patients with RA and analgesia without an opioid is typically higher and use of systemic (and epidural) opioids results in a higher incidence of hypoxic events compared to RA and analgesia with local anesthetics alone^[59]. A reduced incidence of pulmonary infection, an increase in PaO₂, and an overall decrease in pulmonary complications is evident with epidural local anesthetics compared to systemic opioids for postoperative analgesia^[38]. However, meta-analysis has found reduced atelectasis from use of epidural opioids compared to systemic opioids (for postoperative analgesia) and that epidural local anesthetics (continuous) or local anesthetic-opioid mixtures result in reduced postoperative pulmonary morbidity following major abdominal and thoracic surgery versus systemic opioids^[4,60].

Another meta-analysis has shown that RA (especially epidural analgesia) may decrease pulmonary complications in hip fracture surgery since patients were found to have shortened intensive care unit stays and reduced intubation times versus patients receiving systemic postoperative opioids^[34]. A meta-analysis of 141 clinical trials showed a 39% reduction in pneumonia and 60% less pulmonary depression from thoracic epidural anesthesia and analgesia versus GA and postoperative patient controlled analgesia^[39]. Therefore, much of the controversy as to why several randomized trials have not demonstrated a consistent statistical advantage to RA in reducing respiratory complications in the elderly may be lack of differentiation and uniformity of epidural analgesic mixtures, whether or not an opioid or how much opioids (systemic and/or epidural) were used, site of surgery, timing and duration of RA and analgesia, and vertebral level of neuraxial blockade insertion.

ENDOCRINE AND IMMUNE SYSTEMS IN THE ELDERLY

RA/analgesia and endocrine/immune derangement in the elderly

Communicating capability of circulating immune cells and cytokines of the immune system serves as one of the body's major defense systems. There is a corresponding reduction and deterioration of the immune system as human beings age. Concurrently, there are reduced cellular and humoral responses seen throughout the entire immune system with aging. The thymus gland and thymulin secretions undergo an involutionary process and decreased production, respectively, as we age. Hormones responsible for mature T-cell modulation and progenitor phenotypic cell maturation processes are reduced and T lymphocyte number contribution into circulation is lessened with aging. Physiologic and immunological processes of aging result in minor clinically significant change of function and overall condition of older individuals within an unstressed state. Immunological changes with aging become evident when older patients become stressed and moved away from homeostatic states. Therefore, mea-

asures taken to ensure homeostasis and reduce stresses placed on surgical patients will help to preserve function of the immune system.

Regional anesthetic ramifications and endocrine/immune morbidity and mortality in the elderly

GA alone cannot prevent stress response initiation due to surgical trauma in elderly patients. Metabolic effects of surgical stress are hyperglycemia and overall catabolism. RA may provide and maintain the most analogous pre-surgical level of metabolism and physiology during anesthesia for surgery in the elderly and theoretically prevent or reduce surgical stress responses. For example, RA may minimize surgical stress by blocking sympathetic and somatic nervous systems from being activated. Epidural blockade reduces postoperative hyperglycemia and improves glucose tolerance despite plasma insulin concentrations being unchanged^[49]. More stable cardiovascular, hemodynamics and attenuation of stress responses to surgery have been demonstrated with RA^[61]. Metabolic effects of surgical stress, hyperglycemia and catabolism may predispose patients, especially elderly and critically ill patients, to increased morbidity (polyneuropathy, infection, multi-organ dysfunction/failure) and mortality. Plasma glucose normalization and improved glucose tolerance with RA and analgesia can improve perioperative management of optimal glucose control. RA and analgesia can reduce catabolic response to surgery and improve upon gastrointestinal rehabilitation, economy of proteins, and nutritional status of surgical patients, especially in abdominal surgery.

It has been shown that RA and analgesia can preserve humoral and cellular immune functions in surgical patients (especially for procedures below the umbilicus)^[62]. GA and lumbar epidural anesthesia have minor influences on human immune function in absence of surgery, but GA alone may worsen the immunosuppression response that can occur subsequent to surgery. However, RA and analgesia (with local anesthetics) may decrease the postoperative infectious complications from surgery^[63].

IMPLICATIONS OF RA ON AGE AND PATIENT OUTCOME

Patient age alone should not be considered a major risk factor or predictive of risks to undergo anesthesia and surgery. More important factors and better predictors for the elderly are overall physical status, medical history and disease state or condition along with consideration for type of surgery. Anesthetic complication rates increase very little with advancing age in absence of coexisting disease. Number and extent of any coexisting diseases and medical condition(s) are more directly related to elderly patient perioperative risk than does chronological age. Adverse medical conditions indicative of need for concern and predictive of higher surgical risk are diabetes

mellitus, hypertension and ischemic heart disease^[64]. In addition, type and surgical site of planned or emergency operations play an important role as a determinant of risk. Upper abdominal surgical procedures followed by thoracic and open-heart surgical procedures are associated with the highest morbidity and mortality and pose increased risk for elderly surgical patients. Therefore, geriatric patients may be at increased risk of perioperative morbidity and mortality from higher incidence of coexisting disease (4/5th of older patients have at least 1 complicating condition and 1/3 have 3 or more coexisting diseases), but additional issues of concern remain, including type, urgency and potential duration of surgery that serve as important predictors of patient outcome.

Postoperative pain management in the elderly, despite advanced pain management modalities, drug delivery systems and benefits of optimal analgesia, continues to be a problem. Patients and health care providers have become increasingly aware of inadequate postoperative pain relief and that a need exists to better implement current postoperative pain management treatment paradigms and for continued development of new pain management methods. Studies and surveys of surgical patients have reported varying degrees and intensities of pain following surgery and many reports of inadequate postoperative pain management, sometimes necessitating hospital readmission^[65,66].

RA and continuous analgesia delivery systems can provide targeted pain relief and may reduce dependence upon, or minimize amounts of, systemic opioids in the perioperative period. Therefore, optimal postoperative RA and analgesic effects (superior physiologic and analgesic benefits) on outcome may be improved when RA is placed in close proximity to the corresponding dermatome distribution of the surgical site^[4,37,46,67,68].

Choice of analgesic agents used with RA (local anesthetics with or without opioids and other adjuncts) will also influence patient outcome. Central-neuraxial opioids prove effective in controlling postoperative pain, but only epidural local anesthetics have shown ability to attenuate and influence adverse pathophysiological responses that can contribute to perioperative morbidity. Neuraxial local anesthetics are effective through prevention of spinal reflex inhibition of diaphragmatic and gastrointestinal function, suppression of responses to surgical stress, and through blockade of efferent and afferent nerve signals to and from the spinal cord. Epidural local analgesia used without neuraxial opioids may improve patient outcome as a result of a decreased incidence of respiratory complications and earlier recovery of gastrointestinal motility following abdominal surgery^[38,63]. Perioperative RA techniques in the elderly will influence and control perioperative pathophysiological events by (1) reducing neuroendocrine stress response; (2) improving effective pain control; (3) facilitating return of gastrointestinal function (earlier enteral feeding); and (4) earlier patient mobilization (plays an integral role in management of recuperating patients)^[69].

Perioperative RA as part of a multimodal pathway for convalescence of elderly surgical patients has resulted in improved patient outcome, amelioration of many negative pathophysiologic events, and improved analgesia as evidenced by the following studies: (1) Postoperative regional analgesia as part of a perioperative multimodal approach in patients undergoing abdominal-thoracic esophagectomy can result in a shorter time to patient extubation, earlier return of bowel function, superior analgesia, and earlier fulfillment of discharge criteria from an intensive care unit^[70]; (2) Patients participating in a perioperative multimodal pathway following major surgery had a decrease in metabolic and hormonal stress along with improvement in convalescence^[71]; and (3) Patients undergoing colon resection incorporating epidural analgesia and receiving a multimodal approach to surgical rehabilitation showed a decreased length of hospitalization from 6-10 d to a median of 2 d^[72]. Therefore, incorporating perioperative RA techniques and utilizing a multimodal anesthetic approach to surgical rehabilitation may aid in attenuation of pathophysiological surgical responses, reduce the length of hospitalization, and result in accelerated patient recovery for the elderly^[73].

CONCLUSION

To properly assess and consciously consider the many effects of aging, medication, therapy and treatment options in the elderly has resulted in a need for the Geriatric Patient Population to be subspecialized. Epidemiology data identifies the aging population as the most rapidly growing sector within the United States and larger numbers of elderly patients are presenting to the hospital, surgical centers and emergency rooms more frequently as older individual are staying healthier and more active (patients over 65 years are 3.5 times more likely to be operated upon than those under 65). Therefore, consideration of re-defining the roles of healthcare providers must be considered. Orthopedic injury and general surgery remain the most common reasons why the elderly present to the OR and ER. Goals of perioperative management and acute pain control for the elderly remains the same as for those under 65 years except it may often be more difficult as the elderly tend to under-report acute pain, many suffer from chronic pain, others often present with comorbidities, many are complicated due to polypharmacy, others can present with cognitive dysfunction, and several other possible physiologic changes can be associated with aging^[74,75]. Therefore, the issue becomes whether RA/analgesia in the elderly can provide optimal pain control, help to avoid/reduce negative effects of general anesthesia, prevent adverse reactions and avoid the many potential side effects from systemic opioid pain medications (nausea, vomiting, urinary retention, ileus, mental status changes, drowsiness, delirium, cognitive decline and depression).

There can be multiple detrimental effects of poorly controlled pain in the elderly. There is no consistent evi-

dence that regional “directly” improves patient outcome in the elderly, yet RA remains a well-accepted option to: reduce cognitive dysfunction (delirium), helps to minimize stress (tachycardia and hypertension), reduce intra- and post-operative opioids consumption, result in less pulmonary compromise (atelectasis, pneumonia, prolonged mechanical ventilation) and other positive predictors in a host of medical/surgical situations. RA can also offer enthusiastic patient cooperation with postoperative recovery (*e.g.*, physical therapy), superior pain control during dynamic activity^[2], early ambulation and provide for venous thrombosis prevention. In addition, regional can minimize opioid side effects and provide for a more “ideal” pain control environment.

With improved technological interventions and more non-opioid related alternatives to pain management, RA has entered into an era of precision and effective patient care^[76]. There is now the option to target anesthetic care and pain control both inside and outside the hospital and operating room environments. Whenever possible, RA should be considered as a major part of geriatric anesthesia due to its unique “local” acting properties. Since aging alone often results in multiple organ system dysfunction(s) and loss of functional reserve, healthy aging remains important for the elderly. Therefore, RA may provide for more than just optimal pain management, but could prove beneficial due to its many indirect effects in the perioperative environment (*e.g.*, help the elderly to reduce the incidence of muscle wasting with earlier and more robust postoperative physical therapy). So an ultimate solution and optimal goal would be to decrease complication rates in perioperative elderly patients, implement multidisciplinary interventions/actions (multimodal therapy), and practice patient- and surgery-specific RA toward achieving such an endeavor.

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Practical diastology

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Abstract

Left ventricular (LV) diastolic dysfunction is being recognized as an important part in the pre-operative evaluation. Pre-operative LV diastolic dysfunction has been associated with increased risk of post-operative complications. Furthermore guidelines have been published on the assessment of LV diastolic function. However LV diastolic function is significantly influenced by loading conditions which are typically altered during cardiac and non-cardiac surgery. In addition, waveform analysis from the pulmonary artery catheter tend to correlate with diastolic function and loading conditions. The advantage of hemodynamic monitoring being that they are continuously displayed as opposed to intermittent diastolic parameters. Finally if the importance of diastolic function assessment is to estimate filling pressure, the presence of B lines with the use of lung ultrasound is a simpler method in detecting pulmonary edema. Another indirect evidence of either LV systolic or diastolic dysfunction is an abnormal near-infrared spectroscopy value. Finally it might be more important to evaluate right ventricular (RV) diastolic dysfunction as RV dysfunction is significantly associated with pulmonary hypertension and consequently mortality. Such assessment of RV dia-

stolic dysfunction can be obtained continuously with the use of RV pressure waveform monitoring.

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Key words: Diastolic function; Left ventricle; Right ventricle; Lung ultrasound; Pressure waveform

Core tip: Diastology is mainly thought as the evaluation of left ventricular (LV) diastolic function. However evaluation of right ventricular (RV) diastolic function might be as relevant. Furthermore pressure waveform analysis are influenced by filling pressure and therefore might represent another method to continuously assess both LV and RV diastolic function. This is true particularly for RV pressure waveform analysis which correlate with RV diastolic function. Finally as the end-point of diastology is to provide information on cardiac function and filling pressure, the use of near-infrared spectroscopy and lung ultrasound might be the simplest way to evaluate the impact of diastolic dysfunction.

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IS IT IMPORTANT TO EVALUATE DIASTOLIC FUNCTION?

There have been several studies showing the importance of diastolic dysfunction in cardiology^[1] and in cardiac surgery^[2,3]. Most of these studies were limited to the evaluation of baseline left ventricular (LV) diastolic function. Patients were followed post-operatively or on a long term basis. These studies have shown a clear relationship between the presence and severity of LV diastolic dysfunction and their primary end-point which could have

been difficult separation from cardiopulmonary bypass (CPB)^[4,5] or survival^[2]. Baseline assessment of LV diastolic function is relevant because it can be used to stratify patients. In order to illustrate the importance of the pre-operative evaluation of diastolic function a study by Lee *et al*^[6] was published in 2012 in *Anesthesiology*. This was an observational study that included 1048 consecutive adults undergoing elective off-pump coronary artery bypass graft surgery in which the E/E_m (or E/e') was measured preoperatively. The E/E_m is the velocity ratio of the early (E) transmitral flow (TMF) using pulsed-wave (PW) Doppler divided by the early (E_m) mitral annular velocity using tissue Doppler. The primary outcome was occurrence of major adverse cardiac events (MACE), defined as a composite of death, myocardial infarction, malignant ventricular arrhythmia, cardiac dysfunction, or need for new revascularization. Using logistic regression and survival analyses, the authors found that an E/e' ratio more than 15 was independently associated with 30-d MACE (OR = 2.4, 95%CI: 1.4-3.9) and 1-year MACE (HR = 2.1, 95%CI: 1.4-3.1), irrespective of underlying LV ejection fraction. This study is important not only because it re-confirms the association between abnormal LV diastolic function and mortality but also because it stresses the incremental importance of also evaluating LV diastolic function. But can we apply these concepts in the operating room (OR) and the intensive care unit (ICU)?

CAN WE MONITOR DIASTOLIC FUNCTION INTRAOPERATIVELY OR IN THE INTENSIVE CARE UNIT?

It is possible to evaluate LV diastolic function in both the OR and the ICU. In the majority of cases, the evaluation will be obtained following the induction of general anesthesia using transesophageal echocardiography (TEE). However there are numerous pitfalls. One of them is the effect of anesthesia on diastolic function. In a study of 50 patients with pre-operative LV diastolic function, Couture *et al*^[7] compared the transthoracic echocardiographic (TTE) examination obtained before induction of anesthesia to the TEE exam after. Both bi-atrial and bi-ventricular dimensions and diastolic function were analyzed. Following induction of anesthesia, the heart rate decreased, while the mean arterial pressure remained unchanged. There were significant changes in bi-atrial diameter. Opposite changes in LV and right ventricular (RV) dimensions were observed. Reduction in RV systolic function but no changes in LV systolic function was also documented. Most Doppler velocities decreased. In 42% of patients, improvement in LV diastolic function was observed. Therefore when evaluating diastolic function in the OR and in the ICU, it is important to realize that it may not correspond to the pre-operative awake state.

In addition in order to monitor a signal, ideally it has to be continuous. This is not the case for our cur-

rent method of evaluating diastolic function. The word monitoring comes from the Latin “monere” which means warning. For instance, several studies have shown that diastolic function is one of the earliest sign of myocardial ischemia^[8]. Abnormal diastolic function could precede electrocardiographic changes however it would be very difficult to monitor continuously diastolic function in the OR and the ICU. Which parameters should be monitored? The information is also displayed in a different screen on the TEE monitor which can be close or away from the more vital hemodynamic data. In addition, several factors could alter Doppler velocities such as surgical manipulation, bleeding, hemodynamic derangements, *etc.* This would make any diastolic indices very sensitive but poorly specific in the diagnosis of intraoperative myocardial ischemia for instance. How do we evaluate diastolic function and are there other non-echo based monitoring alternatives that could indicate abnormal diastolic function?

ECHOCARDIOGRAPHIC AND NON-ECHOCARDIOGRAPHIC BEDSIDE INDICES OF DIASTOLIC FUNCTION

Several guidelines on the evaluation of LV diastolic function have been published^[9-11]. A review article by Matyal *et al*^[12] in *Anesthesia Analgesia* 2011 gives an excellent overview of the subject. Echocardiographically, LV diastolic dysfunction has been classified as mild (impaired LV relaxation), moderate (pseudonormal pattern), and severe (LV restrictive filling). In addition, LV diastolic function evaluation allows the estimation of LV filling pressures. Algorithms used in the presence or the absence of LV systolic dysfunction have been proposed^[12]. We use a combination of Doppler-derived variables in the diagnosis of LV diastolic dysfunction (Figure 1)^[10] and we have developed a diagnostic algorithm which has been validated (Figure 2)^[5]. The major advantage of TEE compared to TTE in the evaluation of diastolic function is the availability in the majority of patients of an adequate pulmonary venous flow (PVF) signal.

Diastolic dysfunction alters the pressure-volume relationship and could explain some of the observed changes between filling pressure and ventricular volume observed after CPB. Impaired or delayed relaxation (mild diastolic dysfunction) results in decreased LV pressure decay during diastole and prolonged isovolumic relaxation time (IVRT). This will be reflected with higher diastolic filling pressure for the same LV volume. Echocardiographic evaluation of abnormal relaxation using PW Doppler interrogation of the mitral valve or TMF will demonstrate prolonged IVRT, prolonged E-wave deceleration time, and a reduction of the E/A ratio. The PVF PW Doppler signal will show an increased S/D ratio. Tissue Doppler of the mitral annulus will demonstrate an E_m/A_m ratio < 1 while on color M-mode, propagation velocity (V_p) will be decreased. The delayed relaxation abnormality is the most common form of diastolic dysfunction (64% in our

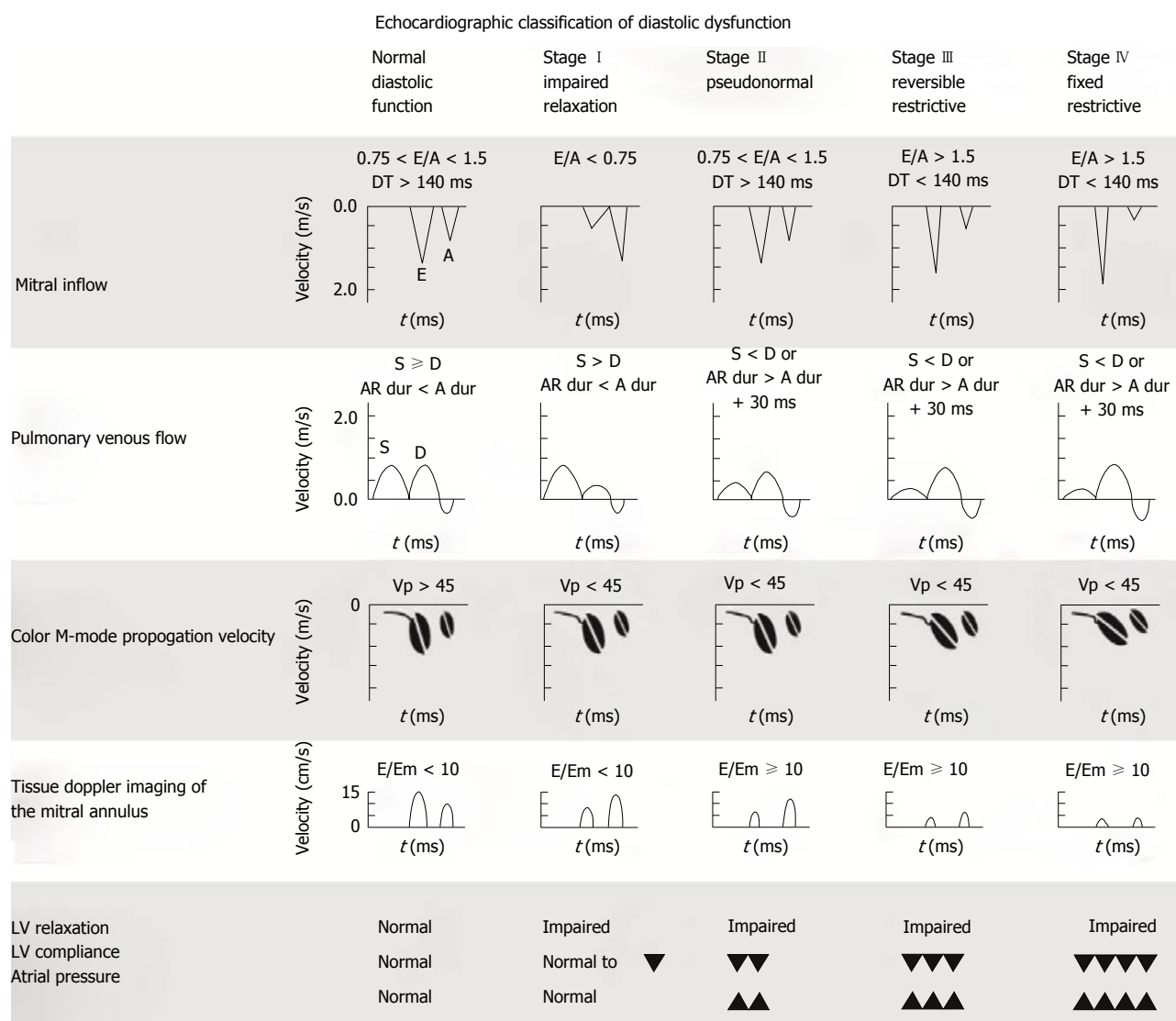


Figure 1 Diastolic function classification. Echocardiographic classification of diastolic dysfunction adapted for transesophageal echocardiography is shown. A: Peak late diastolic transmitral flow velocity; A dur: Duration of mitral inflow A-wave; AR dur: Peak pulmonary venous atrial reversal flow velocity duration; D: Peak diastolic pulmonary venous flow velocity; DT: Deceleration time; E: Peak early diastolic transmitral flow velocity; Em: Peak early diastolic myocardial velocity; LV: Left ventricle; S: Peak systolic pulmonary venous flow velocity; Vp: Flow propagation velocity. With permission of Informa Healthcare adapt from reference^[36].

practice)^[5]. It is commonly associated with LV hypertrophy either due to hypertension or aortic stenosis.

In patients with relaxation abnormalities and increased filling pressure, a moderate or intermediate form of diastolic dysfunction called the pseudonormal pattern is seen. The expression “pseudonormal” is a consequence of the normal looking PW Doppler mitral inflow signal while the PVF pattern is clearly abnormal ($S/D < 1$). With a pseudonormal pattern, the pressure-volume diagram will demonstrate moderate upward elevation of the diastolic waveform. Echocardiographically, it is characterized by reduced IVRT, a pseudonormal E/A ratio and deceleration time, PVF with inverted S/D ratio < 1 and atrial reversal wave velocity exceeding 40 cm/s, abnormal tissue Doppler of the mitral annulus with a reduced E_m/A_m ratio and reduced color M-mode V_p .

Left ventricular restrictive filling abnormality represents a more severe degree of diastolic dysfunction. This is associated with an upward shift of the diastolic

pressure-volume curve. In these patients the following echocardiographic findings are observed: PW Doppler of the mitral inflow reveals shortened IVRT and E-wave deceleration time, a high E/A ratio > 2 ; PW Doppler interrogation of the PVF shows predominant diastolic flow, while tissue Doppler imaging of the mitral annulus demonstrates reduced E_m velocity and decreased color M-mode propagation velocity. This type of abnormality is commonly seen in hemodynamically unstable patients before or after cardiac surgery.

There are however several other elements that are important to assess in order to evaluate LV diastolic function. The patient has to be in sinus rhythm. The heart rate has to be normal because tachycardia by itself can impede filling. The use of a pacemaker will alter filling patterns particularly if only the ventricle is paced. The hemodynamic conditions have to be stable otherwise the Doppler parameters will vary significantly. Finally pericardial disease and RV dysfunction have to be ruled-out. These ele-

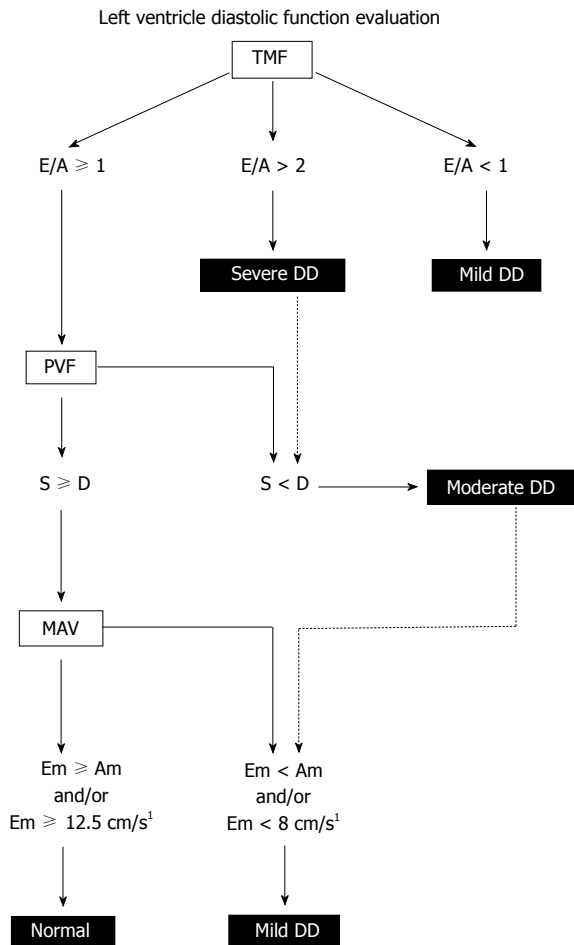


Figure 2 Left ventricle diastolic dysfunction algorithm. LV diastolic function is classified using pulsed wave Doppler of the TMF, PVF and tissue Doppler examination of MAV. Patients with a pacemaker, atrial fibrillation, non-sinus rhythm, mitral stenosis, severe mitral and aortic regurgitation are excluded from analysis. ¹Normal Em is within an 8-12.5 cm/s interval. A: Peak late diastolic TMF velocity; Am: Peak late diastolic MAV; D: Peak diastolic PVF velocity; DD: Diastolic dysfunction; E: Peak early diastolic TMF velocity; Em: Peak early diastolic MAV; LV: Left ventricle; MAV: Mitral annular velocity; PVF: Pulmonary venous flow; S: Peak systolic PVF velocity; TMF: Transmitral flow. With permission of Informa Healthcare adapt from reference^[36].

ments can significantly influence LV diastolic parameters.

Other non-echocardiographic parameters can also be present in the presence of LV diastolic dysfunction. Filling pressures will be typically proportional to the severity of diastolic function. In a study where we evaluated LV diastolic function of 179 consecutive patients we observed that patients with pseudonormal and restrictive patterns had higher pulmonary capillary wedge pressure (PCWP) than those with normal or mild diastolic function^[5]. Restrictive diastolic dysfunction is encountered in less than 5% of our patients undergoing cardiac surgery. In these patients pulmonary hypertension is typically present with “v” waves that are not associated with significant mitral regurgitation (Figure 3). In patients with normal or mild diastolic dysfunction, no predominant “v” waves will be present. Often an “a” wave will be seen on the PCWP tracing.

There are two other markers of diastolic dysfunction that we are currently using. One is the presence of B lines

that can be obtained with the use of lung ultrasound^[13]. The other is related to the use of near-infrared spectroscopy or NIRS^[14]. Discussion on the use of lung ultrasound is beyond the scope of this article but reviews can be consulted^[13,15,16]. The presence of B lines or the so-called comet tail artifact are associated with alveolar-interstitial syndrome. They are typically present in pulmonary edema however the origin of pulmonary edema can be cardiogenic or non-cardiogenic. A paper by Frassi *et al*^[17] in 340 patients has shown a linear relationship between the severity of diastolic function and the number of B lines on lung examination. Another indirect indicator suggestive of abnormal diastolic function can be obtained using near-infrared spectroscopy (NIRS). In a study by Heringlake *et al*^[18] published in *Anesthesiology* in 2011, 1178 patients undergoing cardiac surgery were evaluated pre-operatively in order to obtain baseline NIRS values. The authors observed that patients with NIRS values below 50% have increased risk of one-year mortality. The NIRS values correlated directly with ejection fraction but inversely with the N-terminal pro-B-type natriuretic peptide which is elevated typically in either systolic or diastolic dysfunction. In that regard, Paquet *et al*^[19] completed a study in 2008 in 99 cardiac surgical patients comparing NIRS with the TEE examination. Patients with moderate and severe form of diastolic function had lower NIRS values than those with normal or mild forms^[19]. This suggests that abnormal diastolic function was associated with reduced cardiac output and consequently reduced cerebral perfusion and NIRS values.

IS LEFT MORE IMPORTANT THAN RIGHT VENTRICULAR DIASTOLIC FUNCTION EVALUATION?

There has been much more literature and interest in LV than RV diastolic function however the interest in RV systolic and diastolic function is growing^[20-22]. In 2010 guidelines for the evaluation of RV function were published by Rudski *et al*^[23]. In that article, some parameters were proposed to evaluate RV diastolic function. We have been interested in RV diastolic function for the last 10 years since our first publication in 2002 on unstable patients in the ICU^[24] and in 2005 on the significance of abnormal hepatic venous flow (HVF) before cardiac surgery^[25]. In order to study RV diastolic function, an algorithm was developed (Figure 4) and validated^[5]. In several of our studies, we observed that hemodynamically unstable patients commonly had abnormal RV filling abnormalities^[24]. Initially we were able to attribute the abnormal HVF as a consequence of pulmonary hypertension^[25]. However as we gain more experience in the evaluation of RV function, we observed that the use of RV myocardial performance index which is a dual indicator of RV systolic and diastolic function, was the best predictor of post-operative cardiac failure and mortality in patients undergoing cardiac surgery^[26]. Indeed, pulmonary hypertension became non-significant when RV

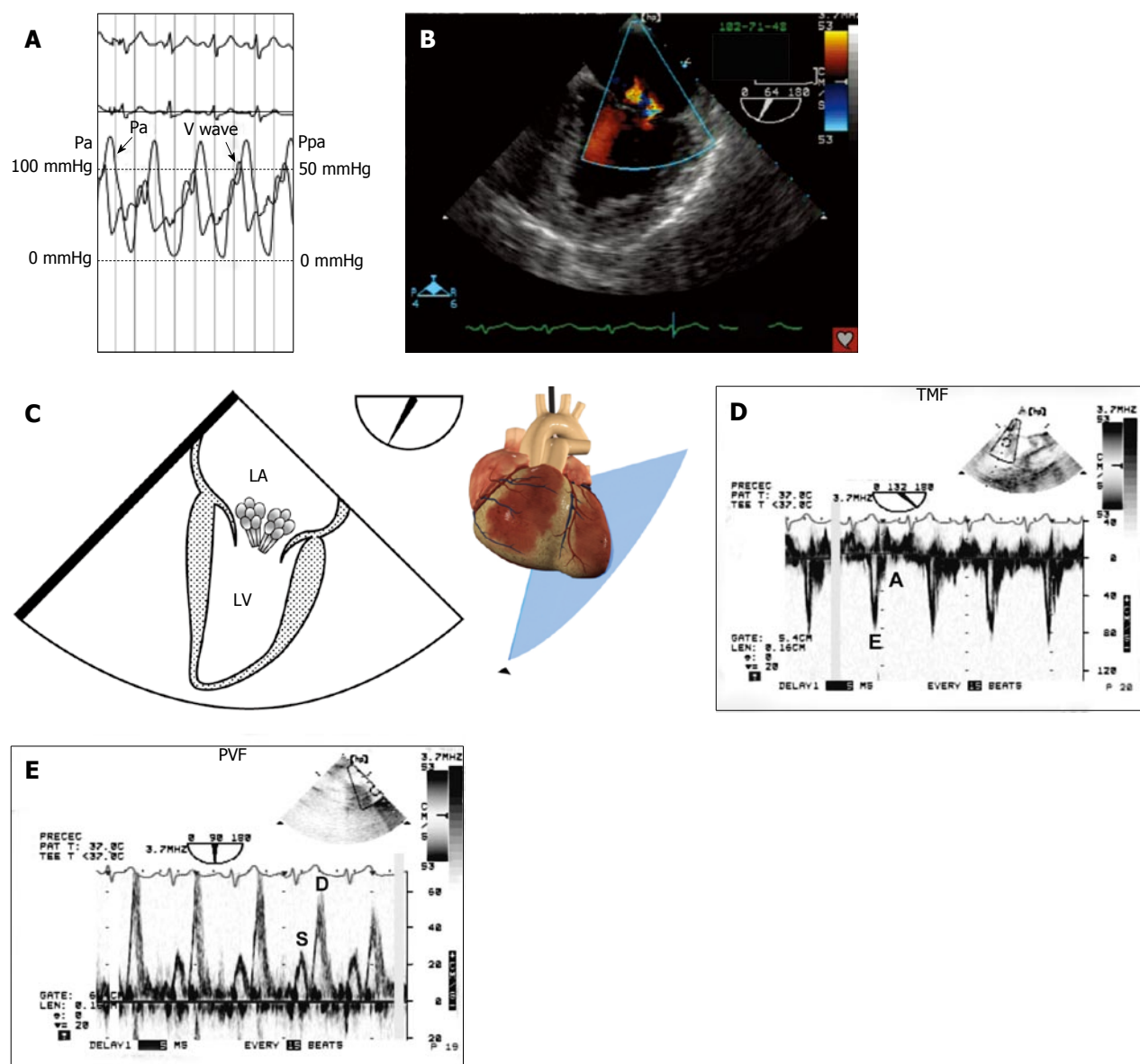


Figure 3 Stage III left ventricle diastolic dysfunction (restrictive filling). A 61-year-old woman with cardiogenic shock is brought to the operating room for emergency coronary revascularization. A: She was hemodynamically unstable on an intra-aortic balloon pump and vasoactive support; B and C: A 50 mmHg "V" wave on the wedged pulmonary artery catheter tracing was seen without any significant mitral regurgitation on color flow imaging; D: TMF showed an E/A ratio > 2 with a deceleration time < 60 ms and isovolumic relaxation time of 40 ms; E: The left upper PVF showed an abnormal S/D ratio with S wave blunting; A: Peak late diastolic TMF velocity; D: Peak diastolic PVF velocity; E: Peak early diastolic TMF velocity. LA: Left atrium; LV: Left ventricle; Pa: Arterial pressure; Ppa: Pulmonary arterial pressure; PVF: Pulmonary venous flow; S: Peak systolic PVF velocity; TMF: Transmittal flow. With permission of Informa Healthcare adapt from reference^[36].

function parameters were considered. Therefore as more severe form of LV diastolic dysfunction are associated with pulmonary hypertension, only those associated with impairment of RV function were associated with poor outcome.

In 2006 we reported the use of RV pressure monitoring in the diagnosis of RV outflow tract obstruction (RVOTO) in 800 consecutive patients^[27]. Following this study, we started to routinely monitor RV pressure waveform^[28-32]. This method was described several years ago in the diagnosis of RV ischemia^[33,34] but not as a continuous monitoring modality. Our group has been using continuous RV pressure waveform monitoring in order to detect changes in RV function during cardiac surgery.

The diagnosis of RV systolic dysfunction, diastolic dysfunction and RVOTO can be obtained instantaneously, in a dynamic fashion, using a pulmonary artery (PA) catheter and continuously transducing the RV port (Paceport, Edwards Lifescience, Irvine, CA)^[27]. The normal RV diastolic slope is typically horizontal due to the normal RV compliance, which is much higher than LV compliance^[22]. When RV pressure is combined with PA pressure monitoring, there should also be no significant differences between the peak systolic PA pressure and the systolic RV pressure (Figure 5).

In RV dysfunction, a progressive change from a horizontal to an oblique diastolic slope will be observed (Figure 5). As RV function deteriorates, it will change to

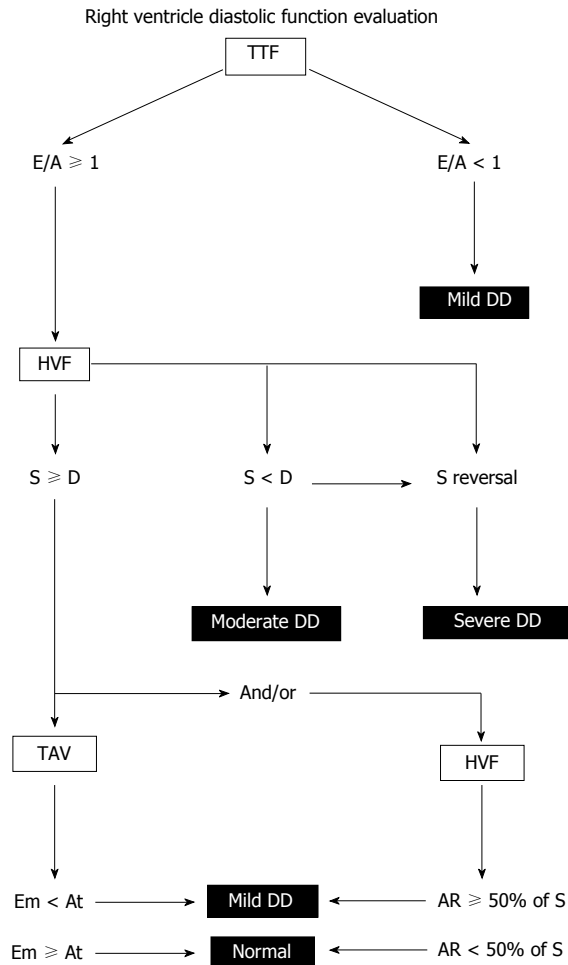


Figure 4 Right ventricle diastolic dysfunction algorithm. Diastolic function is classified by pulsed wave Doppler of the TTF, HVF and tissue Doppler imaging of the TAV. Patients with a pacemaker, atrial fibrillation, non-sinus rhythm, moderate to severe tricuspid regurgitation and tricuspid annuloplasty are excluded from analysis. A: Peak late diastolic TTF velocity; AR: Peak atrial reversal HVF velocity; At: Peak late diastolic TAV; DD: Diastolic dysfunction; D: Peak diastolic HVF velocity; E: Peak early diastolic TTF velocity; Et: Peak early diastolic TAV; HVF: Hepatic venous flow; RV: Right ventricle; S: Peak systolic HVF velocity; TAV: Tricuspid annular velocity; TTF: Transtricuspid flow. With permission of Informa Healthcare adapt from reference^[36].

a square root slope and then equalisation of the RV to PA diastolic pressure. This will correlate with changes in HVF or RV diastolic function. With severe RV systolic dysfunction delayed systolic upstroke (or RV pulsus tardus) and reduction in RV pulse pressure will be observed. As mentioned previously, another useful diagnosis that can be instantaneously made with RV pressure waveform monitoring is RVOTO. This is readily seen whenever the RV systolic pressure is 6 mmHg or more above the PA systolic pressure. The mechanism of RVOTO can be dynamic or mechanical. Dynamic RVOTO with gradients above 25 mmHg are observed in 4% of patients undergoing cardiac surgery and they are associated with hemodynamic instability^[27]. In this situation (which is analogous to dynamic LV outflow tract obstruction associated with systolic anterior motion of the mitral valve), inotropic agents would be contra-indicated however volume and beta-blocking agents can be used if the RVOTO is non-

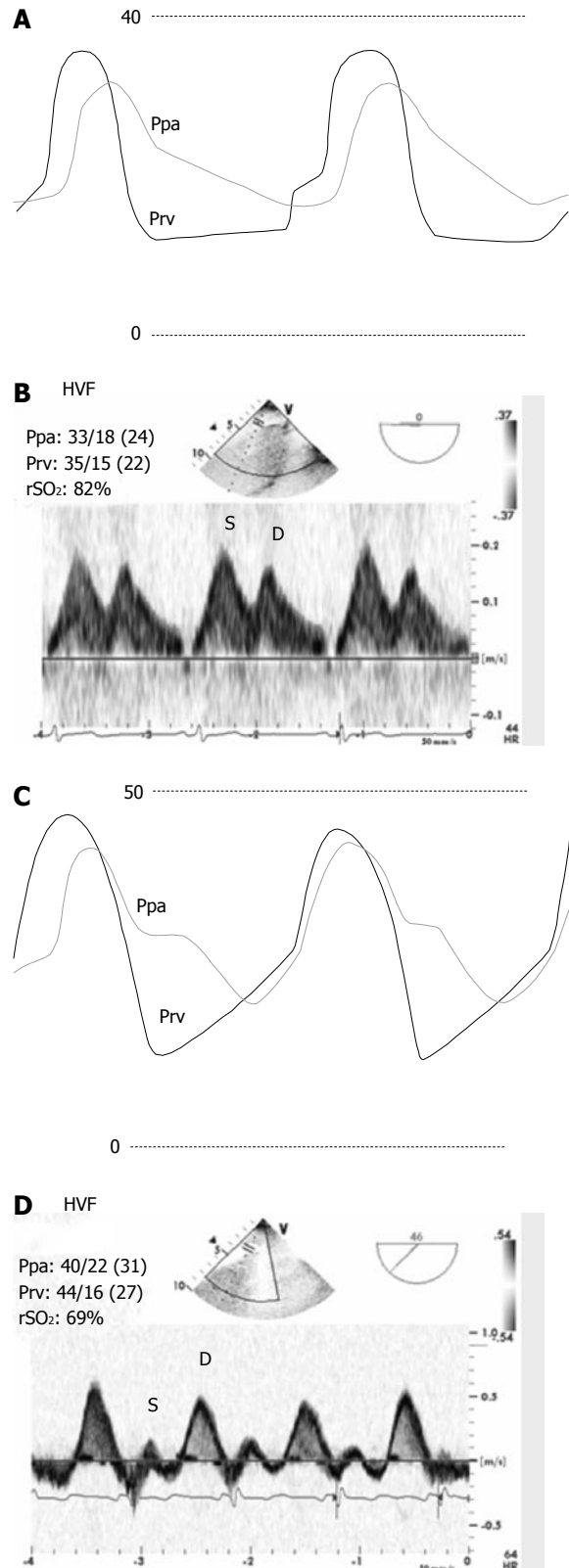


Figure 5 Zoomed right ventricular pressure and pulmonary artery pressure with their corresponding Doppler hepatic venous flow before (A, B) and after cardiopulmonary bypass. Note the change in the diastolic slope of the right ventricular pressure (Prv) waveform and the corresponding change in the systolic (S) to diastolic (D) ratio of the hepatic venous flow. After cardiopulmonary bypass, the regional oxygen saturation of the brain (rSO₂) was lower, but still within normal limits (60% ± 5%). With permission from Wolters Kluwer Health, Lippincott Williams and Wilkins adapt from reference^[44]. HVF: Hepatic venous flow; Ppa: Pulmonary artery pressure.

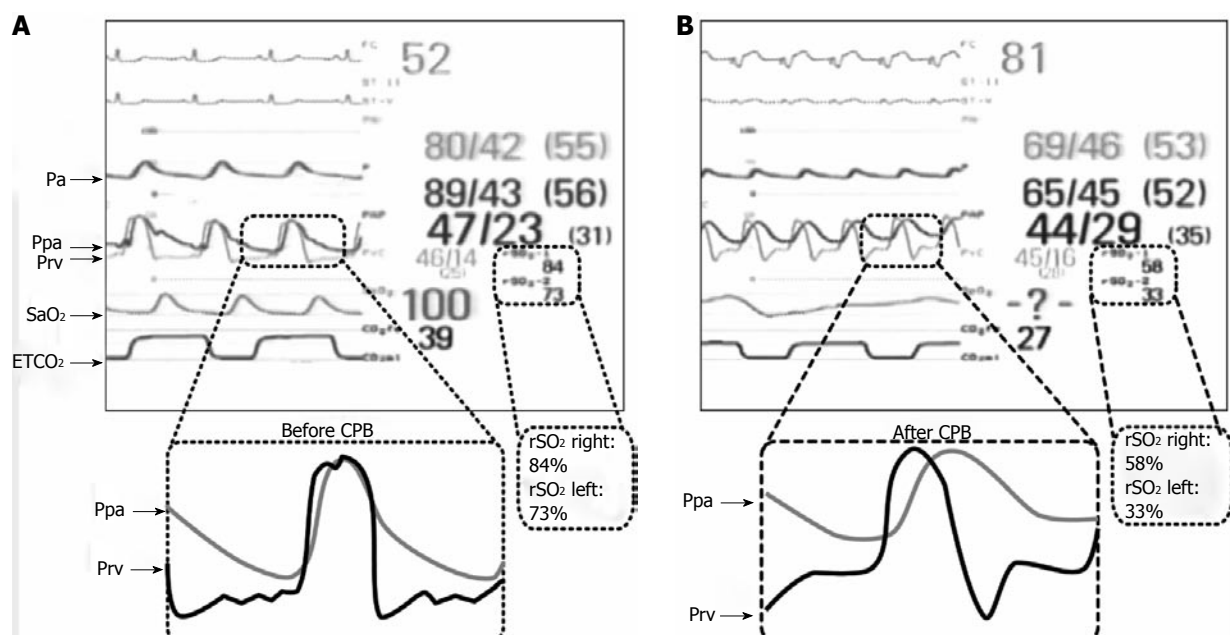


Figure 6 Hemodynamic waveforms combined with regional near infrared spectroscopy values obtained before (A) and after cardiopulmonary bypass (B). The upper near infrared spectroscopy (NIRS) value was obtained from the right lower extremity and the lower NIRS value is from the brain. Note that after cardiopulmonary bypass (CPB), both values were reduced significantly. This was associated with failure to wean from CPB and significant hemodynamic instability. The etiology was a result of acute right ventricular (RV) failure, demonstrated on the right ventricular pressure (Prv) waveform. Note the change Prv from a normal shape before CPB to a square root sign, with diastolic equalisation after CPB. Note also that the pulmonary artery pressure (Ppa) systolic values were lower after CPB and non diagnostic of acute RV failure. The right atrial pressure was 16 mmHg compared to 14 mmHg before CPB. ETCO₂: End-tidal carbon dioxide; Paf: Femoral arterial pressure; Par: Radial arterial pressure; SaO₂: Oxygen saturation. With permission from Wolters Kluwer Health, Lippincott Williams and Wilkins adapt from reference^[44].

mechanical. In the OR, we simultaneously display both the PA and the RV pressure waveform throughout surgery. This technique may be the fastest and easiest way to diagnose hemodynamic instability resulting from RV systolic or diastolic dysfunction or RVOTO. However, when RV dysfunction is suspected, both cardiac and pulmonary echocardiography will be instrumental in determining the etiology and consequences. With RV dysfunction, NIRS values will remain normal (Figure 5). However with RV failure, both abnormal diastolic slope and reduced NIRS values will be observed (Figure 6).

HOW WE APPROACH IT IN THE OPERATING ROOM AND IN THE INTENSIVE CARE UNIT

In the OR and in the ICU, the approach to diastolic function evaluation will be different if the exam is performed in an elective fashion or during an emergency situation. After the induction of anesthesia, in elective cases, as part of our cardiac examination, we will routinely include the evaluation of both LV and RV diastolic function. RV diastolic function using pressure waveform will also be displayed continuously. As we work in a teaching hospital, the components of the evaluation of diastolic function has to be transmitted to trainees especially if they are considering taking the National Board of Echocardiography Perioperative TEE examination. When we perform TEE examination, I will insist that the hemodynamic conditions, the end-tidal carbon dioxide (ETCO₂) (as it

correlates with cardiac output^[35]) and minute ventilation, the NIRS values and the drugs used at that precise moment be noted beside the echocardiographic images. This information allows us to better interpret the TEE images for systolic, diastolic and valvular assessment. In a critical situation, the TTE or TEE exam will be focused^[36,37]. If there are no elevated PA pressure, normal RV diastolic waveform, no B lines, normal oxygen saturation and the size of both left and right atria is normal, diastolic function is unlikely to be significantly abnormal. In that situation both NIRS values and ETCO₂ will be used to evaluate continuously the effect of the interventions.

HOW TO TREAT DIASTOLIC FUNCTION?

In the most recent guidelines on diastolic function^[12], very little information is provided on the treatment of diastolic function. In fact diastolic function is often a result of an underlying process whether ischemic or not. There are however some situations in which information on the severity of diastolic function can help the clinician in managing an unstable patient in the OR and ICU. Fluid responsiveness for instance tends to be more important in patients with normal or mild diastolic function^[38]. If ischemia is associated with diastolic dysfunction, resolution of ischemia will be associated with improvement of diastolic parameters^[39]. Agents such as milrinone have been proposed to improve lusitropy^[40] however we could not confirm this finding in patients with pre-op LV diastolic function^[41]. Interestingly, when LV diastolic function is secondary to RV systolic dysfunction, im-

provement in the latter can lead to resolution of the LV diastolic abnormalities^[42].

CONCLUSION

In summary, the evaluation of both LV and RV diastolic function are important to appreciate. Their prognostic significance is well demonstrated. The endpoint however in dealing with an hypoxic or unstable patients it to maintain adequate oxygen transport. Oxygen transport is the product of arterial oxygen content and cardiac output^[43]. Abnormal diastolic function with elevated filling pressure can alter both of these components. Abnormal oxygenation though elevated filling pressure can be easily diagnosed using bedside lung ultrasound and detecting B lines. Detection of B lines is easier than measuring the E/E_m ratio. If B lines are present, then LV diastolic function evaluation might be relevant in order to determine the cardiogenic or non-cardiogenic nature of pulmonary edema. In the presence of reduced cardiac output, LV diastolic function evaluation might not be as relevant as RV systolic and diastolic function evaluation. The latter can be assessed continuously using RV pressure waveform and the efficacy of the treatment confirmed non-invasively using ETCO₂ and NIRS.

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Lung preconditioning in anesthesia: Review of the literature

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Abstract

Lung injury can arise during or after anesthesia and can lead to a complicated postoperative course with great implications for the patient. Unfortunately, treatment of acute lung injury is at the moment mainly supportive and rates of recovery have not really improved in the recent years. In many cases, lung injury can be anticipated and preventive measures seem possible. This represents a unique challenge to the anesthesiologist, as some new opportunities to reduce the frequency and/or severity of lung injury seem now available. These chances may arise from the potency of preconditioning the lungs before the main injury, with smaller injurious insults. Although preconditioning began to be applied first on the myocardium, experimental studies have shown potentially beneficial results also for the lungs. This review summarizes the main methods of lung preconditioning that have been tried in experimental studies in the literature and the main mechanisms that are perhaps involved. Emphasis is given in the two main methods of preconditioning that seem readily applicable in the clinical praxis, that is ischemic preconditioning, as well as preconditioning with volatile anesthetics. The few, but interesting clinical studies are also summarized and the future research points in this evolving field of anesthesia are stressed.

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Key words: Preconditioning; Ischemic preconditioning; Lung injury; Anesthesia; Volatile anesthetics

Core tip: Currently, the efficacy of lung preconditioning is tested in various experimental studies. The first clinical studies regarding remote ischemic preconditioning have appeared, with conflicting results. This review summarizes the scientific knowledge on this arising research field.

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INTRODUCTION

Acute lung injury (ALI) is diagnosed based on simplified criteria, published in 1994, in a consensus conference: arterial hypoxemia with partial pressure of oxygen to inspired fraction of oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio less than 300 mmHg and less than 200 mmHg to define ALI and acute respiratory distress syndrome (ARDS), respectively, and bilateral radiographic opacities without evidence of left atrial hypertension^[1]. Additionally, some investigators believe that the definitions should specify the level of positive end-expiratory pressure and/or the fraction of inspired oxygen. A recent report - what is now called the Berlin definition - recommends use of three categories of ARDS, based on the degree of hypoxemia: mild ($200 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg}$), moderate ($100 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mmHg}$), and severe ($\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mmHg}$)^[2]. Lung injury and ARDS still carry a high mortality and recent therapeutic efforts have been proved mainly unsuccessful^[3-5].

Preconditioning (PC) was first used as ischemic PC, whereby brief periods of ischemia of myocardium exert a protection against subsequent, more prolonged periods of ischemia^[6,7]. Although PC was first used for the myo-

cardium, it was later applied also to other tissues, such as the lungs^[8]. PC has been achieved not only through ischemia, but also through hypoxemia^[9], catecholamines^[10], pharmaceutical interventions and volatile anesthetics^[7,11]. From the above it is obviously important that in order to apply PC, one should foresee the upcoming injury, as for example in types of surgery that frequently lead to lung injury. On the other hand, a sudden bleeding and ALI resulting from the hemorrhagic shock, is not a scenario appropriate for such a preparation.

LITERATURE RESEARCH

The Medline database of the National Library of Medicine was used to conduct a search of the literature. Keywords used were “lung preconditioning”, “lung preconditioning AND anesthesia” (with and without filter for human studies), “preconditioning AND volatile anesthetics” and “lung ischemic preconditioning” for the years from 1990 until today. Only articles written in the English language were included. From the literature search, a total of 25 articles referring strictly to lung preconditioning were retrieved and from those 5 were conducted on humans.

ANTICIPATED LUNG INJURY DURING ANESTHESIA

During or after anesthesia, ALI can arise under variable circumstances. Some of these may be directly linked to anesthetic interventions itself, such as aspiration of gastric contents, whereas others derive from the surgical intervention, such as aortic cross-clamping^[12,13]. Lung injury can be precipitated by embolic events during orthopaedic surgery, by inflammation and oxidative stress or due to inflammation after aortic surgery^[14-17]. Lung injury can also arise due to a pre-existing illness that has lead the patient to the surgical procedure, such as sepsis, or may arise in the postoperative period as a result of shock^[18,19].

In some instances, such as after thoracic procedures like major pulmonary resection, lung injury is relatively common and can be expected in up to 7% of cases^[20-23]. Sen *et al*^[20] reported ARDS after lung resections in 7.5% of cases with a mortality of 18.8%. In this study, alcohol abuse, fresh frozen plasma use, pneumonectomy and American Society of Anesthesiologists class of patients were significant predictors for development of ARDS postoperatively. In another study^[24], high intraoperative ventilatory pressure, excessive fluid administration, pneumonectomy and preoperative alcohol abuse were found as independent risk factors for primary ALI after lung resection surgery.

Another major entity whose prevalence and significance has received a more appropriate attention in recent years is the transfusion-related acute lung injury (TRALI)^[25]. Criteria for the diagnosis of TRALI have been also introduced, and although a “two hit” model has been proposed, suggesting the significance of the activation of neutrophils and endothelium^[26,27], the pathogenesis re-

mains unclear. Specific therapeutic measures do not exist, and preventive measures that were early introduced such as the use of plasma components of mainly male donors have been criticised, leaving great questionmarks in the prevention of TRALI^[28-30].

Lung injury after cardiac surgery is common and multifactorial and a significant risk factor is considered the transfusion of blood products. However, lung protection strategies have not been always successful^[31,32]. Specifically, remote ischemia of the lower limb was found to have a protective effect on airway resistance in children undergoing heart surgery^[33], but a subsequent larger study showed no effect of remote ischemic preconditioning on PaO₂/FiO₂ ratios or time to extubation after cardiac surgery^[34]. Interestingly, in a recent prospective study it was shown that the major determinant of lung injury after cardiac surgery is not the extracorporeal circulation (heart-lung machine), but atelectasis^[35]. Unfortunately, the study included a very limited number of patients to make any definitive conclusions. Importantly, an analysis of 4366 patients identified high risk cardiac, vascular or thoracic procedures, diabetes mellitus, chronic obstructive pulmonary disease, gastroesophageal reflux disease and alcohol abuse as important predictors for postoperative ALI^[36]. Lobectomy, multilobectomy, pneumonectomy, esophagectomy and lung decortication were considered as high-risk thoracic procedures; whereas high-risk cardiac procedures included coronary artery bypass surgery, valve replacement or multiple valve repair, pericardial resection, aortic arch repair, cardiac transplantation, congenital heart repair and cardiac reoperations. It seems that diseases associated with immunosuppression, such as diabetes mellitus and alcohol abuse, may play an important role in the development of ALI postoperatively.

Lung injury after lung transplantation represents another entity of predictable postoperative lung injury. During lung transplantation, ischemia-reperfusion (IR), one-lung ventilation and inflammation combine and create the appropriate circumstances for the development of ALI, which endangers the viability of the lung transplant^[37]. Postoperative ALI is perhaps the most significant factor for early postoperative mortality after lung transplantation^[38]. The IR injury during lung transplantation takes the form of the primary graft dysfunction, characterized by inflammation and lung fluid dysregulation^[39].

VARIETIES OF LUNG PRECONDITIONING

Ischemic preconditioning

Ischemic PC has been tried successfully in a model of lung transplantation in rats, in which 5 min of ischemia and 10 min of reperfusion were applied before the lung was transplanted^[40]. The researchers found a significant improvement in gas exchange in the transplanted lungs 12 h after transplantation, along with a reduction in thio-barbituric acid reactive species. This was one of the first findings that ischemic PC can attenuate primary graft dysfunction, which is the most significant reason of early

mortality and morbidity after lung transplantation and is caused by ischemia and reperfusion injury of the lung^[39]. Although this effect was studied in previously healthy lungs, it would be very interesting to be tested in marginal donor lungs, in prolonged ischemia duration and in significant pulmonary hypertension of the recipient, which represent cases in which primary graft dysfunction is particularly important^[41]. The beneficial effects of ischemic PC were also verified in a *ex vivo* model^[42]. These investigators found that 15 min but not 5 min of ischemia can significantly attenuate graft dysfunction after 2 h. However, the number of animals per group ($n = 4$) was rather small and unfortunately no conclusion could be drawn as to whether repetitive ischemia offers better outcomes or not. In the setting of primary graft dysfunction, the role of intercellular adhesion molecule-1 (ICAM-1) and P-selectin has been acknowledged, but their role in ischemic PC remains elusive^[43]. Nevertheless, in an earlier study, 10 min of ischemic preconditioning of the lungs resulted in reduced infiltration by neutrophils and reduced production of oxygen-free radicals, which is in accordance with such a mechanism of reduced activity of adhesion molecules^[44]. Of course, the general problem with oxygen radicals is also here an issue, since we cannot tell whether reduced oxygen free radicals is part of the protective mechanism or a consequence of the protection. Future studies should aim at distinguishing between the two before we can draw any certain conclusions.

Remote ischemic PC

Remote ischemic PC, through PC of the lower limbs (3 cycles of 10 min ischemia and 10 min reperfusion) was also tested before hemorrhagic shock (representing global ischemia) lasting 2 h^[45]. The investigators found that remote ischemic PC was protective for the lungs and that, at least partially, this protection derives from the enhancement of heme-oxygenase-1 expression in the lungs. Also in this study the role of neutrophils and the decreased oxidative stress was depicted as a benefit of ischemic preconditioning. An initial work had shown that remote ischemic PC suppresses peripheral blood leukocytes genes important for cytokine synthesis, leukocyte chemotaxis, adhesion, migration and other functions during inflammation^[46]. However, these benefits on gene expression were not translated in a benefit for patients, because remote ischemic PC (lower limb 3 cycles of 10 min ischemia) combined with postconditioning did not improve oxygenation and lung injury, except for an improvement in A-aDO₂ and dynamic lung compliance^[47]. This could be because ischemic PC does not result in changes in the corresponding proteins or because the protection is not strong enough for an injury such as that of ALI after coronary artery bypass graft surgery. The authors postulated that the lack of effect could perhaps be related to the presence of anesthesia, because intact nervous pathways were shown to be a prerequisite for the benefit of preconditioning or because inhalational anesthetics could have obscured any additional benefits of remote ischemic PC^[48]. Another recent study also did not

find any benefit of remote ischemic PC in lung compliance, alveolar-arterial oxygen gradient, oxygen index and time of mechanical ventilation in infants undergoing ventricular septal defect repair^[49]. The authors used 4 cycles of 5 min lower limb ischemia-reperfusion. Although the study was organized for myocardial injury and was not powered for lung function variables, the authors suggested that the use of inhalational anesthetics and steroids may have masked any potential benefit from the ischemic preconditioning. In a study that aimed mainly at the systemic inflammation, an index of lung catabolism was also measured, after applying remote preconditioning to the limb, before knee surgery, and the authors found no significant benefit for lung catabolism^[50]. In a recent and adequately powered study however, 3 cycles of 5 min ischemia and 5 min reperfusion of the upper extremity achieved significant better oxygenation and decreased markers of intestinal injury^[51].

PC through volatile anesthetics

Based on previous reports on the beneficial effect of volatile anesthetics on ischemia/reperfusion of the heart and liver, Liu and colleagues assessed the efficacy of isoflurane in an *ex vivo* model of lung ischemia and reperfusion^[52]. The authors concluded that pretreatment with isoflurane could improve parameters such as vascular resistance and pulmonary edema. The authors further compared sevoflurane and isoflurane in their potential to reduce IR injury and found that administration of 1 MAC (minimum alveolar concentration) for 30 min before IR of either anesthetic reduced several markers of ALI in an *ex vivo* model^[53]. The authors, taking into account studies concerning the effects of anesthetic preconditioning on other organs, mainly the heart, proposed several hypothetical mechanisms, such as a reduction of tumor necrosis factor- α (TNF- α) release, reduced adhesion and migration of neutrophils, decreased generation of oxygen free radicals, suppression of metabolism or use of adenosine triphosphate (ATP) and activation of K_{ATP} channels^[53,54]. Preconditioning with isoflurane also mitigated lung injury from aerosolized lipopolysaccharide in mice^[55]. In that model, early preconditioning (1 h before lung injury) was associated with decreased concentrations of chemotactic chemokines, although it is not clear whether this was the result or a mechanism of protection. In another study, preconditioning with either isoflurane or sevoflurane was successful in improving survival in a rat model of sepsis-induced lung injury^[56]. Although in the case of sevoflurane this was accompanied by a decrease in oxidative stress markers and soluble ICAM-1 levels in plasma, the mechanism of protection still remains elusive. The protection offered by sevoflurane preconditioning was also shown in an *in vivo* model of lung auto-transplantation in swine, in which TNF- α , interleukin-1 (IL-1), lipid peroxides and nitric oxide (NO) were reduced^[57]. Regarding the clinical variables, sevoflurane PC reduced lung edema and improved PO₂ in pulmonary vein of the re-implanted lobe. However, systemic oxygenation was improved only transiently (at

10 min after lung re-implantation, but not at 30 min). Although the duration of sevoflurane preconditioning in that study is not known, the results are encouraging. It remains however elusive whether these advantages are translated into a benefit for lung function in the everyday clinical praxis.

Other types of PC

Other types of preconditioning of the lungs have been also tried, such as whole body heating to 42 °C 16 h before hemorrhagic shock^[58]. The authors found that this kind of stress PC induced the expression of heat-shock-protein 27 (Hsp-27) and preserved alveolar-capillary membrane permeability. A decreased expression of inducible nitric oxide synthase (iNOS) was also noted and *in vitro* experiments confirmed that heat preconditioning readily decreased iNOS expression in alveolar epithelial type II cells. Exercise PC has been also shown to reduce lung edema, inflammation and injury, partially by inducing Hsp-27 expression in lung tissue^[59]. Although these types of PC do not seem easily clinically applicable, another recent study showed that oral administration of sildenafil can prevent lung ischemia-reperfusion injury when administered 2 h before lung injury^[60]. In another study, the role of Hsp-27 was emphasized by the successful induction by hypobaric hypoxia before heatstroke lung injury and the reduction of lung injury^[61]. Lastly, an interesting study showed that dopamine can play an important role in the protection by ischemia-reperfusion injury in the lungs through D1 and D2 receptors^[62].

DISCUSSION

From the above search of the literature it is evident that lung PC during anesthesia is an open research field, clearly requiring more clinical studies. The experimental studies have shown in many instances a protective effect of PC, either with ischemia or pharmacological, but the extrapolation of conclusions in the clinical situation is difficult. Until now, 5 clinical studies could be identified for lung PC during anesthesia^[34,47,49-51], from which only one was able to show a benefit from remote ischemic preconditioning for the lungs^[51]. Important is that this study used as primary endpoint the pulmonary function and included sufficient number of patients, but also the pattern of remote IR (3 cycles of 5 min ischemia and 5 min reperfusion) may have played a role in the success of PC. Nevertheless, more clinical studies specifically studying pulmonary function are urgently needed in order to confirm these findings. In addition, researchers should include more indices of pulmonary function, so that we can have a more complete view of the pulmonary function, but also clinical markers of direct significance, such as time to extubation and intensive care unit stay, in order to comprehend if this potential benefit has any significant effect for the patient. Regarding pharmacological PC, despite the first encouraging experimental results, clinical studies do not exist. Although no significant risks from the above interventions for PC seem probable,

based on these observations, lung preconditioning cannot be recommended in the clinical praxis, until more clinical studies are conducted.

Future research points

Other issues that need to be addressed is which type of PC is the most effective (this may differ between types of lung injury) and also the exact protocol of PC that is the most effective (such as the duration of ischemia or the duration of exposure to a volatile anesthetic or whether early or late preconditioning is most appropriate in each type of lung injury). It is also remarkable that the mechanisms regarding lung preconditioning are largely indirectly extrapolated from heart preconditioning studies, but this is of course not necessarily true. Future studies should focus on examining specific mechanisms for lung preconditioning. Also, not all types of lung injury may be improved by PC. For example, IR injury may be improved, but lung transplantation represents the extreme ischemia/reperfusion and it is not known whether PC really benefits in this context. Also PC for some other important types of lung injury such as TRALI has not at all been examined, although of direct clinical importance. One of the most important issues of course remains the clinical applicability, since a measure needs to be significantly beneficial, inexpensive, devoid of side effects and not extremely complicate the every day clinical practice.

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Acute coagulopathy of trauma: Mechanism, monitoring, management

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Abstract

Coagulopathy is a well-known consequence of trauma and is the most common cause of mortality in the young. However, its cause and management is still controversial. A new concept in the understanding of coagulopathy in trauma is the occurrence of Acute coagulopathy of trauma (ACoT). ACoT is associated with hypo perfusion and tissue trauma as seen in massive injury. The incidence of coagulopathy increases with injury scores and is associated with higher number of ventilator days, higher morbidity and mortality. The process of coagulation is better described by the cell based model with a central role for platelets rather than the older plasma based model. This shift in our understanding supports the theory that ACoT results from the endothelial release of thrombomodulin and activated protein C in the presence of hypoperfusion. This in turn leads on to a hyperfibrinolytic and hypocoagulable state. Viscoelastic hemostatic assays are replacing the older tests like prothrombin time in the assessment of coagulopathy. These tests are accurate, determine the need for transfusion and can be performed at the point of care. Damage control resuscitation includes newer concepts like permissive hypotension, increased use of plasma as a part of massive transfusion protocols and

damage control surgery.

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Key words: Trauma; Coagulopathy; Massive transfusion; Bleeding; Thromboelastography

Core tip: Coagulopathy associated with trauma is a poorly understood and managed complication seen in severely injured patients. Acute coagulopathy of trauma, as it is currently described is attributed to trauma shock and associated tissue hypoperfusion. The traditionally attributed causes of acidosis and hypothermia contribute to a delayed form of coagulopathy, which is now considered different from early coagulopathy. Timely and appropriate use of blood and blood products along with the management of hypotension is termed damage control resuscitation. Early treatment to reverse and prevent acidosis, hypothermia and coagulopathy is the main focus.

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INTRODUCTION

World wide, injury due to trauma is the major cause of morbidity and mortality in young adults^[1,2]. About half of all deaths during the initial hours following trauma are due to uncontrolled bleeding^[3]. Localised anatomical bleeding from vessel or tissue injury is a potentially preventable cause of death and standard trauma protocols prioritise this appropriately^[4]. Another cause for bleeding, which is not as well understood or managed, is due to coagulopathy^[5]. Presence of coagulopathy in injured

patients results in a fourfold increase in overall mortality, higher intensive care unit (ICU) admission rate, longer hospital stay and a higher rate of organ failure^[6,7].

Coagulopathy seen in injured patients was initially considered a response to massive bleeding, dilution associated with massive fluid resuscitation, hypothermia and acidosis. As a result, among the “lethal triad” of trauma, namely, hypothermia, acidosis and coagulopathy, most treatment protocols aim at correcting or preventing hypothermia and acidosis without directly addressing coagulopathy^[8]. This view has undergone a sea change in the last ten years recognizing coagulopathy as an independent prognostic factor and current concepts in damage control resuscitation (DCR) emphasize addressing all three components of the lethal triad following trauma at admission^[9]. Acute coagulopathy of trauma (ACoT), trauma induced coagulopathy or ACoT shock are all newer terms used to describe coagulopathy seen in injured patients^[5].

ACoT has been the subject of intense research especially over the last five years resulting in a large volume of literature. There is however no consensus on its pathophysiology nor is there a recommended management strategy. This is in part because of the difficulty in formatting and testing new guidelines for a condition that is seen in only about 1%-2% of patient population^[10]. There is also a general lack of awareness of the significance of ACoT. This review is an attempt to summarise the state of science in ACoT.

MECHANISM

The initiation of the coagulation pathway always results in the activation of the inflammatory system. When this activation is widespread, the inflammatory response initiates a downward spiral rapidly leading on to organ failure and death. Recent advances in trauma research have provided newer insights into this complex process. An important offshoot of this understanding is the incorporation of aggressive and targeted hemostatic control resuscitation or DCR in trauma protocols^[8,11,12].

A landmark paper by Karim Brohi analyzing data from 1088 United Kingdom civilian trauma patients over 5 years reported that about one fourth of all trauma victims had a disturbed coagulation profile on admission^[1]. This study defined a disturbed coagulation profile as a prothrombin time (PT) or an activated partial PT (aPTT) 1.5 times the normal. Significantly, coagulopathy was more likely in patients with higher injury severity scores and had no relation to the volume of intravenous fluids administered in the pre-hospital setting for resuscitation. This study also found coagulopathy to be an independent predictor of mortality. Karim Brohi's paper set the direction for research on coagulopathy in establishing coagulopathy as an event which set in early. Many other studies found similar results although the definitions for coagulopathy varied. A study by MacLeod *et al*^[7] found the presence of coagulopathy in 28% of trauma patients on admission. Maegele *et al*^[13] in a retrospective study found 34.2% patients coagulopathic on admission follow-

ing blunt trauma. It can be reasonably concluded from these studies that about one third of patients admitted following trauma have early onset coagulopathy.

The last ten years have witnessed a shift in the understanding of the coagulation process from a plasma borne factor cascade with fibrin as a central player to a cell-based theory centred around platelets^[14]. The haemostatic process is now described as occurring in three phases, initiation, amplification and propagation. Initiation occurs when tissue factor activates V, IX, X and produces a small amount of thrombin. The amplification phase involves platelet activation causing thrombin burst, which ultimately leads on to fibrin and clot formation in the propagation phase.

Shock and tissue hypo-perfusion are now considered central to the initiation of ACoT^[15]. This is in contrast to the traditionally accepted causes of coagulopathy in trauma, namely, consumption, dilution, dysfunction, hypothermia and acidosis. According to current concepts, these factors come into play much later. It is therefore easy to understand the mechanism of ACoT by differentiating coagulopathy as early (primary, endogenous response) and late (acquired, systemic response)^[5,8].

Tissue hypo-perfusion

A fine balance between procoagulant and anticoagulant pathways exists to prevent clot propagation beyond the site of injury. Plasmin, responsible for fibrinolysis, exists as plasminogen in its inactive form. Tissue plasminogen activator (tPA) is inhibited by plasminogen activator inhibitor (PAI). Thrombomodulin secreted by the endothelium complexes with thrombin and activates protein C which in turn inactivates factors V and VIII irreversibly thereby disrupting the procoagulant process^[16]. It also inhibits PAI disinhibiting tPA which leads to the conversion of plasminogen to plasmin and results in fibrinolysis.

Tissue hypo-perfusion leads to excessive endothelial expression of thrombomodulin which binds to thrombin and this complex results in the activation of protein C pathway and hence the fibrinolytic cascade^[15]. Brohi *et al*^[15] in an important study involving 208 trauma patients found hypoperfusion (defined as base deficit > 6) to be associated with coagulopathy [defined as activated partial thrombin time (aPTT) or PT values > 1.5 times the normal]. These patients had elevated levels of thrombomodulin-thrombin complex and reduced protein C levels, indicating an increased activation of protein C. Platelet count and fibrinogen levels were found to be normal implying that thrombin was unavailable to cleave fibrinogen and to consume platelets. Thus, they concluded that it is the enhanced activity of activated protein C that is central to ACoT^[17,18].

In a translational mouse model it was demonstrated that a combination of tissue trauma and hypo-perfusion is prerequisite for early coagulopathy to manifest^[3,8]. Hypocoagulability is often seen in the presence of acidosis due to decreased factor activity. However, early in trauma, there appears to be coagulopathy even with mild acidemia. This is due to the shock and state of hypo-perfusion which

results in anticoagulation and hyperfibrinolysis^[5,19,20]. It is seen that platelet counts are generally normal^[5,13,15].

Tissue injury

Endothelial damage secondary to injury exposes sub endothelial type III collagen and tissue factor that trigger the initiation of clot formation and thrombin release. Endothelial injury also releases tPA in the presence of thrombin and in the presence of ischemia, results in excess fibrinolysis. Traumatic brain injury causes release of thromboplastins and phospholipids which also ultimately result in inflammation and fibrinolysis. Injury severity is closely associated with coagulopathy and therefore with mortality^[5,13,15,21]. Hyperfibrinolysis is clearly a direct consequence of shock and tissue injury^[8].

Hypothermia

Hypothermia, defined as core body temperature lower than 35 degrees C, has an incidence of 1.6% to 8.2% in trauma victims^[9]. Hypothermia in trauma occurs either spontaneously as a result of radiation heat loss due to over exposure or secondary to aggressive fluid resuscitation. Impaired heat production due to reduced muscle perfusion also contributes to hypothermia. Hypothermia in trauma is found to be directly related to injury severity.

The activity of proteases decreases linearly and proportionally with temperature resulting primarily in platelet dysfunction^[22-25]. There is a decrease in interaction between vWF and collagen glycoproteins 1b and X leading to decreased platelet activation. Clinically significant effects on coagulation and platelet function are seen below 34 °C. However since most trauma patients present in mild to moderate hypothermia (33 °C-36 °C), it rarely has an effect, in isolation, on coagulation^[5]. Coagulopathy is worsened by the resulting vasoconstriction due to sympathetic response to hypothermia. Hypothermia also leads to acidosis and therefore worsens coagulopathy. Mortality reaches 100% when temperature falls below 32 °C.

Acidosis

Acidosis is common in trauma and is attributed either to hypo-perfusion or administration of chloride-based fluids or a combination of the two. It significantly alters platelet physiology as well as clotting factor activity to varying degrees. Affinity to calcium binding sites is reduced, as is thrombin clot propagation. In general, at a pH of 7.2, activity of factor Xa/Va reduces by 50%, platelet count reduces by 50% and fibrinogen reduces by 35%^[23].

Hemodilution

Aggressive fluid resuscitation leads on to dilution of clotting factors. Transfusing whole blood devoid of clotting factors as well as inhibition of clotting mechanism by colloid infusions contribute to coagulopathy^[26]. Fluid resuscitation can also lead on to a fibrinolytic state by diluting the antifibrinolytic proteins^[27,28].

Inflammation

Trauma induces systemic inflammatory response syn-

drome due to both humoral and systemic activation of inflammatory mediators early in its course^[28]. Inflammatory system is closely related to the coagulation and complement systems. Endothelial activation, by itself and by the activation of coagulation proteases and protein C through thrombomodulin results in a widespread inflammatory response. This response is effected by transmembrane protease receptors on cell surfaces and complement system through the alternate pathway^[16].

To summarise, the pathophysiology of coagulopathy is a complex multifactorial process with several unexplained responses. Shock and tissue hypoperfusion are central to the initiation of early coagulopathy of trauma by the thrombomodulin-activated protein C (aPC) pathway. This is the primary or endogenous response and it occurs very early following injury. As resuscitation proceeds, hemodilution, hypothermia and acidosis further exacerbate coagulopathy either due to loss, by consumption or dilution, inhibition or dysfunction. This is known as the systemic acquired coagulopathy^[17]. It is now generally accepted that primary and secondary coagulopathy are to be considered as separate entities. The role of inflammation and tissue injury in primary coagulopathy is not fully understood^[3]. A late prothrombotic phase sets in after the depletion of aPC and there is a time lag before the liver synthesises protein C. Inflammatory process also shifts the hemostatic response in favour of thrombosis^[12]. There is a real risk of thromboembolic complications during this phase. ACoT is associated with increased mortality, more days on ventilator, longer ICU and hospital stay and greater likelihood of receiving blood and products^[1,7,13,15].

There is opposition to this theory, with one group reporting similarity between disseminated intravascular coagulation (DIC) and the early coagulopathy seen in trauma. This group describes early coagulopathy of trauma as DIC with a fibrinolytic phenotype manifesting as hyperfibrinolysis and consumption coagulopathy contributing to massive haemorrhage. This, at a later stage of trauma, establishes as DIC with a thrombotic phenotype resulting in fibrin clot deposition and subsequent organ dysfunction. It is argued that all the six factors discussed above lead on to similar nonspecific inflammatory and haemostatic responses^[29].

ASSESSMENT AND MONITORING

The main challenges faced in monitoring injured patients are to rapidly diagnose patients who are hypocoagulopathic and in fibrinolysis, to assess adequacy of tissue perfusion and to accurately predict the need for massive transfusion.

All injured patients, especially those following high energy trauma, should be suspected of having ACoT. Massive bleeding, tachycardia, hypotension, weak pulses, altered mentation, oliguria are indicators of severe injury. Presence of hypoperfusion is suspected if there is an increase in base deficit or serum lactate levels. ACoT is defined as a functional reduction in clot strength with a smaller change in clotting time. There is however no clear

consensus on what lab values can determine the presence or absence of ACoT^[30,31].

Routine coagulation tests (RCoT), namely, PT and PTT have been traditionally used to assess coagulation. A value of international normalized ratio > 1.2 is regarded as the clinically significant threshold for defining ACoT^[3]. Plasma based assays, like PT and PTT, have many limitations as they have limited utility in monitoring coagulopathy or in guiding transfusion therapy in trauma^[32]. RCoTs assess a small part of the plasma-based component of coagulopathy pertaining only to thrombin formation. As a generalization, these tests assess only the initial 20 s of the clotting mechanism^[19]. Further, studies have shown no correlation between these assays and the presence of clinically significant bleeding or with clotting factor activity^[33]. These assays were developed half a century ago to monitor haemophilia and anticoagulation therapy. With the shift in understanding of coagulation to a cell based theory and the more recent concepts of ACoT and DCR, there is an urgent need felt for reliable haemostatic assays to guide therapy.

Viscoelastic hemostatic assays (VHA) assess the whole blood components of coagulation including platelet function. The common VHAs in practice are thromboelastography, thromboelastometry and platelet function analysis^[2,34]. These tests have several advantages. They assay the whole blood with all the components of coagulation, results are available in a short time, end points are clinically relevant and they have been shown to correlate well with patients who have clinically significant bleeding requiring transfusion. They also correlate well with the cell based model, hence referred to as cell based assays. Recent studies have shown a hypocoagulable picture in the early phase of trauma with the use of VHA while the results of RCoT in the same group of patients were normal. VHAs can identify patients with increased fibrinolysis^[35] and can be used to predict patients requiring massive transfusion^[31]. One study demonstrated a significantly lower mortality rate in bleeding patients when VHA was used to guide the administration of blood and blood products. There are two main lacunae identified with respect to the use of VHAs in clinical practice. Firstly, there is no universally accepted definition of clinical coagulopathy defined by thromboelastography or thromboelastometry (TEM) and there is a need to standardize the methods^[20]. Secondly, their value in predicting coagulopathy in the patients who are on antiplatelet therapy is not known^[19].

Presence of two or more abnormal values from clot initiation, amplification or clot strength and stability is regarded as clinical coagulopathy by most centers^[36]. TEM has been shown to detect coagulopathy in ten minutes and this is available at the point of care. Rotational thromboelastometry can identify ACoT in 5 min when defined as a clot amplitude lesser than 35 mm^[3]. Some smaller series have even suggested using VHAs for goal directed therapy^[34,37,38]. TEM is also useful in differentiating the causes of coagulopathy thereby suggesting appropriate correction^[31,39].

MANAGEMENT

Currently used guidelines for management of injured patients reflect the deeper understanding of the pathophysiology of trauma in general and coagulopathy in particular. The conventional approach where the primary goal for resuscitation in trauma shock was to maintain blood pressure, urine output and to reverse metabolic effects of tissue hypoperfusion failed to address coagulopathy^[40,41]. In contrast, DCR is targeted at proactively managing the physiological consequences of injury by following a hemostatic resuscitation strategy that controls bleeding in order to avoid death^[42]. Early treatment to reverse and prevent acidosis, hypothermia and coagulopathy is the main focus. Damage control surgery is an operative strategy wherein the focus is shifted from completion of surgical repair to a minimal approach to limit the physiological consequence of surgery superimposed on that caused by trauma. Administration of blood products and factors in order to minimise blood loss, maximise oxygen transport and tissue oxygenation is the main goal. This is done by utilising seven key steps.

It is important to recognize that this approach is reserved only for the most seriously injured patients in coagulopathy amounting to about 10% of trauma victims. Though the involved group is proportionally smaller, this is the group with maximum mortality^[9]. DCR as a structured intervention begins immediately following rapid assessment, continues into the operation room and further in the ICU^[9]. Resuscitation aiming at tissue oxygenation, interventions to prevent or ameliorate coagulopathy and surgical intervention aiming at rapid control of bleeding should take place simultaneously.

Permissive hypotension

Aggressive fluid resuscitation is indicated in injured patients to ensure tissue perfusion^[40,41]. Recent studies focusing on adverse effects of large volume infusions found that patients receiving less than 1500 mL of fluids in the pre-hospital setting had a higher chance of survival than patients who received higher volumes. The incidence of coagulopathy was higher (> 40%) when volumes more than 2000 mL was given^[7,43,44]. Incidence of secondary abdominal compartment syndrome also increased with increased fluid administration^[43]. There is no consensus on the choice of fluid for resuscitation with studies comparing colloids and crystalloids being inconclusive^[19]. Some studies have shown benefit with hypertonic crystalloids and found hypotonic crystalloid administration to be harmful.

Permissive hypotension is based on the concept that maintaining a low volume fluid resuscitation avoids adverse effects of large volume infusions^[19,45]. Also, in order to support clot formation, a lower mean arterial pressure of 65 mmHg and a systolic blood pressure of 90 mmHg is preferable till bleeding is surgically arrested. This strategy is beneficial as long as the delay in achieving such control does not exceed 120 min^[46].

Fluids are used sparingly while maintaining perfu-

sion^[45]. In a recent prospective study involving trauma patients presenting with shock, patients who received hypotensive resuscitation with restricted fluid administration had lesser incidence of coagulopathy and better 24 h postoperative survival rate. Permissive hypotension is contraindicated in the presence of traumatic brain injuries, coronary artery disease or hypertension^[47].

Blood products

Transfusion protocols administering red blood cells (RBCs), plasma and platelets in the ratio of 1:1:1 in patients requiring massive transfusion have been found to lower mortality rates as well as reducing the requirement for multiple transfusions^[9,48,49]. Massive transfusion (MT) protocols are controversial and there are no guidelines or randomised control trials that have evaluated the correct ratio of blood and products to be administered.

There is evidence to suggest that an increased ratio of fresh frozen plasma (FFP) to packed RBC (pRBC) reduces mortality in injured patients receiving MT. Duchesne found a lower mortality rate in patients receiving MT with a FFP to pRBC ratio of 1:1 when compared to ratio of 1:4^[50]. Magele also found a similar reduction in mortality when the ratio was close to 1:1^[13]. Bhangu *et al*^[51] in a meta analysis found a reduced mortality in patients receiving FFP to pRBC in a ratio of 1:2 and no further reduction in mortality was found when the ratio was increased to 1:1. Snyder, in a retrospective study on trauma patients requiring MT, reported a reduced 24 h mortality when FFP and pRBC were given in a ratio of greater than 1:2^[52]. Holcomb *et al*^[49] reported an association between higher ratio of plasma and platelet to blood pRBC with increased survival.

Currently, protocols have been developed to counter the dilutional effect of MT. Early recognition of patients requiring massive transfusion is key and is often very difficult to predict as the definitions require waiting for a period of 24 h. Hence, the trigger for initiating MT protocol is largely based on hemodynamic variables, laboratory tests and injury severity scores^[53]. Selected patients receiving a high ratio of FFP to pRBC during surgery are found to have decreased intraoperative coagulopathic bleeding, and are warm, euvoletic and nonacidotic following surgery^[9,12]. A high ratio of FFP to RBC has shown an improvement in mortality^[54]. European guidelines recommend plasma transfusion at an early stage in patients with massive bleeding^[19]. However, it is important to note that this proactive strategy should not be adopted in patients who have already been stabilised or in the presence of minor injuries to prevent unnecessary exposure to transfusion related complications and risks^[2].

Rewarming

Attempts to prevent loss of body temperature should be initiated as early as possible. Only warmed fluid infusions (at a temperature of 40 °C to 42 °C) should be administered^[17]. Passive and active warming techniques should be adopted. The steps that are suggested to prevent and treat hypothermia include passive methods like covering

the patient to avoid heat loss and active methods using fluid warmers, forced air warmers and in severe cases extracorporeal rewarming^[19]. Operating room should be at a thermally neutral temperature of 28 °C-29 °C^[54].

Correction of acidosis

The severity of shock and hypoperfusion can be assessed indirectly by measuring serum lactates and base deficit. Serial values of lactate are useful in predicting survival as well as in assessing response to therapy. Similarly, base deficit can independently predict mortality and is especially useful in inebriated patients likely to have falsely elevated lactate levels. Restoration of normal perfusion aimed at correcting base deficit and pH is the main stay of treating and preventing acidosis. MT of blood also exacerbates acidosis and requires scrupulous monitoring. It is aggressively managed by maintaining volume with blood and products and administering Tromethamine^[9].

Calcium homeostasis

Calcium is necessary for fibrin clot stabilisation. Hypocalcemia (< 0.9 mmol/ L) should be treated^[55]. Hypocalcemia is aggravated by rapid infusion of blood products and also due to chelation of calcium by the anticoagulant citrate. Low levels of ionised calcium are associated with higher mortality and increased need for blood transfusion.

Pharmacological methods of controlling bleeding

Local modalities: Application of fibrin glue, hemostatic bandages and argon lasers reduce blood loss even in the presence of coagulopathy^[19,54].

Antifibrinolytics: Tranexamic acid (TxA) was studied in a double blinded, randomised, multi centric trial (clinical randomisation of an antifibrinolytic in significant hemorrhage) involving 10060 adult trauma patients, with 1 g of tranexamic acid administered over 10 min, 1 g over the next 8 h, irrespective of the risk of hemorrhage. Another 100067 patients received saline. TxA significantly reduced "all cause" mortality and mortality due to bleeding^[56]. It should be administered within 3 h of trauma, in a dose of 1-2 g over 10min and repeat 1 g over 8 h^[19,54].

Recombinant factor VII: Very high dose of recombinant factor VIIa (rFVIIa) are required for the formation of tissue factor complex to activate the clotting system. It bypasses several steps of coagulation and interacts directly with activated platelets to form thrombin. Early use of rFVIIa was associated with a decreased 24 h and 30 d mortality in severely injured combat patients^[57]. Hospital length of stay, days on ventilator, blood and FFP requirements were shown to be reduced. rFVIIa may be used in blunt trauma where all the standard methods have failed to control bleeding. However, a large multicentric phase III trial was terminated recently due to its futility as the planned reduction in mortality could not be achieved^[54]. The administration of rFVIIa is associated with a higher incidence of thromboembolism. It is imperative that several concomitant factors be maintained at certain levels:

fibrinogen > 1 g/dL, Hb > 7 g/dL, platelets > 50000 cells/L, Ca^{2+} > 0.9 mmol/L, temperature > 34 degree C and pH > 7.2. The therapeutic dosage for this factor is still not known^[58]. Off label, the drug is administered at a dose of 90 µg/kg of body weight. It's safety is not established as yet.

Combination of fibrinogen and prothrombin complex concentrates: Fibrinogen levels are the first to decline in case of haemorrhage^[59]. Use of prothrombin complex concentrates (PCC) can reduce the risk of transfusion associated acute lung injury and other viral infections. In a study on combat related trauma requiring massive transfusion, high fibrinogen to RBC ratio (> 1 g/L to 5 units packed RBCs) was found to decrease death from haemorrhage. A fibrinogen level of > 1.5 g/L should be maintained following trauma^[55] and transfusion of fibrinogen or cryoprecipitate may be considered if it is below this level. PCC or a complex of factors II, VII, IX, X is found to shorten the time to coagulation and reduce blood loss following trauma^[54].

Rapid control of bleeding

Damage control surgery is employed for trauma patients who are in hemorrhagic shock, acidotic (pH < 7.2), hypothermic (temperature < 34 degrees C) and coagulopathic^[19]. These patients are at the ends of their physiological reserves. Damage control surgery involves techniques of planned temporary sacrifice of normal anatomy to preserve physiology like abbreviated laparotomies, packing for uncontrolled bleeding, diversion of injured ureter and so on^[12,20].

Thromboprophylaxis: Pharmacological techniques of thromboprophylaxis should be started 24 h after bleeding has been controlled.

CONCLUSION

The last five years have seen tremendous advances in our understanding of ACoT. Though we are far from having all the answers, it is understood that coagulopathy sets in much earlier than traditionally believed. Trauma shock and tissue hypo perfusion are central to the causation of early ACoT. Routine tests of coagulation are ineffective in diagnosing or monitoring coagulopathy and should be replaced by better tests. Presently viscoelastic hemostatic assays are the most reliable among existing tests in monitoring coagulopathy. Damage control resuscitation is the umbrella term to several measures, including but not limited to permissive hypotension, plasma transfusions, recombinant factors, that can counter worsening of coagulopathy and result in a reduction of morbidity and mortality.

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Comparison of flow rate accuracy and consistency between the on-Q, baxter, and ambu pain infusion devices

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Abstract

AIM: Providing analgesia *via* peripheral nerve catheters attached to an infusion pump is an effective pain management option in children.

METHODS: Portable infusion pumps are being used with increased frequency in pediatric patients. Because these pumps are infusing potentially toxic doses of medications, the accuracy and consistency of these devices becomes very important in this patient population. This study is a comparison of the actual delivery volume of local anesthetic of three elastomeric infusion devices approved for patient use in the ambulatory setting. Three brands of disposable elastomeric infusion devices were used (Five On-Q, Five Baxter, and Five Ambu pumps). Each was filled with 200 mL of Ropivacaine 0.1% and connected to a single, end hole infusion catheter and set to infuse at 12 mL/h. The devices were run simultaneously. The fluid delivered was measured every hour with a graduated column over a tenhour period. The ambient temperature

was also recorded.

RESULTS: There were statistically significant differences in the output from each elastomeric device over the 10 h infusion period when compared to the nominal rate of 12 mL/h. The output from the Ambu and Baxter pumps was less than that set on the regulator, while the output from the On-Q pump was greater than that set on the regulator. The results remained statistically significant after adjusting the nominal rate to correct for differences in temperature. The Ambu infusion device was the most consistent, while the Baxter infusion device was the most accurate. This emphasizes the importance of health care providers understanding the infusion profile of the pump being used for continuous peripheral nerve block, as these alterations in flow could result in inadequate analgesia, early reservoir exhaustion, excessive muscle weakness or potential toxicity, especially when used in pediatric patients.

CONCLUSION: This investigation demonstrates that three modern elastomeric infusion pumps have significantly different output than the nominal rate set on the regulator.

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Key words: Pediatric anesthesia; Pain; Regional anesthesia; Pain pumps; Acute pain

Core tip: This study demonstrates that three single use elastomeric infusion devices have rates that are significantly different from the set nominal delivery volume. These alterations in flow may be clinically significant, resulting in either inadequate analgesia, early exhaustion of the reservoir, excessive muscle weakness or the potential for toxicity, especially when used with pediatric patients. Therefore, in order to provide the best care, physicians must not only take into account the temperature at which the pump will be kept, viscosity of the solution used, and the height of the reservoir but also the

infusion profile of the individual pump being used.

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INTRODUCTION

There are multiple benefits of postoperative perineural local anesthetic infusions have been shown, including potent analgesia, decreased opioid requirements, and improved rehabilitation^[1]. Disposable elastomeric pumps with peri-neural infusions are as effective as patient controlled intravenous pumps for post-operative pain relief^[2]. A prospective descriptive study of children undergoing major orthopedic surgery determined that disposable elastomeric pumps for perioperative continuous peripheral nerve block (CPNB) provided excellent postoperative analgesia with no adverse effects noted^[3]. They concluded that the use of elastomeric disposable pumps for CPNB in children is an effective technique^[3]. Another study confirmed that CPNB is an effective and feasible option in pediatric patients, allowing children to experience earlier ambulation and have shortened hospital stays^[4]. Consequently, portable infusion pumps have been used with increasing frequency to provide peri-neural infusions of local anesthetic for pediatric patients.

Elastomeric pumps exhibit a high degree of acceptance. Patients prefer them over electronically controlled pumps because of their portability, disposability, silent operation, minimal interference with daily activities, ease of use, impact on sleep as well as the relative inexpensive^[5-8]. However, evaluation of recent literature shows that elastomeric pumps tend to over infuse (110%-130%) during the initial 3-8 h of infusion and within the final hours before reservoir exhaustion^[8]. In addition, Chung *et al*^[9] confirmed the notion of a non-uniform drug delivery *via* the elastomeric balloon infusion devices. Inaccuracy or altered flow rates could lead to decreased delivery of the local anesthetic solution with inadequate analgesia or excessive delivery with the risk of toxicity. With a very narrow therapeutic window of analgesia in the pediatric population, both accuracy and consistency of peripheral nerve infusion devices is imperative.

This study compares the performance of three such pumps, which infuse potentially toxic medications. The three pumps compared include the On-Q pain pump, the Baxter Multirate portable elastomeric infusion system, and the Ambu elastomeric infusion device (Figure 1). These infusion pumps deliver medication at a flow rate that is determined by the pressure in the elastomeric reservoir, the flow restriction in the infusion circuit, and the viscosity of the fluid^[10]. The balloon reservoir serves a sustained internal pressure as a driving force and the luer

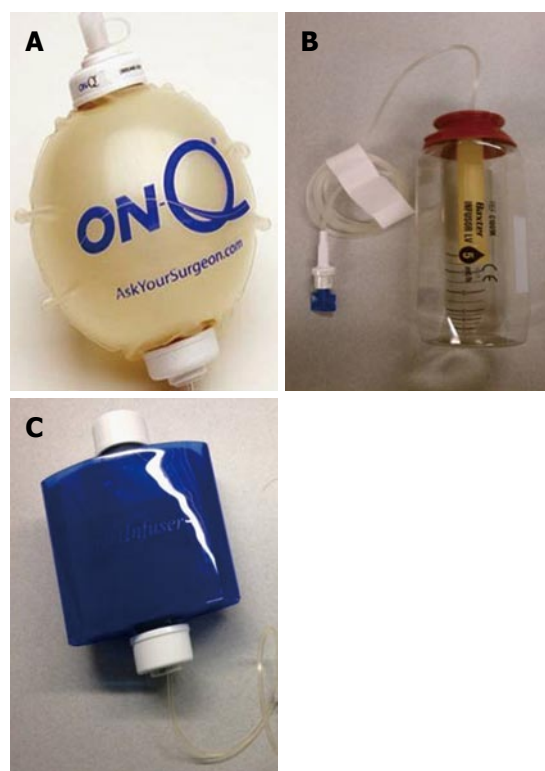


Figure 1 Three pumps compared. A: On-Q pain pump; B: Baxter Multirate portable elastomeric infusion system; C: Ambu elastomeric infusion device.

body makes a resistance as a flow control device. Consequently, the flow rate of these devices is determined by the constant pressure in the elastomeric membrane of the reservoir coupled with various flow control devices^[9]. The manufacturer provided references specifies the accuracy to be $\pm 15\%$ -20% from nominal for the On-Q pump, $\pm 10\%$ for the Baxter pump, and $\pm 15\%$ for the Ambu pump. We compare the accuracy and consistency of these three elastomeric devices approved for patient use in the ambulatory setting.

MATERIALS AND METHODS

No human or animal subjects were used in these studies. Five On-Q infusion devices, 5 Baxter infusion devices, and 5 Ambu infusion devices were filled with 200 mL of 0.1% ropivacaine in normal saline according to the manufacturer's recommendations. All pumps were previously unused. The infusion devices were then attached to a single, end hole infusion catheter and each regulator was set to infuse at 12 mL/h. The devices were placed flat, with the elastomeric reservoir and the distal end luer lock at equal height. Each device was allowed to run for 10 h total, with fluid output measured every hour using a graduated cylinder.

The ambient room temperature measured was between 18.9 °C and 20.7 °C, with an average temperature of 19.8 °C. The pumps vary in the manufacturer's recommendations for temperature management. Baxter pumps are designed to operate at a temperature of 31.1 °C. The flow rate will decrease 2.3% per one degree Celsius and

Table 1 Mean infusion rates for On-Q, Baxter and Ambu pain infusion devices over 10 h

	Hour	#1	#2	#3	#4	#5
On-Q	1	19	19.4	18.6	17.9	18.4
	2	18	18.4	18.4	16.8	18
	3	17.6	18.4	17.9	16.1	17.5
	4	17.8	18	16.7	16.4	17.5
	5	17.6	18.2	15.8	15.4	17.5
	6	17.5	18.2	14.9	16.4	16.9
	7	18.6	18.2	14.9	16.2	16.9
	8	19.3	19.8	14.7	16.1	16.8
	9	18.8	18.4	14.9	14.9	16.6
	10	18.5	19	15.1	14.8	16.6
Baxter	1	10.8	10.4	10.8	10.4	9.8
	2	10.1	10	10.6	10.3	10
	3	10	9.8	10.7	9.9	9.8
	4	9.8	9.9	10.5	10	9.7
	5	9.7	9.5	10.1	10	10
	6	9.8	9.8	10.5	10	9.8
	7	9.6	9.6	10.4	9.8	9.9
	8	10.5	9.8	10.4	10	9.8
	9	10	10.1	10.3	10	9.6
	10	10	10.1	10.7	10.1	9.6
Ambu	1	9.5	9.2	10	8.5	10.2
	2	9.8	9.2	9.8	8.6	9.9
	3	9.8	9.2	9.5	8.6	9.8
	4	9.6	9.2	9.8	8.8	10.2
	5	9.7	9.2	9.8	8.6	9.9
	6	9.6	9.2	9.8	8.9	9.9
	7	9.7	9.2	9.7	8.8	10.4
	8	9.7	9.2	9.9	8.8	10.2
	9	9.4	9.1	9.4	8.5	9.9
	10	9.6	9.2	10	8.7	9.8

this should be accurate within plus or minus 10%. This would lead one to assume that the regulator is designed to be secured to the patient's skin, though this is not specifically mentioned in the package insert. The On-Q pump does specify that it is designed to operate while in contact with the patient's skin, at a temperature of 31 °C. The package insert states flow rate will decrease 1.4% per 0.6 °C in temperature. This should be accurate within plus or minus 15% to 20%. Because the Ambu pump is designed to operate between 20 °C and 24 °C it must be assumed that the flow regulator need not be secured directly to the patient's skin. The manufacturer's state an accuracy within 5% for the Ambu pump. To adjust for the differences in operating temperature, the nominal flow rate was adjusted for the Baxter and On-Q pumps. Adjusted nominal flow rate was 8.9 mL/h for both. Because the Ambu pump is designed to operate at room temperature the nominal flow rate did not require adjustment.

The data are presented as the mean plus or minus that standard deviation as shown in Table 1. The *t* test was used to compare the mean value of pumps one through five for each pump, from hours one through ten, to the standard, temperature corrected value of 8.9 mL/h for the Baxter and On-Q pumps and 12 mL/h for the Ambu pump. Results for each pump are shown in Figure 2. All tests are conducted in SAS 9.20 (by SAS Institute Inc., Cary, NC, United States). A *P* value of less than 0.05 was considered statistically significant.

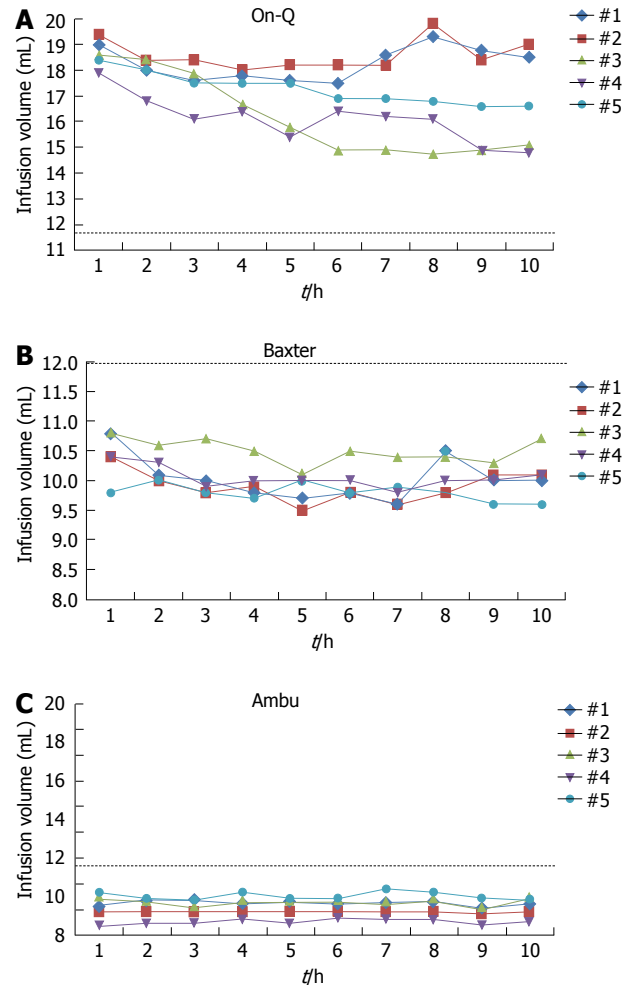


Figure 2 Pump performance over time for three elastomeric portable infusion devices as noted by the title in each panel. A: On-Q pain pump; B: Baxter Multirate portable elastomeric infusion system; C: Ambu elastomeric infusion device. Shown is the infusion rate in milliliters. The constant horizontal line represents the set nominal pump rate of 12 mL/h.

RESULTS

The infusion rates and infusion rate profiles for the three elastomeric pumps tested are shown in Table 1 and Figure 2. The mean output from the devices over the 10 h study period with the associated standard deviation is listed in Table 2.

Accuracy

(*P* < 0.0001). The mean output from each type of elastomeric infusion pump was significantly different from the standard value of 12 mL/h set on the regulators as shown in Table 1. This is consistent with previous studies on different elastomeric infusion devices^[1,8,11]. The On-Q pump's mean output of 17.3 mL/h was significantly higher than the 12 mL/h set on the regulator. This becomes even more significant when using the temperature corrected nominal rate of 8.9 mL/h. The Baxter pump's mean output was 10.1 mL/h with a standard deviation of 0.17. This remains statistically significant after adjusting the nominal rate to 8.9 to account for differences in tem-

Table 2 Mean output, standard deviation and standard error of the infusions pumps over a 10 h time period

Pump	n	Mean	StdDev	Std Err	P value ¹
On-Q	10	17.3	0.62	0.19	< 0.0001
Baxter	10	10.1	0.17	0.05	< 0.0001
AMBU	10	9.5	0.09	0.03	< 0.0001

¹Each pump compared to set rate of 12 mL/h; ¹Baxter and On-Q pumps also compared to the temperature corrected rate of 9.8 mL/h.

perature, however under these circumstances the pump is over versus under infusing. The expected temperature corrected range was 8.0-9.8 mL/h. However, this was the most accurate of the evaluated pumps. The Ambu pump's mean output was 9.5 mL/h with a standard deviation of 0.089, also significantly different from the standard value of 12 mL/h with a $P < 0.0001$.

Consistency

The AMBU pump had the minimal standard deviation and standard error, and is therefore the most consistent, though not the most accurate, of the three evaluated pumps.

DISCUSSION

This study prospectively evaluated the performance of three single-uses, elastomeric infusion devices maintained at room temperature over a 10 h per time. Ideally the nominal flow should be achieved immediately and remain constant throughout the infusion. However, as previous studies have shown, we demonstrate that the infusion rate accuracy and consistency of three portable pumps used to provide CPNB is variable^[1,5,9,10].

Accuracy

The On-Q pump infused faster than the set rate throughout the duration of the infusion, even when corrected for temperature. Per the manufacturers this discrepancy is greatest during the first one to two hours of the infusion, following which they state the rate should decrease and become accurate within $\pm 15\%$ -20% of the nominal rate. In our study, the infusion rate remained greater than 20% above the nominal rate over the entire 10 h period. This increase in flow rate by the On-Q pump may have implications for patient care when applied to continuous regional anesthesia. The reservoir could exhaust earlier than that calculated based on the set rate and expected infusion duration. If the internal reservoir is exhausted early it would require either ending the duration of the infusion sooner than planned or obtaining an additional unit, as refilling the pumps is currently not approved for the majority of devices. In addition, a supra-therapeutic infusion could result in an insensate extremity, muscle weakness, or potential toxicity, especially if used in small pediatric patients.

The Ambu pump, designed to operate at room temperature, under-infused throughout the duration of the study. With an average flow of 9.5 mL/h it never reached

the set nominal rate. The Baxter pump was the most accurate, running at an average of 10.1 mL/h, which is just outside the temperature corrected range of 8.0-9.8 mL/h. Both proved to be more accurate over time than the On-Q pump and did not show the variability during the initial two hours of infusion. As the infusion was only measured for a duration of ten hours, conclusions cannot be drawn about the accuracy at the completion of the infusion.

Temperature

The flow rate of elastomeric pumps is affected by the temperature, the viscosity of the solution and the height of the reservoir. During our study the room temperature was between 18.8 °C and 20.7 °C with an average of 19.8 °C. As described, each pump is designed to operate at a specific temperature, with flow rate increasing as temperature increases and *vice-versa*. According to the manufacturer, Baxter pumps are designed to operate at 31.3 °C, which leads to the assumption that the device should be secured to the patients skin. These instructions are not specifically mentioned in the package insert. The On-Q pump is designed to operate at 31 °C and in this case the package insert clearly states that the flow regulator should be in direct contact with the patients skin. The Ambu pump is designed to operate between 20 °C and 24 °C, implying room temperature. There may be clinically significant changes in output based on the external temperature^[10]. Therefore in this study the nominal flow rate was adjusted to account for the difference in temperature. The variations in operating instructions could be a potential source of confusion to the user and emphasizes the importance of knowing the specific instructions for the pump in use.

Viscosity

When considering viscosity, in addition to changes in temperature, the solution being used must be considered. For example, Baxter pumps are designed to operate at the nominal rate using 5% Dextrose. When 10% Sodium Chloride (NS) is used manufacturers state there will be an approximate 10% increase in flow rate. This study used 0.1% ropivacaine in NS and the infusion rate remained greater than 10% from the temperature corrected nominal rate. We controlled for the height of the pump, as the reservoirs were positioned at the same level as the luer locks.

Consistency

As previously described, the On-Q pump has a flow discrepancy that is greatest during the first one to two hours of the infusion, following which the manufacturer's state the rate should decrease and become accurate within $\pm 15\%$ -20% of the nominal rate. This trend was replicated in this study, where the infusion did prove to be greatest over the first two hours, following by a decreased rate. Whether inconsistencies would arise at the end of the infusion duration was not evaluated in this particular study, but this could have implications as well. The Ambu pump did not show the variability in flow during the initial two

hours as seen with the On-Q pump, nor did the Baxter pump. The Ambu was the most consistent pump (Table 1), having the lowest standard deviation (0.089 mL/h). Prior studies have also found inaccuracies in elastomeric infusion pumps. A study by Chung *et al.*^[9] determined that the flow rate of two elastomeric infusors was not sustained uniformly during the entire delivery period, but rather was in proportion to the internal pressure of the infusor^[9]. The infusion rates of the Accufuser Plus, a single-use, elastomeric pump was affected by the volume in the reservoir^[10]. Overfilling the infusion pump by 100 mL resulted in a decreased overall infusion rate throughout a 10 h infusion period^[10]. In this study each balloon was filled with a 200 mL volume. Whether this impacted our results would require another study evaluating infusion rates from different starting reservoir volumes.

This study demonstrates that three modern, single use elastomeric infusion devices have infusion rates that are significantly different from the set nominal delivery volume. This remained true even after corrected the nominal infusion rate for differences in temperature. These alterations in flow may be clinically significant, resulting in either inadequate analgesia, early exhaustion of the reservoir, excessive muscle weakness or the potential for toxicity, especially when used with small pediatric patients. Therefore, in order to provide the best care, physicians must not only take into account the temperature at which the pump will be kept, viscosity of the solution used, and the height of the reservoir but also the infusion profile of the individual pump being used for CPNB.

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The elastomeric infusion devices used in this study were provided by the manufacturer: (1) On-Q pain pump, I-Flow Corporation, Lake Forest, CA; (2) Ambu A/S (Smart Catheter), Denmark; and (3) Baxter Multirate Infusor, Deerfield, IL.

COMMENTS

Background

Portable elastomeric infusion pain pumps are being used with increased frequency in pediatric patients. Because these pumps are infusing potentially toxic doses of local anesthetic medications, the accuracy and consistency of these devices becomes very important in this patient population. This study is a comparison of the actual delivery volume of local anesthetic of three elastomeric infusion devices approved for patient use in the ambulatory setting with regional anesthesia.

Research frontiers

Ultrasound guided pediatric regional anesthesia has become more popular over the past 5 years. The frontier of this utility includes reduction of narcotic consumption potentially leading to decreased hospital stays and improved and efficient postanesthesia care unit discharges. Also, this may help to reduce the general anesthetic requirements in babies who may be exposed to potential neuroapoptotic agents.

Innovations and breakthroughs

The main breakthrough for this discipline has been the utility of ultrasound for safer and more effective placement of regional anesthesia. In addition the known pharmacokinetics and pharmacodynamics of local anesthetics in children is imperative to avoid toxicity.

Applications

The results suggest that utilizing peripheral nerve catheters and related pain pumps should be done with caution. There is great variability in manufacturing as well as external factors.

Peer review

This is a valuable investigation about three modern, single use elastomeric infusion devices. The finding of significant alterations in flow rate than their set nominal delivery volume among the three devices may provide clinical reference for physicians.

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Predictive value of extravascular lung water indexed to predicted body weight

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Abstract

AIM: To investigate extravascular lung water indexed to predicted body weight (EVLWI_p) and actual body weight (EVLWI_a) on outcome of patients with severe sepsis.

METHODS: Transpulmonary thermodilution was prospectively used to measure cardiovascular hemodynamics, EVLWI_p and EVLWI_a via an arterial catheter placed in each patient within 48 h of meeting the criteria for severe sepsis from a medical intensive care unit (ICU) at a university affiliated hospital. Survival was the single dependent variable. In order to examine and compare the predictive power of EVLWI_p, EVLWI_a and other clinically significant factors in predicting the in-hospital survival status of severe sepsis patients in the medical ICU, a receiver operating characteristic (ROC)

curve method to analyze the significant variables and the area under the ROC curve (AUC) of the variables, *P* value and 95%CI were calculated.

RESULTS: In total, 33 patients were studied. In the ROC curve method analyses, EVLWI_p (the AUC: 0.849; *P* = 0.001, 95%CI: 0.72-0.98) was as predictive for in-hospital survival rate as variables with EVLWI_a (AUC, 0.829; *P* = 0.001, 95%CI: 0.68-0.98). The proportion of patients surviving with a low EVLWI (EVLWI < 10 mL/kg) was better than that of patients with a higher EVLWI, whether indexed by actual (HR = 0.2; *P* = 0.0002, 95%CI: 0.06-0.42) or predicted body weight (HR = 0.13; *P* < 0.0001, 95%CI: 0.05-0.35) during their hospital stay with the Kaplan-Meier method (76% vs 12.5%, respectively).

CONCLUSION: This investigation proposed that EVLWI_p is as good a predictor as EVLWI_a to predict in-hospital survival rate among severe sepsis patients in the medical ICU.

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Key words: Extravascular lung water index; Predicted body weight; Actual body weight; In-hospital survival; Severe sepsis

Core tip: Our study provides the important finding that extravascular lung water index (EVLWI) indexed by predicted body weight is as good as it indexed by actual body weight for in-hospital survival in patients with severe sepsis. Clinicians could monitor EVLWI indexed by predicted or actual body weight in patients with severe sepsis.

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water indexed to predicted body weight. *World J Anesthesiol* 2014; 3(1): 124-128 Available from: URL: <http://www.wjg-net.com/2218-6182/full/v3/i1/124.htm> DOI: <http://dx.doi.org/10.5313/wja.v3.i1.124>

INTRODUCTION

Transpulmonary thermodilution to assess extravascular lung water (EVLW) at the bedside by a pulse-induced contour cardiac output (PiCCO) system, a comparatively less invasive method than the traditionally used pulmonary arterial catheter, has been popular to monitor the hemodynamic status of patients in critical care units^[1]. Measuring EVLW is useful to predict outcome, to diagnose pulmonary edema, to better characterize patients with acute respiratory distress syndrome (ARDS), to guide fluid therapy and to assess the value of new treatments or ventilator setting strategies in septic patients with ARDS^[2].

Previously, one study reported the prognostic value of EVLW indexed to actual body weight (EVLWI_a) in critically ill patients^[3]. However, another study reported that EVLW indexed to predicted body weight (EVLWI_p) may improve correlation with severity and survival in sepsis with ARDS. This is because lung size correlates better with height and gender than that of actual body weight^[4]. On the other hand, Drs. Meyer and Hall thought that the transpulmonary thermodilution technique used to calculate EVLWI_p in theory may be inaccurate in cases of high dead space fraction, which may impair equilibration of cold saline across a portion of the extravascular space^[5].

We have reported that EVLW indexed to actual body weight is an independent predictor for in-hospital survival in medical intensive care unit (ICU) patients with severe sepsis^[6]. We conducted this study to compare the predicted value of EVLWI_p and EVLWI_a on in-hospital survival rates of medical ICU patients with severe sepsis.

MATERIALS AND METHODS

Patients

The population being investigated was recruited from patients admitted to a medical ICU of a university affiliated medical center from 2005 to 2006. The institutional review board approved this study and informed consent was obtained from all of the patients or their surrogates. All enrolled patients were recruited consecutively. Patients were followed-up until death or discharge post enrollment. Patients younger than 18 years old, pregnant or with a terminal malignancy were excluded.

All eligible patients were enrolled within 48 h of meeting the criteria for severe sepsis. Severe sepsis was defined by the consensus committee of the American College of Chest Physicians and Society of Critical Care Medicine^[7]. Patient-specific data were obtained upon enrollment, including demographic data, past medical his-

tory, source of sepsis and Acute Physiology and Chronic Health Evaluation (APACHE) II score. The physiological parameters, including the presence of shock status, and the hemodynamic parameters were assessed on patient enrollment. Shock was defined as systolic blood pressure < 90 mmHg or mean arterial pressure < 60 mmHg. Patient management decisions, including the type and amount of volume resuscitation, were based on the discretion of the primary intensive care physician^[8].

Laboratory serological data and the EVLW measurement

The laboratory serological data (albumin, white blood cell counts and platelets) and oxygenation parameters [PaO₂/FiO₂ ratio, lung injury score (LIS) and chest X-ray (CXR) score (the number of quadrants with > 50% involvement in the alveolar filling process)] were recorded simultaneously as EVLW was made available by the PiCCO system. Additional patient records, such as ventilator settings and shock management during ICU admission, were also available.

The EVLW measurement was based on the transpulmonary thermodilution method. This method was recently introduced as part of the PiCCO plus system (Pulsion Medical System, Munich, Germany). This method only used a single indicator (cold saline solution). Following central venous injection of 10 mL iced 0.9% saline solution, continuous cardiac output (CO) and EVLW measurements were obtained. CO and EVLW determinations were performed immediately following catheter insertion and were employed as the hemodynamic parameters for managing the patients in the medical ICU with severe sepsis.

To facilitate comparing the EVLWI_p and actual body weight, these indices are described by the following terms: EVLWI_p refers to EVLW indexed to predicted body weight and EVLWI_a refers to EVLW indexed to actual body weight. ARDS was considered to be present when the American-European Consensus Conference (AECC) criteria^[9] were met during medical intensive care unit hospitalization after monitoring with the PiCCO system.

Statistical analysis

Survival was the single dependent variable. In order to examine and compare the predictive power of EVLWI_p, EVLWI_a and other clinically significant factors in predicting the in-hospital survival status of severe sepsis patients in the medical ICU, a receiver operating characteristic (ROC) curve method to analyze the significant variables and the area under the ROC curve (AUC) of the variables, *P* value and 95%CI were calculated. Patients were also divided into 2 subgroups according to their optimal cutoff values of EVLW obtained by the ROC curve method. Survival days and rate were compared with these subgroups with different EVLW. Kaplan-Meier curves for cumulative survival during the hospitalization observation period were constructed and compared with the use of the log-rank test. All analyses were conducted using SPSS software (version 10.0, SPSS,

Table 1 Baseline characteristics of all severe sepsis patients in a medical intensive care unit

Characteristics	Value
Patients (<i>n</i>)	33
Baseline characteristics	
Age (yr)	65.67 ± 15.49
Male	69.7%
APACHE II score	24.39 ± 7.921
BMI (kg/m ²)	22.30 ± 5.679
Pneumonia	72.73%
Empyema	3.03%
Primary bloodstream infection	9.09%
Pressure sore infection	6.06%
Urosepsis	9.09%
ARDS	33.30%
Physiology at enrollment	
Prior 24 h I/O balance (mL)	2286 ± 1165
Shock (vasopressor requirement)	84.85%
EVLWI (mL/kg)	16.64 ± 11.93
Oxygenation	
PaO ₂ /FiO ₂ ratio	173.4 ± 87.09
CXR score	2.24 ± 1.30
Lung injury score	2.04 ± 0.86
Laboratory data	
Albumin (g/L)	0.021 ± 0.007
Platelet (109/L)	170.03 ± 135.47
WBC (109/L)	15.91 ± 9.24

Values are expressed as mean ± SD, frequency (%), unless otherwise noted. APACHE: Acute Physiology and Chronic Health Evaluation; BMI: Body mass index; ARDS: Acute respiratory distress syndrome; EVLW: Extravascular lung water; CXR: Chest X ray; WBC: White blood cell.

Table 2 Area under receiver operating characteristic curve of variables to predict in-hospital survival rate of medical intensive care unit patients with severe sepsis

Variable (s)	Area under curve	P value	95%CI
EVLWIp	0.849	0.001	0.72-0.98
EVLWla	0.829	0.001	0.68-0.98
APACHE II score	0.721	0.03	0.54-0.90
LIS	0.706	0.04	0.52-0.89
CXR score	0.708	0.04	0.53-0.89

P value compared by receiver operating characteristic curve method to analyze the significance. EVLWIp: Extravascular lung water indexed to predicted body weight; EVLWla: Extravascular lung water indexed to actual body weight; APACHE: Acute Physiology and Chronic Health Evaluation; LIS: Lung injury score; CXR: Chest X-ray.

Chicago, IL, United States) and Prism 4 for Windows (version 4.03, Graphpad Software Inc., San Diego, CA, United States).

RESULTS

This study enrolled thirty-three patients with severe sepsis. Table 1 lists the demographic and underlying diseases. The sources of sepsis included pneumonia (*n* = 24), empyema (*n* = 1), primary blood stream infection (*n* = 3), pressure sore infection (*n* = 2) and urosepsis (*n* = 3). The incidence of ARDS was 33.3% (11/33), according to the AECC definition. The overall 28 d mortality was 51.5% (17/33).

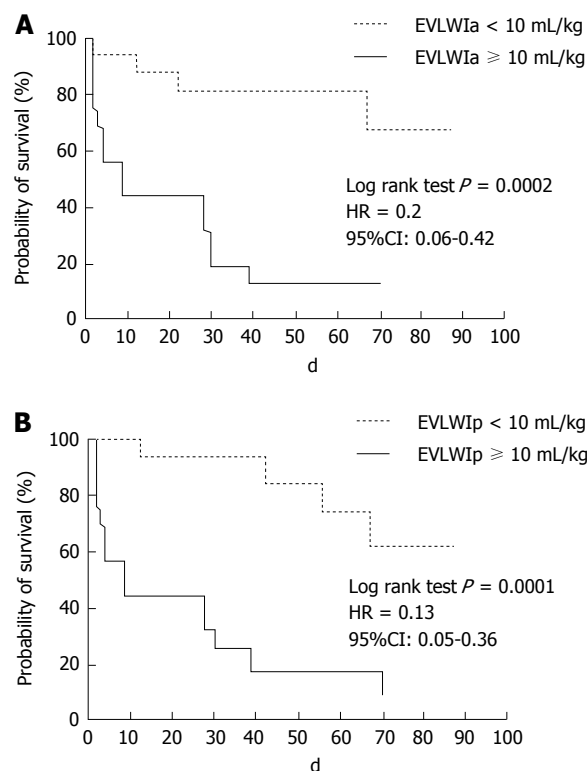


Figure 1 Proportion of patients surviving with a low extravascular lung water. The proportion of patients surviving with a low EVLW (EVLWI < 10 mL/kg) was better than that of those patients with a higher EVLW whether indexed by actual (EVLWla) (A) or predicted body weight (EVLWIp) (B) during their hospital stay with the Kaplan-Meier method (76% vs 12.5%, respectively). ELVMI: Extravascular lung water index.

Upon enrollment, Table 1 lists physiological characteristics, EVLWI, global end-diastolic volume index, systemic vascular resistance index, PaO₂/FiO₂ ratio, LIS and the mean CXR score. Fluid balance (net intake/output) was consistently positive, with a cumulative mean of 2286 ± 1165 mL at 24 h before the EVLW measurement.

In the ROC curve method analysis, the AUC of EVLWIp (0.849) was similar to the AUC of EVLWla (0.829), but larger than that of the APACHE II score (0.721), LIS (0.706) and CXR score (0.708) in Table 2.

The proportion of patients surviving with a low (< 10 mL/kg, 17 patients) and a high (≥ 10 mL/kg) EVLWla were traced during their hospital stay with the Kaplan-Meier method (76% vs 12.5%, respectively; log-rank test, HR = 0.2; *P* = 0.0002, 95%CI: 0.06-0.42) (Figure 1A). The Kaplan-Meier overall survival estimate was also significantly higher for patients with a low EVLWIp (< 10 mL/kg, 17 patients) than for patients with a low EVLWIp (≥ 10 mL/kg) (76% vs 12.5%, respectively; log-rank test, hazard ratio, 0.13; *P* < 0.0001, 95%CI: 0.05-0.35) (Figure 1B).

DISCUSSION

As previous studies have reported, EVLWIp may predict mortality in sepsis with ARDS^[4]. Our study revealed similar results in that EVLW indexed to actual body weight

was a predictor factor of ICU mortality in patients with septic shock; meanwhile, indexing EVLW to predicted body weight did not enhance its discriminatory power as a predictor indicator of mortality.

Although Drs. Meyer *et al.*^[5] thought that the transpulmonary thermodilution technique used to calculate EVLWI_p in theory may be inaccurate in cases of high dead space fraction, which may impair equilibration of cold saline across a portion of the extravascular space, they agreed with the Dr. Phillips study that an average EVLWI_p 16 mL/kg predicted death in sepsis patients with ARDS who had been intubated for 3.5 d.

Our data support the results previously described by Mallat *et al.*^[10] who studied 55 patients with septic shock. In that study, EVLW indexing to actual body weight or predicted body weight is an independent predictor of ICU mortality. In our study, ROC curves showed that both EVLWI_a and EVLWI_p were good discriminators to distinguish between survivors and nonsurvivors. Sakka *et al.*^[3] have shown that EVLW indexed to actual body weight predicted mortality in septic shock patients admitted to the ICU and the measurement of EVLW was done using a thermal-dye dilution method. Nevertheless, since this period, the management of septic shock has changed considerably and the results may be influenced by that study. By demonstrating that EVLWI_a is an independent prognostic factor, we proposed that EVLWI_a measurements should be performed in patients with septic shock and poor outcome should be considered when EVLWI_a values are elevated to more than 10 mL/kg. A similar result was seen in EVLWI_p to predict the outcome of these septic patients. However, further studies are required to assess the effects of EVLW indexed by actual or predicted body weight and the outcome among these patients.

Usually, EVLW measurement has been indexed to actual body weight. However, lung volume was usually determined by height and sex^[11]. Someone reported that EVLW when indexed to predicted body weight was a better prognostic factor of mortality than EVLW indexed to actual body weight in patients with ALI/ARDS^[4,12]. In contrast with these findings, we found that indexing EVLW to predicted or actual body weight was not more precise to differentiate between survivors and nonsurvivors. Therefore, in that study, the outcome between EVLWI_a and EVLWI_p might probably have been linked to the baseline characteristics between the survivors and nonsurvivors.

In fact, our study supports that both EVLWI_a and EVLWI_p are better predictors than other independent variables, including APACHE II score, LIS and CXR score, to predict in-hospital survival rate in medical ICU patients with severe sepsis. However, further studies are warranted to investigate the effects of correcting EVLWI_p and EVLWI_a and the clinical outcome among these patients. Also, validation of the EVLWI_p to gravimetric lung water may be conducted in animal models to compare it to EVLWI_a.

There are some limitations in the current study. Firstly, Frederic Michard reported that the limitations of dilution methods may lead to an underestimation of EVLW

in large pulmonary vascular obstruction, focal lung injury and lung resection, but dilution methods remain an easy and clinically acceptable estimation of EVLW in most critically ill patients, including those with ARDS^[2]. Secondly, our study is limited by a modest sample size. Nevertheless, we have demonstrated the ability of EVLW indexes to predict ICU outcome in septic shock patients. In addition, there has been previous discussion regarding the potential limitations associated with the single indicator transpulmonary thermodilution technique^[13].

In conclusion, this study demonstrated that severe sepsis patients with elevated EVLW were more vulnerable to mortality, whether indexed to predicted or actual body weight. EVLWI_p may provide predictive value to in-hospital survival in patients with severe sepsis as good as EVLWI_a. However, further studies are needed to determine whether correcting elevated EVLWI_p or EVLWI_a would affect clinical outcomes in patients with severe sepsis.

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COMMENTS

Background

Transpulmonary thermodilution to assess extravascular lung water (EVLW) at the bedside by pulse-induced contour cardiac output system, which is comparatively a less invasive method than the traditionally used pulmonary arterial catheter has been popular to monitor the hemodynamic status of patients in the critical care units.

Research frontiers

Their study revealed similar result that EVLW indexed to actual body weight was a predictor factor of intensive care unit (ICU) mortality in patients with septic shock, meanwhile, indexing EVLW to predicted body weight did not enhance its discriminatory power as a predictor indicator of mortality.

Innovations and breakthroughs

This investigation proposed that EVLW indexed to predicted body weight (EVLWI_p) is a good predictor as EVLW indexed to actual body weight to predict in-hospital survival rate among severe sepsis patients in the medical ICU.

Peer review

This study assesses the prognostic value of EVLW in medical ICU patients with severe sepsis. The authors conclude that EVLWI_p is a better predictor of survival than other indices.

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Endoscopic removal of a self-expanding metallic airway stent: A case report

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Abstract

Self-expanding metallic stents are sometimes placed for the management of obstructing airway lesions or conditions such as airway wall malacia or tracheal stenosis. However, endoscopic removal of these devices from the airway can pose extreme challenges for both clinical airway management as well as for the administration of general anesthesia. We report on a 61-year-old man with a complex cardiac history presenting for endoscopic stent removal necessitated by the formation of extensive granulation tissue. Comorbidities included a history of myocardial infarction, an ischemic cardiomyopathy with severe left heart failure (ejection fraction of 25%), mild right heart failure, 2+ tricuspid regurgitation status post tricuspid valve repair, and atrial fibrillation. An automatic external (wearable) cardiac defibrillator (Zoll Life Vest) was also in place. Induction of anesthesia was carried out using etomidate, with maintenance of anesthesia carried out with a propofol infusion (total intravenous anesthesia). Rocuronium was used for neuromuscular blockade. A size 4 iGel su-

praglottic airway and, later, rigid bronchoscopy formed the basis for airway management. Stable conditions were met through the 2-h procedure, and the patient recovered uneventfully. Our successful experience in this case leads us to propose further use of a supraglottic airway in conjunction with total intravenous anesthesia for these procedures.

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Key words: Airway management; Flexible bronchoscope; Rigid bronchoscopy; Self-expanding metallic stents; Supraglottic airway; Total intravenous anesthesia

Core tip: Endoscopic removal of self-expanding metallic airway stents may be necessitated by the formation of extensive granulation tissue, but can pose difficult challenges to both the proceduralist and the anesthesiologist. Total intravenous anesthesia utilizing a propofol infusion and rocuronium for neuromuscular blockade can be useful in such cases. Induction of general anesthesia with etomidate can be useful in patients with poor ventricular function. Airway management can be achieved with an iGel supraglottic airway and later, rigid bronchoscopy.

Ye YA, Machuzak MS, Doyle DJ. Endoscopic removal of a self-expanding metallic airway stent: A case report. *World J Anesthesiol* 2014; 3(1): 129-133 Available from: URL: <http://www.wjgnet.com/2218-6182/full/v3/i1/129.htm> DOI: <http://dx.doi.org/10.5313/wja.v3.i1.129>

INTRODUCTION

The incidence of central airway obstruction is on the rise, paralleled with the increasing incidence of lung cancer^[1-4]. The advent of endoscopic methods has allowed for

less invasive management of these patients, with airway stenting as one of several options available to patients with central airway obstruction^[3,5-9]. Silicone and self-expandable metallic airway stents (SEMS) are of the two main options in managing the airway in such cases. While silicone stents are often the preferred modality, SEMS are frequently used in cases of airway wall malacia or stenosis, especially in the context of malignancy.

SEMS have the advantage over silicone stents of a lower migration rate, thinner wall construction (allowing for greater cross-sectional airway diameter), and conformation to irregular airways^[6]. However, they are prone to excessive granulation and stent fracture^[6]. Indications for SEMS removal include excessive or recurrent granulation, stent failure or fracture, infection, mucous plug formation, stent migration, or achievement of successful treatment^[10-12]. While SEMS placement is usually achievable with relative ease, endoscopic removal of these stents can be very difficult^[10,11,13]. Complications during stent removal may include pneumothorax; tracheal, bronchial, laryngeal or pulmonary artery damage, and airway obstruction during or following stent removal. Furthermore, when a rigid bronchoscope is used, leaks around the bronchoscope can pose a problem, especially when using potent inhalational agents such as sevoflurane^[14]. These issues can pose a great challenge to all participants^[14].

CASE REPORT

The patient was a 61-year-old man who presented for SEMS removal from the lower trachea *via* rigid bronchoscopy. The indications for the stent removal were recurrent bacterial infections, and granulation tissue/stricture formation. His cardiac history included a history of myocardial infarction, ischemic cardiomyopathy with severe left heart failure (ejection fraction of 25%), mild right heart failure, 2+ tricuspid regurgitation status post tricuspid valve repair, and atrial fibrillation. An automatic external (wearable) cardiac defibrillator (AED) (Zoll Life Vest)^[15] was in place. Other past medical history included hypertension, hyperlipidemia, and chronic obstructive pulmonary disease. In 1998, following a severe myocardial infarction he underwent endotracheal intubation, tracheostomy and mechanical ventilation for 3 mo, and subsequently developed tracheal stenosis. His tracheostomy remained for one year before being reversed. Following reversal he continued to have recurrent tracheal stenosis, and underwent a tracheal resection, re-anastomosis and placement of two SEMS, which had remained in place for 13 years. In an attempt to minimize recurrent granulation tissue after his re-anastomosis he also received multiple radiation treatments to his trachea.

At the time of initial presentation to Cleveland Clinic, he had 50%-74% narrowing of the upper and lower third of the trachea. The two stents were found embedded throughout the whole trachea. He previously had a total of 50 bronchoscopic procedures to remove granulation tissue and scarring. He initially presented to our facility

for attempted removal of an infected pacemaker/international classification of diseases lead resulting in recalcitrant bacteremia. Prior to undergoing this procedure, given his history of tracheal stenosis, our interventional pulmonary team was consulted to maximize his airway for endotracheal tube placement. During his initial bronchoscopy it was felt that an attempt at removal was reasonable given the tremendously negative effect on his quality of life from the stents. The SEMS in the upper trachea was removed successfully using a combination of the electrocautery blade and rigid debulking. At this time, we focused on removing his lower SEMS, which remained a challenge given its position in the lower portion of the airway.

The patient had a Mallampati class III airway^[16,17] with no other significant airway abnormalities. His height was 177.8 cm, and weight was 106.8 kg. Physical examination was within normal limits with the exception of a productive cough, expiratory wheeze and occasional stridor. Given his cardiac history, he was judged to be American Heart Association IV. Blood pressure on day of the procedure was 109/67 mmHg, with a pulse rate of 61/min. Hemoglobin was 9.7 g/dL. Blood biochemistry was within normal limits. His electrocardiogram showed normal sinus rhythm, and echocardiography revealed a left ventricular ejection fraction of 25%. His chest X-ray showed bilateral scattered densities, but otherwise free of focal consolidations or masses. On the morning of the procedure, he had received the following oral medications: potassium 10mEq, primidone 50 mg, gabapentin 300 mg, and metoprolol 25 mg. He had been off clopidogrel for 6 d^[18,19].

We proceeded with general anesthesia, opting for total intravenous anesthesia (TIVA). His wearable AED was removed after induction due to the likelihood of using cautery. The patient was induced with the following intravenous drugs: etomidate 14 lidocaine 50 mg, midazolam 2 mg, of rocuronium 50 mg, and a 120 mcg/kg per minute propofol infusion. Following induction, he was intubated with a size 4 iGel supraglottic airway (SGA)^[20-22] without difficulty. After SGA placement, the patient's blood pressure dropped slightly to 100/65. Subsequently, the propofol infusion was decreased to 90 mcg/kg per minute; a phenylephrine infusion of 50 mcg/min was started for a total of 15 min. Blood pressure responded adequately. After the patient was fully anesthetized, a flexible bronchoscope was introduced through the iGel SGA and advanced to the tracheobronchial tree. A full airway inspection was performed with the flexible bronchoscope. The iGel SGA was then removed and an orange-stripe (13.2 mm) bronchial rigid scope was introduced (Bryan-Dumon). Ventilation was achieved through the side arm of the rigid bronchoscope.

Several precautionary measures were taken prior to the removal phase in the event that the stent could not be removed or unforeseen airway obstruction occurred. Ventilation with 100% oxygenation was achieved prior to the periods of apnea required during cautery. To prepare for possible SEMS fracture during the removal phase,

balloon dilators were ready so as to facilitate in dissecting the SEMS from the airway wall, expanding the airway in case of collapse and tamponading bleeding. An electrocautery knife was then used to make long cuts through the overgrown granulation tissue and scar in the lower trachea. This was done in order to facilitate debulking of this tissue with the rigid beveled tip. Once the tissue was debulked, sections of the SEMS were able to be separated from the airway wall. As more of the stent was liberated, it was felt appropriate to attempt removal. Approximately 90%-95% of the lower tracheal stent was removed *via* forceps. The patient was maintained with two more 10 mg boluses of rocuronium through the case. Pressure controlled ventilation with 15 lpm O₂ delivery was used with appropriate pauses during cauterization. He was maintained on an average pressure of 27 cm H₂O, positive end expiratory pressure of 3 cm H₂O, minute ventilation of 3.7 L/min, inspiratory to expiratory ratio of 1:2, and a respiratory rate of 12/min. Through the 2 h case, the patient's blood pressure ranged from 100/65 to 145/100 mmHg, and heart rate ranged from 50 to 65/min. Oxygen saturation from pulse oximetry remained between 90%-100%. The patient received 700 mL of normal saline solution, and had an estimated blood loss of 5 mL. Towards the end of the case, the patient received 50 mcg of fentanyl, 20 mg of lidocaine, and 4 mg of ondansetron. For reversal of the rocuronium, he received 2.5 mg of neostigmine and 0.5 mg of glycopyrrolate. After confirming spontaneous breathing, strong hand grip, and sustained head lift for 5 s, the patient was extubated without difficulty. He was able to communicate shortly after extubation. He recovered in the post-anesthesia care unit without any post-operative nausea or vomiting or respiratory complications. End-of-operation blood pressure was 130/70 mmHg, heart rate was 51/min, respiratory rate was 16/min, and oxygen saturation was 97% on 3 lpm O₂ delivered *via* nasal cannula.

DISCUSSION

Two of the main concerns in removal of SEMS are the risk of airway obstruction from stent fracture or bleeding during stent removal. Additionally, the use of electrocautery devices and balloon dilatation necessitates full communication between the surgeon and the anesthesiologist. We initially elected to use an iGel, a supraglottic airway, given the patient's previous upper tracheal stent, which might have led to difficulties with attempted use of an endotracheal tube (ETT). A previous case series comparing the i-Gel to ETTs found comparable ventilation overall^[23]. Further, iGels are superior to ETTs regarding ease of insertion; compared to laryngeal mask airways, iGels also guarantee proper positioning for supraglottic ventilation. Given the need to switch between ventilation with various devices, the iGel allowed for a rapid and easy transition between ventilation through the bronchoscope and through the iGel. While the iGel does not guarantee a definite airway compared to the ETT^[14], we shortly

replaced the iGel with a rigid bronchoscope that allowed for a more defined airway. During the removal phase, a clear communication line was made between the interventional pulmonologist and the anesthesiologist^[14]. The patient was oxygenated with 100% oxygen, which helped maintain adequate oxygenation throughout periods of apnea during cauterization.

Overall, our patient did well with the supraglottic airway management device followed by ventilation *via* rigid bronchoscope, requiring only one trial of placement without trauma, and minimal use of anesthetic agents through the two-hour case. He recovered without difficulty, with only a brief period of coughing, and recovered well the post-anesthetic care unit to go home that same day.

Current practice has leaned towards using balanced anesthesia with both intravenous and inhalational agents, although the debate on this topic remains in evolution^[24,27]. As discussed below, in bronchoscopic cases we tend to avoid the use of potent inhalational agents both because of concerns for operating room pollution and the fact that delivery of the agent to the patient can at times be unreliable^[14]. One of the concerns with the use of TIVA is inadvertent consciousness during the procedure^[28,29]; in our patient, we were able to monitor depth of anesthesia with Bispectral Index monitoring, maintaining a level of less than 50 through the case.

This concern notwithstanding, however, there are several advantages of using TIVA in bronchoscopy procedures. As noted above, even with procedures not involving the airway, there are concerns over contamination of the work-space environment by inhalant anesthetics. In removal of the SEMS, the airway circuit had to be periodically disrupted and disconnected to allow for introduction of different types of bronchoscopes, introducing the possibility of leakage of various gas into the operating room; the use of TIVA allows for avoidance of contamination. Studies comparing TIVA and inhalational anesthetics found better surgical field view in endoscopic sinus surgery with decreased operative time and reduced intraoperative bleeding^[30,31]. During the surgery, there was little bleeding in the trachea, and the surgical field view was clear. Other benefits of TIVA include less post-operative nausea and vomiting^[32-35], resulting in better post-operative recovery. In our case, the patient reported no post-operative nausea or vomiting, and was able to be discharged the same day of surgery.

Anesthetic agents can have an adverse effect on patients with heart failure, causing diminished cardiac reserve by depressing the sympathetic system and myocardium, as well as modifying cardiovascular control mechanisms^[36]. Etomidate is a carboxylated imidazole derivative that enhances GABA activity, and is commonly used as an induction agent in patients with a history of heart failure as it causes minimal cardiac depression compared to induction agents such as propofol. The standard induction dose of etomidate is 0.3 mg/kg^[37]. Only in supratherapeutic doses does etomidate have a negative inotropic effect^[37]. Etomidate infusions have

been shown to inhibit 11-beta-hydroxylase activity, leading to suppression of adrenocorticoid synthesis^[38]; it is debatable whether this happens with single boluses of etomidate^[39-44]. Another advantage of using etomidate for induction includes its rapid onset effect with short period of action; etomidate has also been shown to maintain hemodynamic stability in patients with hypovolemia or shock^[45]. We used a 14 mg induction bolus for our patient, and he was able to maintain adequate hemodynamic stability through the case, only requiring 15 min of phenylephrine infusion of 50 mcg/min.

Cases similar to ours have been reported. Chawla *et al*^[11] described a case of a patient who developed cough and dyspnea one and a half years after SEMS placement. The authors identified “stenosis above the level of stent with granulation tissue inside the stent, stent fracture in lower part and stent migration to right main bronchus”, necessitating stent removal under general anesthesia with the assistance of a rigid bronchoscope. Fruchter *et al*^[13] conducted a retrospective review of patients requiring tracheobronchial stent placement after lung transplantation in which the SEMS had to be removed. In six of the 24 patients receiving a SEMS, the stent “had to be removed due to excessive granulation tissue formation and stent obstruction” with the average time from placement to removal being 30 mo. Of these six patients, the stent was able to be completely removed in all but one case, and no major complications were encountered. This series differed from our case in that the procedures were carried out under conscious sedation rather than general anesthesia, and utilized flexible bronchoscopy rather than rigid bronchoscopy.

In conclusion, a patient with multiple severe comorbidities did well with our anesthetic technique of using a supraglottic airway management device, TIVA and etomidate for removal of a SEMS. Future SEMS removal may proceed with such a similar technique.

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Dexmedetomidine vs propofol in intensive care unit patients

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Abstract

Dexmedetomidine is indicated as a sedative agent in intensive care units (ICUs). While several clinical trials and two meta-analyses have compared this agent with propofol or midazolam, the results were variable depending on the specific end-point (*e.g.*, duration of mechanical ventilation, ICU mortality, maintaining a target depth of sedation, incidence of delirium episodes, length of hospital stay). Hence, the effectiveness of this new agent *vs* the comparators seems to be controversial. Trial sequential analysis (TSA) is a statistical technique that can estimate the optimal, cumulative number of patients that would be needed to generate a conclusive result. We therefore applied a TSA model to the most recent meta-analysis evaluating dexmedetomidine. A total of 10 randomized controlled trials were included in our analysis. According to our results, the comparison of dexmedetomidine *vs* propofol showed no proof of incremental effectiveness for the end-points of length of ICUs stay and incidence of delirium episodes. In contrast, futility (*i.e.*, proof of no incremental effectiveness) was demonstrated for the end-point of mechanical ventilation. Hence, the results for the comparison of dexmedetomidine *vs* propofol were inconclusive for the first two end-points; on the other hand, conclusiveness was reached for the third end-point. We conclude that the place of dexmedetomidine in therapy of critically ill patients is very uncertain and further con-

trolled trials are still needed.

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Key words: Dexmedetomidine; Propofol; Midazolam; Sedation; Intensive care unit; Mechanical ventilation; Hospital stay; Meta-analysis; Trial sequential analysis

Core tip: Dexmedetomidine, a sedative agent for critically ill patients, has been studied in several randomized trials and in two meta-analyses. The clinical results were conflicting because of the diversity of the end-points and the small size of most studies. Since trial sequential analysis can improve the interpretation of controversial meta-analyses, we applied this technique to dexmedetomidine. According to our results, the comparison of dexmedetomidine *vs* propofol showed no proof of incremental effectiveness (for length of intensive care unit (ICU) stay and incidence of delirium) or of no incremental effectiveness (for duration of mechanical ventilation). Hence, the therapeutic role of dexmedetomidine in ICU is still uncertain.

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TO THE EDITOR

Dexmedetomidine is increasingly being used as a sedative agent in intensive care units (ICUs)^[1,2]. Several clinical trials have compared this relatively new agent with propofol or midazolam^[2], based on the end-point of maintaining a target depth of sedation (*i.e.*, score of 0 to -3 according to the Richmond Agitation Sedation Scale). Most of these trials have shown non-inferiority^[3] or no difference^[4,5] for dexmedetomidine *vs* the comparator. Sedative

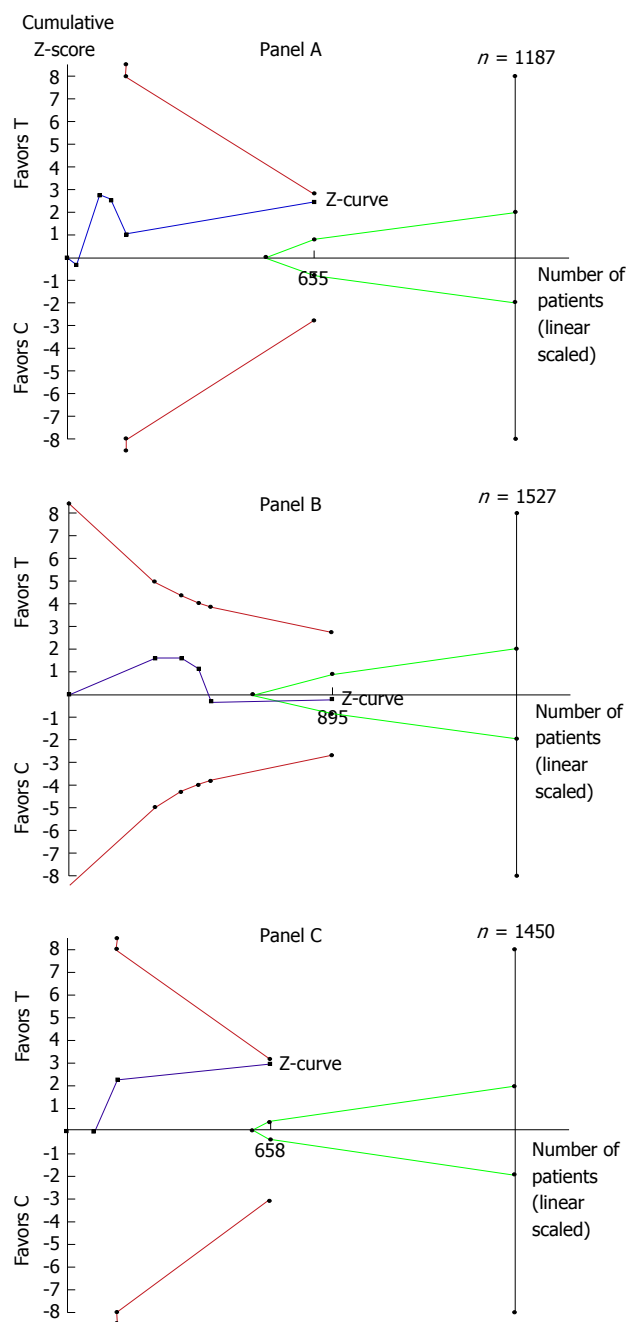


Figure 1 Trial sequential analysis of 10 randomized controlled trials evaluating dexmedetomidine *vs* propofol according to the end-points of length of Intensive Care Unit stay (in days, Panel A), length of mechanical ventilation (in days, Panel B) and delirium episodes (Panel C). In the Z-curve (represented in blue), individual trials correspond to individual segments; trials are plotted in chronological order (from left to right). The X-axis indicates the cumulative number of patients; the starting point of the Z-curve is always at X = 0, *i.e.*, inclusion of no trials. Abbreviations and symbols: Red lines are the boundaries for superiority or inferiority, and green lines for futility (*i.e.*, proof of no incremental effectiveness). T: Treatment arm (dexmedetomidine); C: Control arm (propofol).

agents are often associated with clinically relevant adverse events (*e.g.*, prolonged mechanical ventilation, prolonged ICU stay and high incidence of neurocognitive adverse events like delirium). Dexmedetomidine is supposed to lower the incidence of these events^[3] but the effectiveness of this new agent *vs* the comparators is still uncertain.

Two meta-analyses^[1,6] have evaluated the effectiveness of dexmedetomidine as a sedative agent in ICUs. The most recent one was conducted by Xia *et al*^[1] and included 10 randomized controlled trials that compared dexmedetomidine with propofol according to a variety of end-points (namely: length of ICU stay, ICU mortality, duration of mechanical ventilation and incidence of delirium episodes). The pooled results showed no difference between the two treatment strategies in duration of mechanical ventilation (5 trials, 895 patients) and ICU mortality (5 trials, 267 patients). On the other hand, dexmedetomidine showed a significantly lower incidence of delirium (3 trials, 658 patients) and shorter length of ICU stay (5 trials, 655 patients) than propofol.

Trial sequential analysis (TSA)^[7] is a relatively new technique that can be applied to the clinical material included in a meta-analysis. The main advantage of TSA lies in its ability to re-interpret a non-significant meta-analysis and, in particular, to differentiate its results between inconclusiveness (*i.e.*, no proof of difference) and demonstrated non-inferiority/futility (*i.e.*, proof of no difference). Another advantage is that TSA estimates the “optimal information size” for the comparison under examination and is therefore able to indicate how many patients would be required to generate a conclusive result^[8-12]. As regards its limitations, on the one hand TSA shares virtually all limitations already known for meta-analysis; on the other hand, one specific limitation of TSA is represented by the need to declare a pre-specified margin for the incremental clinical benefit (*i.e.*, the threshold separating a clinically irrelevant benefit from clinically relevant one); this margin is essentially the same as that commonly employed for sample size estimation or non-inferiority statistics.

To test to which degree the results of the above mentioned meta-analysis were conclusive and to determine the optimal information size for this therapeutic problem, we carried out a TSA to re-analyze the data of Xia *et al*^[1]. Our analysis examined the following three end-points: length of ICU stay, duration of mechanical ventilation and incidence of delirium episodes. Our assumptions included two-sided testing, type 1 error = 5%, power = 80%. The assumption of no difference (or margin) was defined as a difference of ≤ 1 d for the end-point of length of ICU stay, a difference of ≤ 6 h for the end-point of duration of mechanical ventilation, and a relative risk reduction of $\leq 40\%$ for the incidence of delirium episodes. As usual, the output of the analysis was represented by the Z-curve graph; in this graph, the boundaries for superiority, inferiority and futility were determined according to the O’Brien-Fleming alpha-spending function. All calculations were carried out using specific statistical software (TSA, User Manual for TSA, Copenhagen Trial Unit 2011, software downloadable at www.ctu.dk/tsa).

Figure 1 summarizes the results of our TSA. Overall, our findings indicate that the comparison of dexmedetomidine *vs* propofol is inconclusive (*i.e.*, no proof of incremental effectiveness) for the two end-points of length

of ICU stay (Panel A) and incidence of delirium episodes (Panel C). On the other hand, our results demonstrate futility (*i.e.*, proof of no incremental effectiveness) for the end-point of mechanical ventilation (Panel B). As shown in Figure 1, the last point of the Z-curve remained within the area of inconclusiveness (since the curve did not cross any boundaries) in Panels A and C; in contrast, in Panel B, the Z-curve crossed the boundary of futility and therefore reached a conclusive but negative result. More importantly, in the two panels showing inconclusiveness (*i.e.*, Panels A and C), the number of patients enrolled in the available trials was much lower than the optimal information size as determined by the TSA model.

We conclude that further data are still needed to assess the place of dexmedetomidine in therapy of critically ill patients.

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In press

- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature

of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

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- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

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Personal author(s)

- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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- 12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

Patent (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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