The material included in the publication has not undergone peer review or review by the Editorial Board of Anesthesia and Analgesia for this publication. Any of the material in this publication may have been transmitted by the author to IARS in various forms of electronic medium. IARS has used its best efforts to receive and format electronic submissions for this publication but has not reviewed each abstract for the purpose of textual error correction and is not liable in any way for any formatting, textual, or grammatical error or inaccuracy. ©2010 International Anesthesia Research Society
Table of Contents

Ultrasound Guided Regional Anesthesia in Infants, Children and Adolescents
Santhanam Suresh, MD FAAP .......................... 1
Vice Chairman, Department of Pediatric Anesthesiology, Children's Memorial Hospital
Prof. of Anesthesiology & Pediatrics, Northwestern University's Feinberg School of Medicine, Chicago, IL

Neuromuscular Blockers and their Reversal in 2010
François Donati, PhD, MD .............................. 6
Professor, Department of Anesthesiology
Université de montréal
Montréal, Québec, Canada

Anaphylactic and Anaphylactoid Reactions in the Surgical Patient
Jerrold H. Levy, MD, FAHA ............................. 11
Professor and Deputy Chair for Research, Emory University School of Medicine
Co-Director of Cardiothoracic Anesthesiology, Cardiothoracic Anesthesiology and Critical Care
Emory Healthcare, Atlanta, Georgia

Update on Thoracic Epidurals: Are the Benefits Worth the Risks?
Hugo K. Van Aken, MD, PhD, FANZCA, FRCA .... 17
Professor, Department of Anesthesiology and Intensive Care,
University Hospital Muenster
Muenster, Germany

Perioperative Glucose Control
George M. Hall, MB, BS, PhD, DSc, (Med), CBiol,
FSB, FRCA, FCARCSI ............................... 24
Professor of Anaesthesia
St George's University of London
London, United Kingdom

Can Regional Anesthesia Coexist with DVT Prophylaxis?
Terese T. Horlocker, MD ............................. 28
Department of Anesthesiology
Mayo Clinic, Rochester, MN

Does Blood Save Lives?
Colleen Koch, MD, MS, MBA ........................ 34
Professor of Anesthesiology,
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University
Department of Cardiothoracic Anesthesia
Cleveland Clinic Foundation, Cleveland, Ohio

Neuroanesthesia for the Occasional Neuroanesthesiologist
Adrian W. Gelb ........................................... 36
Professor & Vice Chair
Department of Anesthesia & Perioperative Care
University of California San Francisco

Perioperative Control Of Hypertension: When Does It Adversely Affect Perioperative Outcome?
John W. Sear, MA, PhD, FFARCS, FANZCA .... 39
Nuffield Department of Anesthetics,
University of Oxford, John Radcliffe Hospital
Oxford, United Kingdom

Perioperative Approach to Patients with Respiratory Disease: Is There a Role for Pulmonary Function Evaluation?
Thomas J. Gal, MD ................................. 46
Emeritus Professor of Anesthesiology
University of Virginia Health System,
Charlottesville, Virginia

Vexing Pediatric Anesthesia Issues for the Generalist Anesthesiologist
Peter J. Davis, MD ................................. 50
Anesthesiologist-in-Chief, Children's Hospital of Pittsburgh
Professor of Anesthesiology & Pediatrics
University of Pittsburgh School of Medicine,
Pittsburgh, Pennsylvania

Valvular Heart Disease in the Patient Undergoing Noncardiac Surgery
Nancy A. Nussmeier, MD ............................. 54
Chair, Department of Anesthesiology
SUNY Upstate Medical University, Syracuse, NY

Postoperative Nausea and Vomiting: Past, Present, and Future
Paul F. White, PhD, MD, FANZCA .................... 60
Department of Anesthesiology & Pain Management,
University of Texas Southwestern Medical Center,
Dallas, Texas and the Departments of Anesthesia at Policlinico Abano Terme and Parma University in Italy, and Cedars Sinai Medical Center in Los Angeles

(continued)
## Table of Contents, continued

**News You Can Use:**

**Obstetric Anesthesia in the 21st Century**
*Cynthia A. Wong, MD.*
Professor, Northwestern University
Feinberg School of Medicine
Medical Director, Obstetric Anesthesiology
Northwestern Memorial Hospital, Chicago, IL

---

**Obstructive Sleep Apnea Patients:**
*A Challenge for Anesthesiologists*

*Frances Chung, MD FRCPC.*
Professor of Anesthesia, Department of Anesthesia
University Health Network, University of Toronto
Toronto, Ontario, Canada

---

**Does fluid restriction improve outcomes of surgical patients?**
*Tong J Gan, MD, FRCA, MHS.*
Department of Anesthesiology,
Duke University Medical Center,
North Carolina, USA

---

**What’s New in Critical Care Medicine?**

*Robert N. Sladen, MD.*
Professor and Executive Vice-Chair; and Chief, Division of Critical Care
Department of Anesthesiology
College of Physicians & Surgeons
of Columbia University
New York, NY

---

**How does an injury cause pain?**

*Tony L. Yaksh, PhD.*
Department of Anesthesiology,
University of California, San Diego

---

**Update on Malignant Hyperthermia**

*Denise Wedel, MD.*
Professor of Anesthesiology
Mayo Clinic College of Medicine
Ultrasound Guided Regional Anesthesia in Infants, Children and Adolescents

Santhanam Suresh, MD FAAP
Vice Chairman, Department of Pediatric Anesthesiology, Children's Memorial Hospital
Prof. of Anesthesiology & Pediatrics, Northwestern University's Feinberg School of Medicine, Chicago, IL

INTRODUCTION
Regional anesthesia is experiencing resurgence in pediatric anesthesia. The use of a variety of techniques has improved with the use of ultrasound guidance. The increased safety of performing regional anesthesia with US-guidance has encouraged the practitioner to attempt to perform more difficult blocks compared to previously described using landmark techniques. The use of US-guidance can also allow minimal volumes of local anesthetics thereby decreasing the potential risk of toxicity. This lecture will describe the equipment used for ultrasound guided pediatric regional anesthesia along with common applications of ultrasound guided nerve blocks. Central neuraxial as well as peripheral nerve blocks will be described with clinical techniques as well as images for reference while performing these blocks. Comprehensive reviews are available for greater depth of knowledge in this relatively newer field in pediatric anesthesia.

EQUIPMENT
As the field of regional anesthesia is exploding, the use of ultrasound imaging is undergoing constant improvement. Several ultrasound imaging systems with the capability of offering a variety of applications including echocardiography have entered the market with greater emphasis on user-friendliness and portability. This may be of greater importance in the pediatric population since most of these blocks are performed in the operating room under general anesthesia. In children, it may be easier to perform regional anesthesia with deep sedation or under general anesthesia US probes commonly used in children include a high frequency hockey stick probe and a linear 25 mm high frequency probe. Since most of the neurovascular structures are located superficially in children, visualization of neural structures is easier with a high frequency probe. The physics and equipment descriptions can be found in textbooks on US guided regional anesthesia. US guidance can be used for central neuraxial blocks as well as for peripheral nerve blocks. A brief description of each of these blocks will be provided at this refresher course.

(i) Central neuraxial blocks:

Epidural Analgesia: Ultrasound imaging seems promising for use either pre-procedurally (prior to puncture) or during block performance (US-aided), although the latter may be most suitable in infants and children under 5 years of age where there is lack of significant ossification. The largely cartilaginous posterior vertebral column of neonates and infants enables good US beam penetration to view the spinal structures and can in some cases may enable a view of the needle tip trajectory.

TECHNIQUES

Sonoanatomy: A moderate-high frequency probe (hockey stick, 13-6 frequency probe) is utilized using a paramedian longitudinal view. The ‘window’ between the two spinous processes (appearing as a saw tooth hypoechoic structure) will allow the operator to visualize the anterior complex (anterior duramater, and the posterior longitudinal ligament), the posterior duramater and the ligamentum flavum. Our preference is to visualize the neuraxis using a paramedian approach. In a paramedian longitudinal view at the thoracic spine, the spinous processes are represented by slanted hyperechoic lines beneath the homogeneous-appearing paravertebral muscle mass. Dorsal shadowing will be apparent deep to the spinous processes and other posterior vertebral elements. The highly hyperechoic ligamentum flavum and dura mater are captured lying in the alternate ‘windows’, and the underlying spinal cord appears largely hypoechoic with an outer bright covering of the pia and a central line of hyperechogenicity (median sulcus). In the first report of US imaging in central blockade, Chawathe et al. performed a pilot study in 12 patients (1 day old to 13 months) to evaluate the possibility of detecting catheters, and verifying their placement, within the epidural space after placement (within 24 hours) via the direct lumbar route. The important point from this paper is that US imaging (specifically using the midline approach) of static structures such as catheters can be performed, yet only reliably in very young patients where much of the posterior bony elements of the spinal column may exist as cartilage allowing good US beam penetration. An optimal angle of probe alignment needs to be evaluated in children and surrogate markers for viewing needles and catheters may be necessary to facilitate a dynamic technique. Willschke et al placed epidural catheters under real-time US-guidance using a paramedian longitudinal imaging plane in 35 neonates. Needle tip entry and the injection of local anesthetic solution within the epidural space were used to confirm epidural placement. Epidural catheters could only be identified via surrogacy through tissue movement (i.e., downward movement of the duramater) and fluid injection. This is the preferred technique that we use. It is important to
note that loss of resistance has to be carried out with the use of saline since LOR with air will obliterate the US imaging of the structures.

Caudal Needle Placement

Caudal blocks, including both single-shot caudal and lumbar or thoracic epidural catheters advanced from the caudal epidural space (thus avoiding the spinal cord), is a commonly practiced regional anesthesia technique in children. Although this technique is practiced with the identification of landmarks, there is a small, but not insignificant chance for failure.

Sonoanatomy: Ultrasound imaging at the midline using both transverse and longitudinal alignment of the probe should be performed prior to needle placement in order to appreciate the patient's anatomy and to identify the sacroccygeal ligament, dural sac and cauda equina. A linear high-frequency small footprint or hockey-stick probe is a suitable choice, although a larger footprint may be used when viewing the longitudinal axis to allow an adequate field of view. Placing the probe initially in a transverse plane at the coccyx and scanning in a cephalad direction can help with landmark identification particularly during training in sonoanatomy. This view allows a good delineation of the sacral hiatus; the sacral cornua are viewed laterally (as "humps") and the sacral hiatus is located between an upper hyperechoic line representing the sacroccygeal membrane/ligament and an inferior hyperechoic line representing the dorum of the pelvic surface (base) of the sacrum. Placing the probe longitudinally between the sacral cornua will capture the dorsal surface of the sacrum, the dorsal aspect of the pelvic surface of the sacrum and the sacroccygeal ligament. The sacroccygeal ligament covers the sacral base beyond the end of the dorum of the sacrum. It appears as a relatively thick linear hyperechoic band, sloping caudally. The sacral hiatus is identified as a hypoechoic space located between the dorum of the sacrum and the dorsal side of the pelvic surface of the sacrum. In older patients where the structures may be ossified at the midline, the paramedian longitudinal view may be necessary since it will allow the US beam to penetrate the spaces on either side of the spinous processes. This paramedian view would allow appreciation of the ventral movement of the duramater during fluid injection, but would not allow a real-time view of the needle along its axis.

Technique: During or after skin puncture with the needle, both transverse and longitudinal sonographic planes can be used for confirming caudal epidural needle placement. Roberts at al. published a prospective observational study of 60 children, in which they determined whether a saline test bolus could be reliably imaged with US in order to confirm cannula placement in the caudal epidural space. (Roberts, 2005 #29203; Roberts, 2005 #29204) The longitudinal plane may allow a view of the long axis of the needle as it penetrates the sacroccygeal ligament. This technique may be particularly beneficial to allow adjustments in needle angle to ensure adequate length of advancement and depth of penetration without intradiscal placement. This is our preferred technique. When introducing a catheter into the caudal space to reach the lumbar or thoracic spine, a similar technique to the above is used for cannula placement and the catheter is viewed during advancement using US imaging at the level of the spine above the sacrum.

(ii) Upper Extremity Blocks

The most common approach to the brachial plexus in infants and children is the axillary approach and the supraclavicular approach. With the advent of US guidance, the interscalene approach has resurfaced as a viable technique for placement of a catheter.

Interscalene Block

Sonoanatomy: A small footprint hockey stick probe will allow optimal recognition of the superficial structures in this region for infants and small children. In a transverse oblique plane at the level of the cricoid cartilage and at the posterolateral aspect of the sternocleidomastoid muscle, the superficially-located sternocleidomastoid muscle appears triangular in shape and overlies the internal jugular vein and common carotid artery. In small infants, the US-probe footprint is wide enough to capture the great vessels along the brachial plexus in the same image screen. Lateral to the vessels and deep to the sternocleidomastoid muscle lies the anterior scalene muscle, and more posterolaterally, the middle and posterior scalene muscle (the latter two often appearing as a single mass). The hyperechoic (bright)-appearing tissue forming a lining around the muscles is presumably the fibrous tissue of the interscalene sheath. Brachial plexus trunks and/or roots in this sagittal oblique section are usually visualized as three (or more) round or oval-shaped hypoechoic (grey or dark) structures, lying between the scalenus anterior and medius muscles. It is important to note that the dorsal scalapar artery is located in the scalenus medius, this may predispose the patient to develop a hematoma if the block is performed using an in-plane technique. Continuous interscalene blockade was performed for a 10-year old girl in the Philippines during a plastic surgery medical mission with an intravenous catheter. Without the availability of perineural catheters as well as stimulating needles, a 22 gauge Angiocath® was used for the block, utilizing an in-plane alignment to the posterior edge of the probe using the US equipment borrowed from the obstetric suite. This case demonstrates the ubiquitous nature of US equipment in most medical centers across the globe.
Supraclavicular Block

**Sonoanatomy:** The probe is placed along the upper border of the clavicle. The carotid and the internal jugular vein are recognized. The probe is moved laterally while looking for the pulsation of the subclavian artery. The supraclavicular brachial plexus is located lateral to the artery and appears hyperechoic mixed with hypoechoic shadows in a grape like fashion surrounding the artery. With the probe placed perpendicular to the anterior axillary fold, a short-axis view of the neurovascular bundle can be obtained; the biceps brachii and coracobrachialis muscles are seen laterally; the triceps brachii muscle is medial and deep to the biceps brachii muscle. The anechoic and circular pulsating axillary artery lies centrally, adjacent to both the biceps brachii and coracobrachialis muscles, and is surrounded by the terminal branches of the brachial plexus. The median nerve is typically located superficial and between the axillary artery and biceps brachii muscle, the ulnar nerve is commonly located medial and superficial to the artery, and the radial nerve often lies deep to the artery at the midline. At this level, the musculocutaneous nerve is located between the biceps brachii and coracobrachialis muscles.

**Technique:** The supraclavicular block is performed using a high frequency hockey stick or linear probe. The subclavian artery is identified, and the subclavian vein is accessed using an in-plane approach from laterally or using an out of plane technique from superiorly. Nerve stimulation can be used in conjunction with US-guidance for this block.

**Comment:** When performing a supraclavicular block there is a greater risk of pneumothorax as the apex of the lung lies just medial to the first rib, not far from the plexus; the distance of the plexus from the lung being especially short in children. It is critical to ensure that clear visibility of the needle shaft and tip is obtained by aligning the needle in-plane to the ultrasound probe at all times. Auscultation of the lungs should be performed before and after performance of the block as well as prior to discharge to detect clinical signs of pneumothorax. A simple algorithm to check neural viability prior to performance of the block is used in our institution to perform the block after surgery. The viability of nerves is performed using a ‘thumbs up’ sign for radial nerve; flexion of PIP for median nerve and finger scissoring for the ulnar nerve. This has proved to be valuable especially in children who may have fractures and may be prone for damage.

Axillary Block

**Sonoanatomy:** With the probe placed perpendicular to the anterior axillary fold, a short-axis view of the neurovascular bundle can be obtained; the biceps brachii and coracobrachialis muscles are seen laterally; the triceps brachii muscle is medial and deep to the biceps brachii muscle. The anechoic and circular pulsating axillary artery lies centrally, adjacent to both the biceps brachii and coracobrachialis muscles, and is surrounded by the terminal branches of the brachial plexus. The median nerve is typically located superficial and between the axillary artery and biceps brachii muscle, the ulnar nerve is commonly located medial and superficial to the artery, and the radial nerve often lies deep to the artery at the midline. At this level, the musculocutaneous nerve is located between the biceps brachii and coracobrachialis muscles.

**Technique:** The terminal nerves are visualized in an axial plane, the probe is placed in the axillary fold. A needle is placed in an in-plane approach to access the median, radial and ulnar nerves individually. Local anesthetic solution is placed to surround the plexus in its entirety to provide an adequate blockade. We feel that the use of ultrasound may allow reduction in dosing for the block although further studies are required to prove the pharmacodynamic ability of US guidance with decreased volumes for axillary blocks in children.

**Comment:** Multiple injections and needle redirections are commonly required to ensure circumferential spread of the local anesthetic solution around each of the individual nerves. Since there is an abundance of vessels in this region, complete avoidance of vessel puncture can be a challenge even when utilizing ultrasound imaging. It is important to understand that the plexus remains very close to the surface and hence the needle should be directed cautiously while this block is attempted. Smaller doses can be used to provide an adequate blockade of this plexus in infants and children.

Lower Extremity Block

Femoral Nerve Block

**Sonoanatomy:** Similar to using conventional technique, arterial pulsations of the femoral artery is the key landmark when using US guidance for femoral nerve blockade. With the probe placed at the level of and parallel to the inguinal crease, the nerve appears lateral to the large, circular and anechoic femoral artery (color Doppler may be used to identify the femoral artery and vein). The nerve often appears triangular in shape and may be variable in size. The fascia lata (most superficial) and iliaca (immediately adjacent to the nerve and in fact separating the nerve from the artery) are seen superficial to the femoral nerve and often appear as bright and longitudinally angled echogenic signals.

**Technique:** A linear high frequency US probe is placed at the level of the inguinal crease and using an in-plane approach, the femoral nerve is accessed from the lateral aspect. Once the needle enters the fascia iliaca compartment, local anesthetic solution is injected to envelope the nerve entirely. If a nerve stimulator is used adjunctly, quadriceps contraction is elucidated. Although one cannot be sure about intraneural injection while using US guidance, it may be prudent to place the needle in the fascia iliaca compartment and not place it directly into the neural plexus. An out of plane technique may facilitate easier placement of a catheter for postoperative pain control.

Sciatic Nerve Block:

**Sonoanatomy:** The sciatic nerve block is commonly used in children for providing analgesia for lower extremity surgery. We use it in combination with a femoral nerve block for providing analgesia for knee surgery. The sciatic nerve is imaged easily at the level of US guidance with decreased volumes for axillary blocks in children.
of the popliteal crease. The biceps femoris tendon is identified. The popliteal artery is identified with the popliteal vein superficial to the artery. The tibial nerve is located immediately superficial to the nerve in most patients and should be used a landmark for imaging the nerve. On scanning further laterally, the common peroneal nerve can be located.

**Technique:** In the supine, lateral or prone position, the popliteal fossa crease is identified, a linear US probe is placed at the level of the popliteal crease. The popliteal artery is identified, the popliteal vein is superficial to it, and superficial to that structure is the tibial nerve. The US probe is moved laterally to visualize the common peroneal nerve. The probe is advanced cephalad to where the common peroneal and tibial nerves coalesce to form the single sciatic nerve. A needle is placed in an in-plane orientation; the sciatic nerve can be stimulated if a stimulating needle is used to elicit inversion or eversion of the foot.

**BLOCKADE OF THE ANTERIOR TRUNK**
Among many blocks performed at the anterior trunk, ilioinguinal/iliohypogastric nerve blockade is one of the most commonly performed blocks for surgery in the inguinal region and may be one of the most common peripheral nerve blocks in children. (Pediatric Regional Anesthesia Network PRAN, 2010) Various other nerve blocks are also becoming popular to provide analgesia for procedures in the umbilical or epigastric regions. Ultrasonography can be particularly beneficial for truncal blocks in children due to the close anatomical relations between the nerves and various critical abdominal structures.

**Ilioinguinal/Iliohypogastric Nerve Block**

**Sonoantomy:** A linear high frequency probe is placed immediately medial to the superior aspect of the anterior superior iliac spine (ASIS) to capture a short-axis view of the ilioinguinal nerve sandwiched between the internal oblique abdominal and transverse abdominal muscles. The ASIS appears hypoechoic (due to dorsal shadowing beyond the highly-reflective periosteum) and nodular-shaped at the lateral edge of the screen. The lateral abdominal muscles will appear with multiple hyperechoic dots within a hypoechoic background. The nerve can be identified as an elliptical-oval shaped structure with a hyperechoic film surrounding a hypoechoic core.\(^\text{12}\) A recent study examined the use of ilioinguinal nerve blocks in addition to a caudal block for prolonging the duration of analgesia; it was demonstrated that the block was effective only in patients undergoing hernia repair.\(^\text{13}\)

**Technique:** A hockey stick probe will be suitable for many infants and younger children, since the nerves are closely situated beneath the skin (8 mm on average) and medial (7 mm on average) to the ASIS. The probe is placed with the axis pointed towards the umbilicus. A needle is inserted in an in-plane approach between the internal oblique and the transversus abdominis muscle. Local anesthetic solution is injected to hydro-dissect between the two layers thereby providing a blockade of the L1 nerve root. We use a volume of 0.1mL/kg with a total maximum volume of 5mL for this blockade.

**Rectus Sheath Block**

**Sonoantomy:** The rectus sheath is located between the rectus abdominis muscle and the posterior rectus sheath. A small footprint probe will be suitable for viewing unilaterial anatomy. The anterior and posterior aspects of the rectus sheath and the enclosed rectus abdominis muscle are visualized. The sheath appears hyperechoic with multiple linear layers, lying on the anterior and posterior aspects of the rectus muscle.

**Technique:** A linear high frequency probe is placed on the abdominal wall lateral to the umbilicus. Using an in-plane approach and coming in from laterally, a needle is inserted posterior to the rectus abdominis muscle but anterior to the posterior rectus sheath. Superior displacement of the rectus abdominis muscle is seen with injection of the local anesthetic solution. This block can be used for umbilical hernia repairs as well as most midline abdominal surgeries involving the T10 distribution.\(^\text{14}\)

**Transversus Abdominis Plane (TAP) Block**

**Sonoantomy:** The layers of the abdominal wall can be easily distinguished using ultrasonography. The thoraco-lumbar nerve roots (T10 to L1) provide the sensory supply to the abdominal wall. The nerves run in a plane between the internal oblique and transversus abdominis muscle, hence referred to as the transversus abdominis plane or TAP. A linear probe placed along the lateral aspect of the abdomen can distinguish the various layers of the abdomen including from superficially, fascia/fat, external oblique, internal oblique and the transversus abdominis muscle. A blockade at this level can provide analgesia for anterior abdominal wall surgery. This may be especially useful in infants and children who may have underlying coagulopathy, spinal dysraphism or as a rescue block following a failed neuraxial blockade. The block has been demonstrated to be effective for abdominal surgery in the adult population.\(^\text{15}\)

**Technique:** A simple step by step approach to this block has been recently described.\(^\text{16}\) A linear high frequency probe or a hockey stick probe is used for the procedure. Recognize the various layers of the abdomen. A needle is inserted in the in-plane technique to enter the plane between the transversus abdominis and the internal oblique. Local anesthetic...
solution (0.2mL/kg) is injected. The downward movement of the transversus abdominis signifies correct placement of the needle in the TAP plane.

Conclusion: US-guidance for peripheral and central neuraxial blocks is becoming the mainstay of regional anesthesia in children. As equipment improves and becomes more cost-effective, the use of US guidance may become the norm rather than the exception. Multiple hands-on workshops offered by the IARS, ASA, ASRA and SPA may shed greater insight into some of the common techniques. The steep learning curve for US guidance can be offset by offering it as part of the routine curriculum for training residents and fellows in anesthesia training programs. Future studies with greater importance for pharmacodynamics and technique enhancement with importance to surgery-specific blocks may allow for better utilization of nerve blocks in infants, children and adolescents.

REFERENCES

Almost thirty years ago, residual neuromuscular blockade was documented in a surprisingly high proportion of patients (30%), despite an almost systematic use of anticholinesterase agents. Since then, even with the development of shorter-acting neuromuscular blockers, pharmacological reversal, and more widespread use of nerve stimulation, residual paralysis is still a problem that has been associated with episodes of hypoxia, respiratory distress, airway obstruction, atelectasis, and patient discomfort, as well as increased mortality. Since the introduction of rocuronium and cisatracurium in the mid 1990s, no new blocking agents have been introduced into clinical practice. A new reversal drug, sugammadex, is available in certain countries, but not in the United States or Canada. With this background in mind, three questions should be asked. First, when are neuromuscular blocking agents indicated, and if they are indicated, how should they be used? Second, if neuromuscular blocking agents are used, how can we best avoid residual paralysis? Third, how can current and future reversal agents be used in anesthetic practice?

INDICATIONS FOR NEUROMUSCULAR BLOCKING AGENTS

Neuromuscular blocking agents are used to facilitate tracheal intubation, provide muscle relaxation and immobility during surgical procedures, and facilitate mechanical ventilation. In all instances, however, the need for unconsciousness and analgesia is present. With the availability of short acting analgesic drugs such as remifentanil and new airway devices, such as the laryngeal mask airway (LMA), the need for neuromuscular blocking agents has been reexamined. Many studies showed that intubating conditions improved when propofol was given with increasing doses of remifentanil. Still, intubating conditions are better with neuromuscular blocking agents, even when compared with remifentanil doses as high as 4 µg/kg. Insertion of LMAs requires less relaxation than endotracheal intubation. There are few studies that correlated surgical conditions with the degree of neuromuscular blockade, but improvement in the quality of the surgical field has been obtained with neuromuscular blocking agents. Some studies have identified neuromuscular blocking agents as a risk factor of awareness. Although an association can be found in clinical studies, the underlying problem is not the presence of neuromuscular blocking agents in these cases, but the lack of anesthetic and analgesic drugs. The problem of awareness is addressed by administration of more anesthesia, not less neuromuscular blocking agents.

PHYSIOLOGICAL CONSEQUENCES OF NEUROMUSCULAR BLOCKADE

Clinically the most important targets of neuromuscular blocking agents are muscles of the respiratory system, those of the upper airway, and those that protect the lungs against aspiration. However, most studies on the effects of neuromuscular blocking agents involved measurement of the force of contraction of the adductor pollicis in response to electrical stimulation of the ulnar nerve, most often using the train-of-four (TOF) mode, ie, four stimuli separated by a 0.5-sec interval, because monitoring at the thumb is convenient. To get clinically meaningful information, it is important to be aware of the correlations between the TOF recordings obtained at the thumb and the respiratory effects of neuromuscular blocking agents. The TOF response is generally expressed as the fourth to first twitch ratio (TOF ratio).

Respiratory system.

Patients can maintain a normal tidal and minute ventilation in spite of profound muscle paralysis characterized by the complete lack of TOF response, because the diaphragm is particularly resistant to the effects of neuromuscular blockers. However, vital capacity, essential for coughing, is reduced at low levels of neuromuscular blockade, ie, at a TOF ratio ~ 0.5. Maximum expiratory and inspiratory pressures are reduced when the TOF ratio is <0.7.

Upper airway.

Upper airway patency is dependent upon the coordinated action of a several muscles, and it is difficult to consider them separately. Nevertheless, three muscles, the geniohyoid, the masseter and the genioglossus, have been found to be as sensitive, and possibly more sensitive to neuromuscular blocking agents than the adductor pollicis when stimulated with the TOF mode. It is quite possible that other muscles ensuring upper airway patency are as sensitive, since the airway size is greatly reduced when TOF ratio ~ 0.7. In volunteers, it was also noted that a TOF ratio >0.86 was required for a subject to hold a tongue depressor between his/her teeth against attempts by another person to remove it.®
Protection against aspiration.

Swallowing is a very efficient mechanism protecting the tracheobronchial tree from aspiration of fluids or solids. Upper esophageal sphincter tone measured by manometry has been found to be reduced by more than 50% when the TOF ratio = 0.7. Following the administration of neuromuscular blocking agents, these values go back to normal only at a TOF ratio >0.9.13 Moreover, an increased incidence of laryngeal aspiration was noted when the TOF ratio went under the 0.9 threshold.

DEFINING THE RESIDUAL PARALYSIS THRESHOLD

For many years, residual paralysis was defined by the presence of a TOF ratio <0.7. This threshold was determined in the 1970s based on respiratory data obtained from a limited number of healthy volunteers.14 No significant decrease in inspiratory and expiratory pressures were noted at a TOF ratio = 0.7, but the effects of neuromuscular blockade on the maintenance of upper airway patency and swallowing were not considered. In the 1990s, a TOF ratio of 0.9 was suggested as a requirement to eliminate the possibility of the residual neuromuscular blocking effects. This new threshold is now widely accepted in the definition of residual paralysis, and it emphasizes the significance of neuromuscular blockade effects on all components of the respiratory system, including the upper airway.12,13

INCIDENCE OF RESIDUAL PARALYSIS

In 1979, a Danish group found a 30% incidence of residual paralysis, based on the measurement of a TOF ratio < 0.7 in the postanesthetic recovery unit (PACU). The majority of patients had received neostigmine, but neuromuscular monitoring was not a widespread practice. It should be noted that only a limited number of long-acting nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, gallamine) were available at that time. Further, if the current definition of residual paralysis ie, a TOF ratio = 0.9, had been applied to those results, the incidence of residual paralysis would have reached 72%! Using the threshold of 0.9, subsequent studies found incidences ranging from 0% to 95%,15 and close examination of these studies can identify some risk factors associated with residual paralysis.

Duration of action of neuromuscular blocking agents.

Unquestionably, the use of an intermediate-acting (atracurium, vecuronium, cisatracurium, rocuronium) instead of long-acting agents reduces the incidence of residual paralysis, no matter what TOF threshold is chosen as a definition of residual paralysis.15 However, even with intermediate-acting agents, the incidence of residual paralysis remains high: using the 0.9 threshold, an overall 41% incidence has been reported, and even with the conservative threshold of 0.7, the incidence still reached 12%!15 Long-acting agents are associated with incidences of 72% and 35%; depending on the threshold selected. Therefore, switching to shorter acting neuromuscular blocking drugs does not eliminate the problem completely.

Monitoring

A distinction must be made between devices that only stimulate and those equipped with a sensor that makes measurements and records the response. When the device includes a stimulator only, the anesthesiologist must assess the magnitude of the elicited movement by visual or tactile means. Over a TOF ratio value range between 0.4 and 0.9, it is difficult, if not impossible, to detect whether the fourth twitch is less than the first.19 The use of this so-called “subjective” evaluation can explain, in part, the high incidence of residual paralysis reported in the literature and the persistence of the problem in spite of monitoring. With devices equipped with accelerometry or displacement sensors that can measure accurately the TOF ratio, the incidence of residual paralysis should equal zero if anesthesiologists keep patients intubated until a 0.9 threshold is reached or exceeded. Studies show that in practice, anesthesiologists sometimes extubate patients early, but overall, the incidence of residual paralysis (defined as a T4/T1 ratio <0.9) is reduced if accelerometers are used.17,18

Anticholinesterase agents.

When neuromuscular blocking drugs with intermediate duration of action became available, some anesthesiologists thought they could omit anticholinesterase agents to reverse neuromuscular blockade at the end of a procedure. In fact, in some countries and some hospitals, the use of anticholinesterase agents is not common. However, without the administration of anticholinesterase agents, the incidence of residual paralysis is high. For example, a 62% incidence, as defined by a 0.9 threshold, was reported with intermediate-acting neuromuscular blockers.19 In the same facility, over several years, a follow-up of strict practices produced an impressive reduction in the incidence of residual paralysis from 62% in 1995 to 3.5% in 2004, as defined by a TOF ratio < 0.9. Over the same period, the proportion of patients receiving anticholinesterase agents increased from 6% to 42%.19

Other factors.

Residual paralysis appears to be more common in the elderly, and older patients are also more subject to complications arising from residual paralysis.19 The administration of neuromuscular blocking agents as an infusion rather than intermittent boluses increases the risk of residual paralysis.15 It is conceivable that administration of halogenated agents would lead to more residual paralysis than intravenous anesthesia, because halogenated agents...
potentiate neuromuscular blockade, but there are no studies to corroborate such a hypothesis.

**CLINICAL EFFECTS OF RESIDUAL PARALYSIS**

Neuromuscular blocking agents are not the only drugs likely to produce respiratory depression in a clinical setting, but large-scale studies have indicated that residual paralysis increases the number of respiratory complications.

**Respiratory complications.**

Recently, a group of patients with complications such as hypoxia, upper airway obstruction and the need for an intervention to ensure adequate breathing was compared with a control group with no such complications. The mean TOF ratio was only 0.62 in the complications group, compared with 0.98 in the control group. In a study involving 49 patients who received pancuronium, the incidence of hypoxemia (saturation reduced by >5% compared with baseline values) reached 60% in patients with a TOF ratio < 0.7 and only 10% in the other patients. In another study, patients managed with an accelerometer during anesthesia had a higher TOF ratio in the recovery room. They also had fewer episodes of hypoxemia and required interventions to improve oxygenation less frequently than those with no monitoring and a lower TOF ratio.

**Atelectasis.**

One of the few randomized trials investigating the consequences of residual paralysis involved patients given pancuronium, atracurium or vecuronium followed by neostigmine at the end of the procedure. As expected, a TOF ratio < 0.7 was found more often in patients receiving pancuronium (30%), a long-acting neuromuscular blocker, than in those who received atracurium or vecuronium (5%), two intermediate-acting neuromuscular blockers. The incidence of atelectasis confirmed by chest X-ray two days after surgery was three times higher (17%) in patients who had residual paralysis (TOF ratio < 0.7) in the recovery room than in the other patients (5%). This indicates that short-term residual paralysis can have long-term consequences.

**Mortality.**

A Dutch study examined mortality attributed to anesthesia in over 800,000 patients, and the authors attempted to identify the factors predicting coma and death. Among the possible pre- or intraoperative actions having a positive influence on outcome, management issues such as the availability of an anesthesiologist were found to be important factors. The only pharmacological treatment that correlated with improved patient outcome was the administration of a reversal agent for neuromuscular blockade, which was associated with a 10-fold reduction in the incidence of mortality and coma.

**PREVENTING RESIDUAL PARALYSIS**

It is essential to avoid residual paralysis in the PACU in extubated patients, and there is solid physiological and epidemiological evidence for this recommendation. Strategies to prevent residual paralysis are based on judicious use of anticholinesterase agents, and a strict practice guidelines based on adequate monitoring, whenever neuromuscular blocking drugs are administered (Table 1).

**Anticholinesterase agents.**

Neostigmine, edrophonium, and pyridostigmine are used to reverse neuromuscular blockade. Edrophonium has a rapid onset, but is not as effective as neostigmine for deep blocks. Pyridostigmine has a slow onset, which makes it ill-suited to the reversal of intermediate-acting neuromuscular agents. Discussion will therefore focus on neostigmine, which remains the most commonly used anticholinesterase agent, although many principles can also apply to edrophonium and pyridostigmine. The effectiveness of anticholinesterase agents is limited by a ceiling effect; for instance, neostigmine reduces the intensity of neuromuscular blockade in a dose-dependent manner up to 0.04 - 0.05 mg/kg, but higher doses have little if any additional benefit. In addition, the agent must be injected only when sufficient spontaneous recovery is observed. It is recommended to wait until there are four visible twitches following TOF stimulation before administering neostigmine. If no fade is visible, significant residual blockade is possible, but adequate reversal requires only 0.02-0.03 mg/kg of neostigmine. If three or fewer twitches are visible, it is preferable to maintain anesthesia until there are four visible twitches and then give neostigmine at the usual 0.04-0.05 mg/kg doses. When the reversal agent is administered too early, recovery might be incomplete, and residual paralysis difficult to diagnose, as human senses cannot detect fade when the TOF ratio is 0.4 or greater.

**Choice of neuromuscular blocking agent.**

Long-acting neuromuscular blocking agents should be avoided in patients for whom extubation is planned at the end of the procedure. None of the intermediate-acting neuromuscular blockers (rocuronium, cisatracurium, vecuronium or atracurium) produce significantly less residual paralysis than the others. Nevertheless, they should be administered in doses such that, at the end of the surgery, spontaneous recovery is sufficient for the anticholinesterase agent to be effective.

**Monitoring.**

The limitations encountered with traditional monitoring, namely the visual or tactile evaluation of a patient’s responses to TOF stimulation, have led some authors to recommend the compulsory use of so-called “objective” monitoring, which involves a...
display of TOF ratio measurements.\textsuperscript{25} Unfortunately, currently available devices such as accelerometers and displacement sensors are often fragile and prone to breakage in everyday clinical practice.

**FUTURE DIRECTIONS**

Residual paralysis is the result of limitations in the pharmacology of the currently available neuromuscular blocking agents and their antagonists. Efforts have been made to develop short-acting neuromuscular blockers such as gantacurium, with a fast recovery profile that would, in practice, eliminate the possibility of residual paralysis. Currently, none of these products is available. An alternative approach has been to develop products that accelerate neuromuscular recovery. Sugammadex is the result of these efforts, but despite its availability in Europe and elsewhere, it is not yet available in North America.

**Pharmacology of sugammadex**

Sugammadex is a gamma-cyclodextrin, a ring-shaped molecule made up of eight sugars with the addition of negatively-charged side chains. The rocuronium molecule, which is charged positively, has a size that fits well into the hole of sugammadex molecule and is bound by the adjoining negative charges.\textsuperscript{26} As a result, sugammadex inactivates rocuronium molecules and indirectly decreases the intensity of neuromuscular blockade. Once bound, the kidney excretes the sugammadex-rocuronium complex. To a lesser extent, sugammadex also shows an affinity for vecuronium and pancuronium; however, it has no affinity for other neuromuscular blockers such as succinylcholine, atracurium, cisatracurium, and doxacurium.

**Dosage**

In clinical trials, the effectiveness of sugammadex has been studied in three typical situations:

- **moderate blockade**, ie, only two twitches are visible following TOF stimulation;
- **deep blockade**, defined as no twitches seen after TOF stimulation and only 1-2 responses after post-tetanic count (PTC);
- **3-5 minutes after rocuronium administration**, ie, when the failure of direct laryngoscopy and tracheal intubation is noted.

The dose of sugammadex required depends on the depth of blockade and optimal results are obtained with 2, 4, and 16 mg/kg for moderate blockade,\textsuperscript{27} deep blockade,\textsuperscript{28} and failure to intubate,\textsuperscript{29} respectively. These dosages are valid for both rocuronium and vecuronium (Table 1). The recovery time following sugammadex administration is exceptionally fast, ie, approximately 2 minutes.

**Role of sugammadex in clinical practice.**

At the time of writing (early 2010), sugammadex had been available for clinical use in a number of countries, including those of the European Union, for over one year. Unfortunately, it is not available in the USA or Canada. The Food and Drug Administration (FDA) raised concerns over possible allergic reactions in volunteers receiving large doses.\textsuperscript{30} In countries where the drug is available, use is generally restricted because of its high cost (approximately $100 for a standard 200 mg dose). The advantage of this drug is that it is effective at every level of blockade, which is not the case with neostigmine; however, the situations where sugammadex would be particularly useful are those requiring relatively high doses, and thus greater expense. Actually, neostigmine is reasonably effective when it is administered at two visible twitches in response to TOF stimulation, and even more so if there are four. In the case of deep blockade, neostigmine is not very effective, but the sugammadex dose required at that point is $\geq 4$ mg/kg. As a result, it is still too early to recommend the administration of large rocuronium doses during surgery while depending on a sugammadex safety net to reverse neuromuscular blockade. Furthermore, the potential for rapid antagonism by sugammadex should not lead the frivolous use of neuromuscular blocking agents in the management of a difficult airway.

**CONCLUSION**

Residual paralysis undoubtedly contributes to a large proportion of postoperative respiratory complications such as hypoxia, hypoventilation, airway obstruction, atelectasis, and even death. Adequate monitoring, preferably based on the objective assessment of neuromuscular blockade, is required for a reliable diagnosis. However, monitoring cannot replace rigorous practices. A reversal strategy must be planned from the initial administration of a neuromuscular blocking agent, which should have intermediate duration of action and be given in a dose that is appropriate for the planned duration of the surgical procedure. Neuromuscular blockade should be monitored throughout the anesthetic to ensure sufficient recovery in order for neostigmine to have an optimal effect. Sugammadex could increase flexibility, but it will not eliminate the need for appropriate clinical choices regarding dosage of neuromuscular blocking agents. Irrespective of the approach, the goal should be to bring the TOF ratio to $\geq 0.9$ before emergence from anesthesia and extubation.
Table 1: Strategy for neuromuscular blockade reversal at the end of the intervention

<table>
<thead>
<tr>
<th>Number of TOF twitches at the adductor pollicis</th>
<th>Other data</th>
<th>If atracurium, cisatracurium, rocuronium or vecuronium used</th>
<th>If rocuronium or vecuronium used and if sugammadex available</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>PTC = 0</td>
<td>Ventilate patient, wait for 4 twitches</td>
<td>Sugammadex, 8-16 mg/kg</td>
</tr>
<tr>
<td>0</td>
<td>PTC ≥ 1</td>
<td>Ventilate patient, wait for 4 twitches</td>
<td>Aunmmsaz, 4 mg/kg</td>
</tr>
<tr>
<td>1-3</td>
<td></td>
<td>Ventilate patient, wait for 4 twitches</td>
<td>Sugammadex, 2 mg/kg</td>
</tr>
<tr>
<td>4</td>
<td>TOF fade present</td>
<td>Neostigmine, 0.04-0.05 mg/kg</td>
<td>Sugammadex, 2mg/kg</td>
</tr>
<tr>
<td>4</td>
<td>TOF fade not detected by sight or touch</td>
<td>Neostigmine, 0.02-0.03 mg/kg or edrophonium, 0.2-0.3 mg/kg</td>
<td>Neostigmine, 2.0 mg/kg</td>
</tr>
<tr>
<td>4</td>
<td>Documented 14T1 ≥ 0.9</td>
<td>Reversal not required</td>
<td>Reversal not required</td>
</tr>
</tbody>
</table>

REFERENCES

Anaphylactic and Anaphylactoid Reactions in the Surgical Patient

Jerold H. Levy, MD, FAHA
Professor and Deputy Chair for Research, Emory University School of Medicine
Co-Director of Cardiothoracic Anesthesiology, Cardiothoracic Anesthesiology and Critical Care
Emory Healthcare, Atlanta, Georgia

INTRODUCTION

Surgical patients are exposed to multiple foreign substances in the perioperative period including drugs, blood products, or environmental antigens such as latex. Because any substance can produce an allergic or adverse reaction, clinicians must be ready to manage patients in this perioperative environment. The most life-threatening form of an allergic reaction is anaphylaxis, however, the clinical presentation of anaphylaxis may represent different immune and nonimmune responses. There is confusion in the literature about the term anaphylaxis, and multiple terms have been reported to describe this reaction. In recent years, anaphylaxis has been redefined as a severe, life-threatening, generalized or systemic hypersensitivity reaction, mainly mediated by immunoglobulin E (IgE) antibodies. Further, anaphylaxis represents a serious allergic reaction that is rapid in onset and may cause death. The term anaphylactoid, often used to describe for non-IgE-mediated reactions, is confusing and probably should no longer be used. For the practicing clinician, anaphylaxis is best defined as a clinical syndrome characterized by acute cardiopulmonary collapse following antigen (also called allergen) exposure. Much of the confusion about anaphylaxis in the literature is because many older anesthetic agents (e.g., d-tubocurarine) could directly degranulate mast cells. The incidence of immune-mediated anaphylaxis during anesthesia ranges from 1 in 10,000 to 1 in 20,000 based on recent reports. This presentation will define the spectrum of life-threatening anaphylactic and allergic reactions an anesthesiologist may encounter.

ADVERSE DRUG REACTIONS

Adverse drug reactions (ADRs) are common in hospitalized patients. Reports suggest the overall incidence of serious ADRs was 6.7% and of fatal ADRs was 0.32% from data evaluating 39 prospective studies from US hospitals. A recent study noted fatal adverse drug reactions account for nearly 3% of all deaths in the general population, and noted hemorrhage is responsible for ~2/3 of the fatal adverse drug reactions and antithrombotic agents are involved in more than half of the suspected fatal adverse drug reactions. Most serious predictable adverse drug reactions are in fact not allergic mediated events and related to other causes that include the amount of drug in the body (overdosage), unintended administration route, or known side effects (i.e., opioid related nausea). However, some drugs have direct effects on inflammatory cells (i.e., heparin, histamine releasing agents). Unfortunately, patients often refer to any adverse drug effects as being allergic in nature. Anesthetic drugs can also produce hypotension via different mechanisms (e.g., propofol induced vasodilation) complicating the diagnosis of perioperative adverse drug reactions. Allergic drug reactions are often differentiated from other adverse drugs reactions because they are unpredictable and dose-independent (i.e., reactions due to latex allergy from latex gloves).

ALLERGY AND ANAPHYLAXIS

Allergic reactions and anaphylaxis have the same pathophysiologic mechanisms, as both are immune mediated and due to previous exposure to the antigen or a substance of similar structure. Richet and Portier first used the word anaphylaxis (ana -against, prophylaxis – protection) to describe the marked shock and resulting death that sometimes occurred in dogs immediately following a second challenge with a foreign antigen. The term “allergy” was introduced in 1906, but is now often used to describe IgE-mediated allergic disease. The basis of acute allergic reactions including anaphylaxis is the release of inflammatory mediators released by mast cells and basophils when an allergen interacts with membrane-bound IgE.

PATHOPHYSIOLOGY

Anaphylaxis and allergy result from the release of inflammatory mediators including membrane-derived lipids, cytokines, and chemokines. When the offending antigen and IgE bind on the surface of mast cells and basophils, preformed storage granules are released that contain histamine and tryptase. Other membrane-derived lipid mediators are released including leukotrienes, prostaglandins, and other factors. These inflammatory substances have a critical role in producing acute cardiopulmonary dysfunction, characterized by a symptom complex of bronchospasm and upper airway edema in the respiratory system, vasodilation and increased capillary permeability in the cardiovascular system, and urticaria in the cutaneus system. Cardiovascular collapse during anaphylaxis results from the effects of multiple mediators on the heart and vasculature. The vasodilation seen clinically can result from a spectrum of different mediators that interact with vascular endothelium and/or vascular smooth muscle. Why some individuals develop severe cardiopulmonary dysfunction instead of
minor cutaneous reactions is unknown, but may relate to systemic compared to local release of inflammatory mediators.\textsuperscript{14,21} Interestingly, the original description of anaphylaxis from sea anemone toxin represents an IgG-mediated response. IgG mechanisms will be further discussed in protamine reactions that follow.

**VASODILATORY SHOCK AND ANAPHYLAXIS**

Vasodilatory shock occurs in anaphylaxis because of multiple mechanisms that include: excessive activation of vasodilators that increase nitric oxide synthesis to activate soluble guanylate cyclase and increase cGMP, and increased prostacyclin synthesis that activates soluble adenylate cyclase and produces cAMP. Collectively, this produces vasodilation and shock.\textsuperscript{1,18} Other mediators that are released by non IgE mechanisms may also produce shock by different mechanisms (e.g., protamine induced acute pulmonary vasoconstriction) and heparin will be discussed in non IgE mediated reactions.\textsuperscript{1,18}

**RECOGNITION OF ANAPHYLAXIS**

Because any parenterally administered agent can cause death from anaphylaxis, anesthesiologists must diagnose and treat the acute cardiopulmonary changes that can occur. Studies from Europe suggest that perioperative drug induced anaphylaxis may be increasing. The onset and severity of the reaction relate to the mediator’s specific end organ effects. Antigenic challenge in a sensitized individual usually produces immediate clinical manifestations, but the onset may be delayed 2-20 minutes.\textsuperscript{14,20,21} The manifestations and course of anaphylaxis are variable, ranging from minor clinical changes including urticaria to cardiopulmonary collapse including severe bronchospasm, vasodilatory shock, and pulmonary vascular injury in certain cases, leading to death. The enigma of anaphylaxis is the unpredictability of the event, the severity of the attack, and the lack of a prior allergic history.\textsuperscript{14,20,21}

**NON-IGE MEDIATED REACTIONS**

Other immunologic and nonimmunologic mechanisms release inflammatory mediators independent of IgE, creating a clinical syndrome identical with anaphylaxis. Polymorphonuclear leukocyte (neutrophil) activation can occur following complement activation by immunologic (antibody mediated: IgM, IgG-antigen activation) or non-immunologic (heparin, protamine, endotoxin, cardiopulmonary bypass) pathways.\textsuperscript{22,23,24} Complement fragments of C3 and C5 (C3a and C5a) release histamine from mast cells and basophils, contract smooth muscle, and increase capillary permeability. In addition, C5a binds receptors on neutrophils and platelets, causing chemotaxis, aggregation, and activation.\textsuperscript{21-24} Aggregated leukocytes embolize to various organs producing microvascular occlusion and liberation of inflammatory products including oxygen-free radicals, lysosomal enzymes and arachidonic acid metabolites (i.e. prostaglandins and leukotrienes). IgG antibodies directed against antigenic determinants or granulocyte surfaces can also activate leukocytes, and are thought to be responsible for the clinical expressions of transfusion reactions, pulmonary vasoconstriction following protamine reactions, and transfusion related acute lung injury (TRALI).\textsuperscript{25-27}

**HEPARIN, HIT, AND KININ GENERATION**

Following heparin administration, IgG antibody formation is common. These antibodies bind heparin-PF4 complexes on the platelet surface to form immune complexes that activate platelets to promote thrombin formation and thrombosis.\textsuperscript{22} His is the clinical manifestation of heparin induced thrombocytopenia (HIT). Nearly 7-50% of heparin-treated patients form heparin-PF4 antibodies.\textsuperscript{22} However, recent reports about allergic reactions to heparin from China were because of an oversulfated chondroitin sulfate contaminant that directly activated the kinin-kallikrein pathway to produce bradykinin, a potent vasoactive mediator. In addition, this contaminant induced generation of C3a and C5a.\textsuperscript{24} Angiotensin converting enzyme inhibitors also may potentially increase bradykinin levels, and this is the mechanism of vasodilation, angioedema, and cough that can occur with their use.\textsuperscript{1}

**ANGIOEDEMA**

Angioedema is the rapid swelling of skin, mucosa, and submucosal tissues most commonly produced by allergic reactions, but also by ACE inhibitors as noted above.\textsuperscript{29} Oral, laryngeal, and pharyngeal swelling can occur with acute airway compromise needing urgent airway control. There are also inherited qualitative and quantitative deficiencies of the complement C1 esterase inhibitor (C1-INH) called hereditary angioedema (HAE). Patients with HAE also have recurrent episodes of gastrointestinal manifestations of the disease. Bradykinin plays a critical role in angioedema as previously noted. Therapy of attacks includes symptomatic management and C1-INH from C1-INH concentrates. Patients with this history and documented HAE need short-term prophylaxis before surgery or dental treatment because tissue injury activates complement to increase C1-INH levels and also antifibrinolytics that inhibit plasmin mediated activation. New therapies are also being studied in this life threatening disease.\textsuperscript{18} A C1-INH concentrate (Cimryze\textsuperscript{TM}) is currently FDA-approved indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with Hereditary Angioedema (HAE).\textsuperscript{29}
NON-IMMUNOLOGIC RELEASE OF HISTAMINE

Many diverse molecular structures administered during the perioperative period degranulate mast cells to release histamine in a dose-dependent, nonimmunologic fashion.\(^\text{30-33}\) Intravenous administration of morphine, atracurium, or vancomycin can release histamine, producing vasodilation and urticaria along the vein of administration. Although the cardiovascular effects of histamine release can be treated effectively with intravenous volume administration and/or catecholamines, the responses in different individuals may vary.\(^1\) The newer neuromuscular blocking agents (e.g., rocuronium and cisatracurium) lack histamine releasing effects but can produce direct vasodilation and false-positive cutaneous responses that can confuse allergy testing and interpretation.\(^{31,34}\) The mechanisms involved in nonimmunologic histamine release represent degranulation of mast cells but not basophils by cellular activation and stimulation of phospholipase activity in mast cells.\(^{25}\)

TREATMENT PLAN

Most anesthetic drugs and agents administered perioperatively have been reported to produce anaphylaxis.\(^{1}\) Therefore, a plan for treating anaphylactic reactions must be established before the event.\(^1\) Airway maintenance, 100% oxygen administration, intravascular volume expansion, and epinephrine are essential to treat the hypotension and hypoxia that results from vasodilation, increased capillary permeability, and bronchospasm.\(^{1}\) Table 2 lists a protocol for management of anaphylaxis during general anesthesia, with representative doses for a 70-kilogram adult. Therapy must be titrated to needed effects with careful monitoring. The route of administration of epinephrine and the dose depends on the patient’s condition.\(^1\) Rapid and timely intervention with common sense must be used to treat anaphylaxis effectively.

Reactions may be protracted with persistent hypotension, pulmonary hypertension and right ventricular dysfunction, lower respiratory obstruction, or laryngeal obstruction that persist 5 to 32 hours despite vigorous therapy.\(^{24}\) Novel therapeutic approaches for shock and/or right ventricular failure are currently under investigation.\(^{39}\) During general anesthesia patients may have altered sympathoadrenergic responses to acute anaphylactic shock. In addition, the patient during spinal or epidural anesthesia may be partially sympathectomized, needing earlier intervention with even larger doses of epinephrine and other catecholamines.\(^{39}\) Additional hemodynamic monitoring including radial and pulmonary artery catheterization may be needed when hypotension persists despite therapeutic interventions as listed. Following anaphylaxis, patients should be carefully monitored for 24 hours as they may develop recurrence of manifestations following successful treatment and covered with corticosteroids for the acute event.\(^1\)

After the initial resuscitation, norepinephrine is also an effective agent that should be considered for treating shock and dopamine should be avoided.\(^{37}\) Based on the efficacy of vasopressin in reversing vasodilatory shock, it should also be considered in therapy of anaphylactic shock not responding to therapy.\(^{1,18,38}\) There are increasing laboratory and clinical reports supporting the use of vasopressin in anaphylactic shock.\(^{19,40}\) When available, the use of transesophageal echocardiography in an intubated patient, or potentially transthoracic echocardiography can be useful in diagnosing the cause of acute or persistent cardiovascular dysfunction.\(^1\)

PRETREATMENT FOR ALLERGIC REACTIONS

Hypersensitivity reactions are more likely to occur in patients with a history of allergy, atopy, or asthma. However, this does not make it mandatory to pretreat these patients with antihistamines and/or corticosteroid because there is no data in the literature to suggest that pretreatment is effective for true anaphylactic reactions. Most of the literature on pretreatment is from studies evaluating patients with previous radiocontrast media reactions that are non-immunologic mechanisms. Although attempts to pretreat patients for anaphylaxis to latex have been used, there is no data to support this as an effective preventative measure and removal of latex from the perioperative environment is important. In fact, pretreatment may lull physicians into a false sense of security. Further, even when large doses of corticosteroids have been administered, life threatening anaphylactic reactions have occurred.\(^{41}\) Allergists have used immunospecific pretreatment therapies, but these are not practical for perioperative use.

MANAGEMENT OF THE ALLERGIC PATIENT

Patients presenting with an allergic history need to be carefully evaluated. Patients may report allergy when the reaction was a predictable adverse drug reaction. However, for practical and medicolegal purposes, that class of drug should be avoided if possible when the history is consistent with an allergic reaction, and preservative free alternatives should be chosen. The problem occurs whenever multiple drugs are simultaneously administered or when patients present with muscle relaxant reactions because of the risk of cross reactivity to the biquarternary ammonium ions in the molecule. In this situation, skin testing may be required to see what the patient is can safely be administered.

EPIDEMIOLOGY OF ANAPHYLAXIS: AGENTS IMPLICATED

Although any molecule can produce anaphylaxis, the drugs typically associated with producing perioperative anaphylaxis include antibiotics,
blood products, neuromuscular blocking drugs (NMBDs), polypeptides (aprotinin, latex, and protamine), and intravascular volume expanders. During surgery, the risk of anaphylaxis is reported to be between 1:3500 and 1:20,000, with a mortality rate of 4% and an additional 2% surviving with severe brain damage. More recent data suggest the incidence of perioperative anaphylaxis is 1 in 10,000–20,000. Patients undergoing major surgery are an increased risk group, because of the multiple blood products, polypeptides, and potential for impaired cardiovascular function. Mertes reported an epidemiological study from 99-01 of 789 reactions diagnosed by clinical history, skin tests, and/or specific IgE in 518 cases (66%) and nonimmune reactions in 271 cases (34%). The most common causes were NMBAs (58.2%), latex (16.7%), and antibiotics (15.1%), of which rocuronium (43%) and succinylcholine (22.6%) were the most common NMBAs reported. The positive predictive value of tryptase for the diagnosis of anaphylaxis in their study was 92.6%; the negative predictive value was 54.3%. The agents most often implicated will be discussed.

**latex Allergy**

Latex represents an environmental agent often associated as a cause of perioperative anaphylaxis. Health care workers, children with spina bifida and urogenital abnormalities, and certain food allergies have also been recognized as individuals at increased risk for anaphylaxis to latex. Brown reported a 24% incidence of irritant or contact dermatitis and a 12.5% incidence of latex-specific IgE positivity in Anesthesiologists. Of this group, 10% were clinically asymptomatic although IgE positive. A history of atopy was also a significant risk factor for latex sensitization. Brown suggests these individuals are in their early stages of sensitization and perhaps, by avoiding latex exposure, their progression to symptomatic disease can be prevented.

Patients allergic to both tropical fruits (e.g., bananas, avocados, and kiwis) and stone fruits have also been reported to have antibodies that cross-react with latex. Multiple attempts are being made to reduce latex exposure to both healthcare workers and patients. If latex allergy occurs, then strict avoidance of latex from gloves and other sources needs to be considered, following recommendations as reported. Because latex is such a widespread environmental antigen, this represents a daunting task.

**Neuromuscular Blocking Agents**

Neuromuscular blocking agents (NMBAs) have several unique molecular features that make them potential allergens. All neuromuscular blocking drugs are functionally divalent and are thus capable of cross-linking cell-surface IgE and causing mediator release from mast cells and basophils without binding or haptenizing to larger carrier molecules. NMBAs have also been implicated in epidemiological studies of anesthetic drug-induced anaphylaxis. Epidemiological data from France suggest that NMBAs are responsible for 62–81% of reactions, depending on the time period evaluated. Rocuronium is the NMA most reported from France. We and others have reported previously that aminosteroidal compounds as well as benzylisoquinoline-derived agents produce positive weal and flare responses when injected intradermally. Estimates of anaphylactic reactions in anesthesia vary, but data suggests that false-positive skin tests may overestimate the incidence of rocuronium-induced anaphylactic reactions. The differences noted in the incidence of reactions may reflect the potential for false-positive weal and flare responses. NMBAs can also produce direct vasodilation by multiple mechanisms, which include calcium channel blockade. The false-positive skin tests that were reported to be biopsy-negative for mast cell degranulation clearly confound interpreting skin tests in patients who have had life-threatening cardiopulmonary collapse. Dilute solutions of NMBAs need to be used when skin testing for potential allergic reactions to these agents. However, the exact concentration that should be used is unclear. Since skin-testing procedures are important in evaluating potential drug allergies, the threshold for direct vasodilating and false-positive effects must be determined whenever subjects are skin-tested for a particular drug.

**polypeptides and blood products**

Polypeptides are larger molecular weight molecules that pose greater potential to be antigenic, and include aprotinin, latex, and protamine. Diabetic patients receiving protamine containing insulin as neutral protamine Hagedorn (NPH) or protamine insulin have a 10-30 fold increased risk for anaphylactic reactions to protamine when used for heparin reversal, with a risk of 0.6-2% in this patient population. Because protamine is often given with blood products, protamine is often implicated as the causative agent in adverse reactions, especially in cardiac surgical patients. Platelet and other allogeneic blood transfusions can produce a series of adverse reactions by multiple mechanisms, and blood products have a greater potential for allergic reactions including TRALI. Although antigen avoidance is one of the most important considerations in preventing anaphylaxis, this is not always possible, especially with certain agents where alternatives are not available. Protamine is an important example of where alternatives are under investigation, but not currently available.

**Evaluating the Patient Following Anaphylaxis**

A detailed history is one of the most important considerations to evaluate a patient following...
anaphylaxis, determining what agents were administered, and what the temporal sequence was. Also, after resuscitation collect a red top tube (serum) for mast cell tryptase, preferably within 1-2 hours of the reaction, and then repeat 24 hours later. Serum can also be collected postmortem, which may be important for you medicolegally. Most hospital laboratories will need to send this test to a reference laboratory. If tryptase is positive, sending the patient for an allergy consultation may be useful if the temporal sequence is confusing, and the agent responsible needs further investigation. Often, a positive mast cell tryptase usually represents an IgE mediated reaction (i.e., anaphylaxis) but vancomycin and other histamine releasers can also increase tryptase. Negative mast cell tryptase tests are rarely associated with positive skin tests and antibody tests. IgG reactions due to protamine, or blood products are unlikely to increase tryptase. Few laboratory based tests are available for determining immunologic testing, so skin testing is required if better differentiation of the agent responsible is required.

CONCLUSIONS

Anaphylaxis represents an important potential problem and an important cause of life threatening events. Clinicians must be able to recognize and treat these life threatening events if they occur. Clinicians should remember that test doses may produce anaphylaxis. There are few in vitro tests available to assess patients at high risk for reexposure anaphylaxis. Anaphylactic reactions represent a continuing challenge, but rapid diagnosis and treatment are important in preventing adverse clinical outcomes.

SUGGESTED WEB SITES:

AnaphylaxisWeb.com, FDA.gov

REFERENCES

34. Levy JH, Davis GK, Duggan J, Szlam F: Determination of the hemodynamics and histamine release of rocuronium (Org 9426) when administered in increased doses under N2O/O2-sufentanil anesthesia. Anesth Analg 1994; 78: 318-21


Update on Thoracic Epidurals: Are the Benefits Worth the Risks?

Hugo K. Van Aken, MD, PhD, FANZCA, FRCA
Professor, Department of Anesthesiology and Intensive Care,
University Hospital Muenster
Muenster, Germany

INTRODUCTION
Thoracic epidural anesthesia has been established as a cornerstone in the perioperative care after thoracic and major abdominal surgery providing most effective analgesia.1,2 Beyond its analgesic properties, TEAs effects on the postoperative neurohumoral stress response, cardiovascular pathophysiology and intestinal dysfunction have been in the focus of both clinical and experimental investigations for years.3,4
However, as an invasive technique TEA is related to specific complications even when contraindications are properly considered. There is an ongoing debate whether these risks of TEA and its consumption of procedural resources in the perioperative period are worth the benefits with respect to outcome and organ protection.

The purpose of this lecture is to outweigh the perioperative risks related to TEA and analgesic technique and the benefits of TEA with respect to the cardiovascular system, the intestinal tract and the host immune response to the perioperative spread of malignant cells.

INCREASED SYMPATHETIC ACTIVITY AND THE STRESS RESPONSE
The term stress usually describes a state of increased sympathetic activity that is accompanied by distinct changes in the host’s hormonal and immune response as well as the coagulation system.7 Stress is caused by a multitude of situations of physical danger or factual injury to the organism but also can be induced solely by emotional tension or fear of adverse events.8-10 The stress response, that has been highly conserved throughout evolution, can turn against the host in the case of coexisting cardiovascular disease. In these patients, even watching a soccer game lasting increases the risk of acute coronary syndromes and significant arrhythmias.11

There are different synergistic mechanisms involved in cardiac complications during stress. Increased catecholamine levels increase afterload of the left ventricle. Tachycardia further increases workload of the heart while decreasing the time for coronary perfusion.12 While healthy coronary arteries relax to compensate for the higher need of oxygen, altered and stenotic coronary arteries are not able to relax or even constrict on sympathetic stimulation.13 Raised CRH-levels reduce cardiac NO-release and increase the endothelin production. This aggravates coronary endothelial dysfunction.14 Stress can induce a pro-coagulatory state in the absence of any trauma.15 Finally, the early phase of stressful events is characterized by an proinflammatory response that may lead to plaque instability via the activation of matrix-metalloproteinases.16,17 This fatal triad triggers acute coronary syndromes and myocardial infarction during and after stressfull events.

In the perioperative period, surgery and related interventions induce stress responses. Endotracheal intubation alone has been shown to be related to a marked increase of norepinephrine and prolactin.18,19 Both after minimal invasive and major open surgery increased serum levels of stress hormones were recorded.20-22 A pro-coagulant state has been repeatedly shown after major abdominal and orthopaedic surgery and persists weeks after surgery.21,23,24 As a consequence of this constellation, cardiovascular mortality accounts for 63% of perioperative mortality in a high risk patient population and is still responsible for 30% of perioperative mortality in low risk patients.25

TEA AND SYMPATHETIC BLOCK
TEA has been intensively investigated with respect to its effect on perioperative pathophysiology and outcome. In the scientific discussion, segmental temporary sympathetic block is assumed to be related to the beneficial effects.26

However, both clinical and experimental data on sympathetic activity during TEA are scarce and needs to interpreted carefully. Level of epidural catheter insertion, volume and concentration of local anesthetics as well as the methodological limits of sympathetic activity measurement needs to be considered.27,28 Microneurography is the only technique that allows direct quantitative insight into abdominal sympathetic activity. It is, however, highly limited in spatial resolution and restricted to animal experimental studies.29 Many data were derived from indirect techniques relying on measurements of altered effector organ function during sympathetic block.29 These parameters are, however, prone to affection by microvascular anatomy, emotional and thermoregulatory state or the presence of general anesthesia.30,32

TEA is supposed to induce a segmental sympathetic block covering at least the levels of sensory block. Depending on the level of insertion, this block includes cardiac sympathetic efferent fibres in high TEA and low cervical epidural anesthesia and splanchnic sympathetic nerves in the case of midthoracic TEA. The sympathetic block should be restricted to a segmental block with compensatory...
increased sympathetic activity in the segments below the intended block. This concept is based on two microneurographic studies in cats and rabbits conclusively demonstrating abdominal sympathetic block when mid-thoracic sympathetic roots were covered by TEA.33,34

In contrast to this, a clinical study failed to show thoracic sympathetic block within the sensory block in TEA using 4.2 ml Bupivacaine 0.75% injected at Th6-Th9.35 In contrast to these negative findings, recently a thoracic sympathetic block was preoperatively demonstrated by thermography in TEA induced by low concentration and high volume of local anesthetic.29 During midthoracic TEA, the decrease of skin temperature in Th4 – Th12 was significantly less pronounced compared to sham group, demonstrating reduced sympathetic vasoconstrictive activity. Similarly, in a rat model of continuous TEA an early and sustained increase in skin temperature in the dermatomes Th1, Th6 and Th12 was recorded.27 In another rat model, 30µl Lidocaine 2% injected epidurally at the level of Th6 induced increase in thoracic and abdominal skin temperature as qualitatively demonstrated by thermography.30

However, it is still unclear whether a limited segmental high thoracic sensory block is accompanied by a limited sympathetic block. In experimental TEA in cats, high TEA with 0.1ml/kg Lidocaine 1% induced cardiac sympathetic block (Th1 – Th4) but increased renal sympathetic nerve activity (Th8) as recorded by microneurography. In the same study, lumbar epidural anesthesia induced renal sympathetic block and increased cardiac sympathetic block via baroreceptor-reflexes. There are no data concerning sensoric block in this model.34 Clinical data on a restricted segmental block of sympathetic activity in TEA is inconclusive until today. In human, limited upper thoracic sensory block reaching Th6 occurred during high TEA induced by 4.2 ml Bupivacaine 0.75%. In these patients, however, skin temperature in the feet also increased, suggesting unrestricted sympathetic block including splanchnic segments.35 In contrast to this, 4 ml Bupivacaine 0.5% injected at Th4 induced sensory block down to Th8 but did not affect sympathetic activity in the lower legs.34 Consequently, the concentration of local anesthetic might not only determine the intensity but also extent of the sympathetic block (35,36). A higher volume of Bupivacaine 0.25% injected at a midthoracic level induced a sympathetic block including the complete sympathetic innervation of the legs.29

**ANTI-ISCHEMIC EFFECTS OF TEA IN CARDIAC AND NON-CARDIAC SURGERY**

TEA has been repeatedly shown to decrease adverse perioperative cardiac events.3,37 A superior pain relief with concomitant reduction of the postoperative stress response and systemic sympathetic activity is most likely to contribute to this effect.3,38,39 Furthermore, regional sympathetic block including cardiac sympathetic nerves reduces not only ischemic pain but preserves coronary perfusion during cold pressor testing. This effect was most pronounced in stenotic vessels.40,41 These data support findings of perioperative anti-ischemic effects of TEA both in cardiac and in non-cardiac surgery. TEA reduced diastolic dysfunction in patients with CAD undergoing operative revascularization.42 Diastolic dysfunction has been reported to be an early sign of cardiac ischemia. While in this study no effect on systolic function was recorded, an earlier study revealed improved systolic function and wall motion in coronary artery disease. Troponin release and long term survival after CABG underline the cardioprotective potential of TEA in that study.43 In experimental myocardial ischemia TEA reduced infarct size.12 Due to the low incidence of complications and limited study sizes, two meta-analyses failed to prove decreased myocardial infarction after TEA in cardiac surgery,44,45 while in non-cardiac high risk surgical patients postoperatively continued TEA prevented myocardial infarction.39 However, a recent meta-analysis showed a decreased rate of combined end-points myocardial infarction and mortality after cardiac surgery in the presence of neuraxial blockade.44

**INTESTINAL PERFUSION**

Safeguarding intestinal perfusion is a critical issue in the mainenance of intestinal function and integrity of mucosal barrier. TEA reversed impaired intraoperative intestinal oxygenation during major surgery and protected intestinal barrier function in experimental hypoxemia.46,47 In acute experimental pancreatitis and in sepsis TEA improved mucosal capillary perfusion.48,49 In healthy rats a shift from intermittent to continuous capillary perfusion in the face of mild hypotension was recorded during TEA.50 Similarly, in patients undergoing esophagectomy continuous epidural infusion of Bupivacaine without a bolus dose increased anastomotic mucosal blood flow compared to the control group.51 In these studies, TEA was associated with no or only moderate hypotension. After esophagectomy the postoperative increase in cardiac output during the weaning procedure was blunted by TEA, thereby suggesting altered hemodynamic regulation.51

However, a number of clinical and experimental studies revealed adverse effects of TEA on parameters of intestinal perfusion.52-55 Only recently in 10 patients undergoing esophagectomy TEA has been demonstrated to reduce laser Doppler flow in the distal gastric tube mucosa.56 All these studies reported substantial deterioration in systemic hemodynamic parameters. Mean arterial pressure was reduced by 20 – 50% after induction or during maintenance of TEA (52,53,55,56). Cardiac output remained stable in only one of these studies,55 but was decreased up to 35% in two other.52,56 Furthermore, as far as data are
provided, the animal experimental studies revealing adverse perfusion effects of TEA are related to an extended or total sympathetic block.\textsuperscript{52,51} The clinical study described a sensoric block reaching Th4.\textsuperscript{54} Since sympathetic block has been found to exceed sensoric block in epidural anaesthesia and sympathetic preganglionary neurons origin not higher than Th1, the sensoric level of Th4 suggest an almost complete craniocaudal sympathetic block in these patients.\textsuperscript{79}

In conclusion, TEA seems to exert beneficial effects on intestinal perfusion as long as its hemodynamic consequences are adequately controlled.

**INTESTINAL MOTILITY**

Postoperatively, paralytic ileus and abdominal sepsis are life-threatening to the patient and have tremendous economic impact.\textsuperscript{57} Pain, increased sympathetic tone, the use of systemic opioid analgesia and intestinal neuroinflammatory processes contribute to intestinal hypomotility.\textsuperscript{58} The faster resolution of postoperative ileus after major open surgery is widely undisputed and attributed to superior pain therapy, reduced opioid consumption and sympathetic block.\textsuperscript{5,59} In a direct comparison to lidocain-PCIA, epidural application of lidocaine was shown to be more effective concerning pain control and resolution of hypomotility after colonic surgery.\textsuperscript{60} TEA resulted in a faster resolution of postoperative ileus after major non-intestinal surgery also.\textsuperscript{61}

The use of TEA in the setting of fast-track-regimen and minimal invasive approaches for major procedures has been questioned.\textsuperscript{6} Two recent studies of TEA after laparoscopic surgery reported improved bowel motility,\textsuperscript{62,63} while one other did not prove an effect of TEA.\textsuperscript{64} However, differences in study design, technique of TEA and the surgical procedures do hinder comparison and interpretation of the data. The faster resolution of ileus was demonstrated on the background of a non-accelerated standard care. Surgery lasted about 3h and the surgical cases included major resections, such as hemicolecotomy, in 12\% to 55\%.\textsuperscript{62,63} In contrast to this, TEA failed to exert beneficial effects when added to an established fast-track-program after laparoscopic sigmoidal resection with a duration of surgery of 2h.\textsuperscript{64}

**ANASTOMOTIC PERFUSION AND PATENCY**

The impact of TEA on anastomotic perfusion and healing of anastomosis is still unclear.

In colorectal surgery TEA has been found to decrease anastomotic blood flow and improved gastric and transverse colonic blood flow.\textsuperscript{54} After esophagectomy, reduction in the already compromised mucosal circulation of the oral end of the gastric tube was more pronounced compared to the aboral end.\textsuperscript{56} In both studies, however, significant systemic hemodynamic alterations were present. In contrast to this, 1h (sedated patients) and 18h (awake and extubated patients) anastomotic mucosal blood flow was increased in TEA after esophageal resection.\textsuperscript{51}

Data on anastomotic patency is also equivocal until today. Both increased rate of insufficiency and improved anastomotic healing has been reported.\textsuperscript{85} The latter finding is supported by a recent retrospective analysis of esophageal anastomosis, demonstrating a 70\% risk-reduction for anastomotic leak in the TEA group (66). This protective effect might be of tremendous importance in the light of the five-fold increase in mortality in patients with anastomotic leak.

**TEA AND OUTCOM**

TEA provides superior pain therapy in a wide range of thoracic and abdominal surgery.\textsuperscript{1} However, procedure specific effectivity should be recognized. While effectivity of TEA in colonic resection is well documented little benefit is reported after hysterectomy. However, all of these studies described a significantly improved pain control in TEA, lasting up to two weeks after surgery.\textsuperscript{62-64} Superior pain therapy and ameliorated metabolic response are related to improved quality of life after colonic resection.\textsuperscript{65,68} A recent meta-analysis of pulmonary effects of TEA revealed a reduced rate of pneumonia after TEA, most probably due to earlier mobilisation, reduced opioid-consumption and improved coughing.\textsuperscript{59}

Rodgers and coworker demonstrated a 30\% relative risk reduction of fatal outcome after surgery in unselected patients with neuraxial anesthesia. The evaluation included lumbar and spinal anesthesia.\textsuperscript{1} These findings were corroborated by Wu, who retrospectively demonstrated mortality in the TEA-group after colectomy and lung resections.\textsuperscript{70,71} In cardiac surgery an actual meta-analysis shows reduction of the combined outcomes myocardial ischemia and mortality, reduced renal failure and reduced need for ventilation in TEA for cardiac surgery.\textsuperscript{44}

**TEA AND TUMOR SPREAD**

Tumor resection is a most important therapeutic strategy in the cure or control of malignant diseases. However, the procedure carries oncologic risk for the patients. Surgical manipulation promote systemic spread of tumor cells, which predicts a poor outcome.\textsuperscript{72,73} The influence of surgical stress on the immune function impairs the host’s ability to eliminate the circulating tumor cells. This includes suppression of Natural Killer cell function, increased Th2-T-cell-activity and reduced innate immune reactivity.\textsuperscript{74}

Only recently two retrospective studies demonstrated reduced tumor recurrence rate and improved survival after regional anesthesia in two important tumor entities.\textsuperscript{75,76} These studies attracted attention to regional anesthesia as a potential tool to influence long-term outcome by perioperative
measures. Morphine has been repeatedly shown to reduce Natural Killer cell activity and to promote growth in experimental colonic cancer metastasis and experimental breast cancer. Hypothermia and adrenergic response also promote experimental tumor growth. Tumor growth can be prevented by effective sympathetic block and analgesia in mice. The observed protective effects of regional anesthesia might be therefore based both on an opioid-sparing effect and on reduced neurohumoral stress response.

RISKS OF TEA

The beneficial effects of TEA can be demonstrated in large patient populations and a favourable perioperative outcome can usually not be specifically attributed to epidural anesthesia. But albeit the number needed to harm is far higher than the number needed to treat, the complications of TEA are very specifically attributable to TEA and finally to the attending anaesthesiologist. This constellation leads to forensic risks and precautions to use TEA in critical patients, although they might profit most. There are three major risk categories to be considered: a) epidural bleeding, b) the unnecessary withdrawal of low dose aspirin in cardiovascular or cerebrovascular risk patients and c) epidural infection.

EPIDURAL BLEEDING

Epidural bleeding after epidural anesthesia has an estimated incidence of 1:2,700 to 1:5,400. This marked range of risk is related to different practice of perioperative thrombembolism prophylaxis and the implementation of specific guidelines for the use of epidural analgesia and anesthesia. The incidence of epidural hematoma further differs with the site of insertion and the procedure. While obstetric patients have a low rate of epidural bleeding, perioperative lumbar epidural anesthesia is more frequently complicated by bloody puncture and epidural hematoma than thoracic epidural catheterization. Recently, in a series of 10,000 TEA no epidural hematoma was described. Elderly female scheduled for lower limb arthroplasty have been repeatedly found to carry an especially high risk. In these patients alternative therapeutic strategies needs to be considered: Pre-existing coagulation disorders and the use of anticoagulant or antiplatelet drugs are the most prominent risk factors of perioperative epidural hematoma. Furthermore, aged patients are at increased risk of epidural complications, most probably due to age related alterations of spinal anatomy and to impaired renal function with unexpectedly prolonged drug effects. For example, even a mild impairment of renal function increase the time of effective anticoagulation by low molecular weight heparin (LMWH) from 6.6 to 9.9 hours. In case of severe renal impairment LMWH effect lasts more than 15 hours. Finally, repeated and bloody puncture increase the risk of epidural bleeding.

WITHDRAWAL OF ASPIRIN

In the western countries approximately 1.8 million coronary stents are implanted each year and 500,000 strokes occur annually in the European Union. The high incidence of cardiovascular and cerebrovascular diseases in surgical patients results in an increased use of antiplatelet and anticoagulant drugs for secondary prophylaxis in patients scheduled for TEA.

The withdrawal of antiplatelet drugs leads to rebound effects with increased rate of thromboembolic events. This rebound effect is aggravated by the prothrombotic and proinflammatory state induced by surgery. In case of antiplatelet drug discontinuation within 3 weeks after stenting, mortality is to 30 - 86%. Late stent thrombosis after antiplatelet drug discontinuation can occur more than one year after stenting. Consequently it has become consensus to continue antiplatelet medication in almost all surgical cases. Only in emergency intracranial, spinal and intraocular surgery, in which bleeding is potentially catastrophic, cessation and bridging with tirofiban and Heparin is recommended.

The use of perioperative TEA must not lead to cessation of low dose acetylsalicylic acid prescribed for secondary prophylaxis. There is most probably no increase in the rate of spinal epidural hematoma during low dose ASS intake. However, the combination of ASS with other anticoagulant or antiplatelet drugs must be excluded in case TEA is planned. Standard operating procedures assuring the beginning of thromboembolic prophylaxis after surgery are suitable to increase the use of TEA in patients on ASS-prophylaxis.

When TEA is planned in patients using other antiplatelet or anticoagulant drugs, specific time intervals should be kept between the last medication and catheter removal as reviewed earlier in detail. Since catheter removal is a critical phase with increased incidence of epidural bleeding, neurologic surveillance must be assured until 24 h after catheter removal. This notion is emphasized by recent data from the UK reporting delayed diagnosis in 4 of 5 cases of epidural hematoma with persistent harm. Only one patient was treated in time and reached full recovery.

INFECTIOUS COMPLICATIONS

TEA is an invasive analgesic technique and as such inevitably associated with the risk of local infectious complications. Iatrogenic pathogen inoculation and haematogenous infection of the insertion site or the epidural catheter are the potential causes of infection within the vertebral canal. Estimates of incidence vary widely. Recent data from Germany report an incidence of 1 abscess in 10,000 patients with TEA (1). In the UK an incidence of 1:24,000 epidural abscesses was found after perioperative neuraxial blockade with 10 of 13 cases in the study.
period related to epidural anesthesia.\textsuperscript{87} Epidural abscess with spinal cord and radicular compression is the predominant complication after TEA and usually caused by staphylococcus aureus. Meningitis has also been reported with a lower incidence. It is usually caused by streptococcus species.\textsuperscript{99,100} Infectious complications may occur as early as day 2 but usually present beginning from day 4 or later. They are often, but not always, accompanied by signs of infection of the insertion site and most often present with incomplete or unspecific symptoms. This frequently results in delayed diagnosis and underlines the necessity of close clinical observation and high level of suspicion.\textsuperscript{87} The prognosis of infectious complications is better than that of epidural bleeding. All patients with meningitis reached full recovery and approximately 50 % of patients with epidural abscesses recover without permanent disability.\textsuperscript{87}

**CONCLUSIONS**

TEA provides optimal pain therapy in a wide range of surgical procedures and might reduce perioperative morbidity and mortality after major abdominal and thoracic surgery. Furthermore TEA might influence tumor progression after oncologic surgery. However, due to the low overall incidence of postoperative complications in many surgical procedures and the uncertainty concerning the incidence of epidural bleeding and infectious complications, procedure-specific evidence-based recommendations concerning TEA are still hard to make.

**REFERENCES**


IARS 2010 REVIEW COURSE LECTURES


There has been increasing interest in recent years in the glycemic control of surgical patients. The seminal paper of Van den Berghe and colleagues, who showed in 2001 that mortality and morbidity in critically ill surgical patients was improved with intensive insulin therapy, has been hugely influential in stimulating research in this area. By 2008 a meta-analysis comparing tight glucose control with usual care in critically ill patients evaluated 29 randomized controlled trials and concluded that there were no beneficial effects of tight control on mortality but this regimen was associated with an increased risk of hypoglycemia. Three large trials published after this meta-analysis also failed to show benefits of intensive insulin therapy in critically ill patients. A recent meta-analysis in 2009 again concluded that tight glucose control did not improve mortality and significantly increased the risk of hypoglycemia. There was some benefit, however, in patients admitted to a surgical critical care unit.

In comparison to the many studies investigating glycemic control in critically ill patients, there is a paucity of studies examining surgical patients with the exception of cardiac surgery. In order to reach recommendations for the glycemic management of surgical patients that are logical, achievable and safe the following key topics will be discussed:

- pathophysiology of the hyperglycemic response to surgery
- deleterious effects of hyperglycemia and hypoglycemia
- clinical studies of glycemic control in surgical patients
- benefits and risks of glycemic control.

**PATHOPHYSIOLOGY OF THE HYPERGLYCEMIC RESPONSE TO SURGERY**

An increase in blood glucose concentration during and after surgery is a well recognised component of the “stress response”. The increase in blood glucose reflects the severity of surgery, for example 10-20 mg/dl (0.6-1.1 mmol/l) in surface surgery and 55-90 mg/dl (3.1-5.0 mmol/l) in major vascular and cardiac surgery. Hepatic glycogenolysis and gluconeogenesis are enhanced by an increase in catabolic hormone secretion (norepinephrine, epinephrine, cortisol and growth hormone) in response to surgical trauma. There is an initial failure of insulin secretion to respond to the glycemic stimulus of surgery that is followed postoperatively by the recovery of secretion but with lack of functional effectiveness – insulin resistance. Thus the perioperative period is characterized by functional insulin insufficiency. The mechanisms responsible for the lack of functional insulin are poorly understood and include the inhibitory effects of volatile anesthetic agents and circulating catecholamines on pancreatic beta cell function and the effects of starvation and circulating cytokines in inducing insulin resistance. The obvious method of overcoming this lack of functional insulin is the administration of exogenous insulin, but preoperative carbohydrate loading has been found to improve insulin resistance after major surgery and the use of an insulin “sensitizer”, such as metformin, may improve insulin resistance.

The physiological responses to surgery are similar to those found in an injured wild animal in which they evolved to aid survival. It is difficult with the current clinical emphasis on maintaining normoglycemia to consider that an increase in blood glucose perioperatively could be beneficial. Furthermore, there is considerable observational evidence to show that hyperglycemia, irrespective of cause, is associated with adverse outcomes in hospitalized patients. Nevertheless an acute increase in circulating glucose perioperatively may be necessary as an obligatory energy source for immune cells, particularly lymphocytes and also to ensure a concentration gradient of glucose from blood to the injured tissues that are relatively avascular.

**DELETERIOUS EFFECTS OF HYPERGLYCEMIA AND HYPOGLYCEMIA**

Acute hyperglycemia has many harmful effects such as impaired endothelial NO generation with decreased vasodilatation, increased expression of endothelial and leucocyte adhesion molecules, reduced complement function, impaired neutrophil function and increased cytokine synthesis. Together these changes enhance the inflammatory response to injury and likelihood of infection. Many of these responses are shown at glucose concentrations of 180-200 mg/dl (10.0-11.1 mmol/l). The use of insulin to reduce hyperglycemia has been shown to decrease endothelial activation, protect hepatic mitochondria, stimulate glucose uptake, improve the circulating lipid profile and decrease circulating inflammatory markers. Pro-inflammatory cytokines are increased by acute hyperglycemia in the absence of injury and can then perpetuate the raised glucose by inducing peripheral insulin resistance. Current evidence suggests that any beneficial effects of insulin treatment result from a decrease in circulating glucose values.
Hypoglycemia is an obvious risk from the use of insulin infusions to control glucose perioperatively. The brain is particularly vulnerable to hypoglycemia, especially the superficial layers of the cortex. The two meta-analyses examining glucose control in critically ill patients reported relative risks of 5.12 and 6.06 respectively for hypoglycemia in the intervention groups. In diabetic patients hospitalized in general wards it has been shown that patients with hypoglycemia have increased duration of stay and greater mortality during and after admission. It is possible that any benefit of glycemic control in the larger group of critically ill patients without hypoglycemia is more than opposed by serious adverse events in the subgroup who develop hypoglycemia.

GLYCEMIC CONTROL IN SURGICAL PATIENTS

Most of the surgical studies have been undertaken on cardiac patients usually with cardiopulmonary bypass. Cardiac surgery is of particular interest following the demonstration of the beneficial effects of a glucose-insulin-potassium infusion in patients with acute myocardial infarction, although this was not confirmed by a later trial and the long established observation of increased infection rates in diabetic patients. Several retrospective studies have shown beneficial effects of intraoperative control of blood glucose with improved mortality, major morbidity, decreased duration of hospital stay and decreased wound infection. Many of these studies had methodological problems and included predominantly diabetic patients. A recent randomized controlled trial compared tight intraoperative glucose control (target glucose 80-100 mg/dl, 4.5-5.6 mmol/l) with conventional treatment (target glucose < 200 mg/dl, 11.1 mmol/l) in patients, non-diabetic and diabetic, undergoing on-pump coronary artery bypass grafting. There was no decrease in perioperative mortality and morbidity. The pros and cons of tight glycemic control in cardiac surgery remain controversial.

Glycemic control after surgery has been shown to decrease the risk of wound infection in diabetic patients. Studies on non-diabetic patients are conspicuously lacking. A retrospective survey of patients undergoing peripheral vascular surgery found that increased circulating glucose values postoperatively were an independent risk factor for infection. The use of intensive insulin therapy after brain surgery to achieve target blood glucose values of 80-110 mg/dl (4.4-6.1 mmol/l) compared with conventional treatment – blood glucose < 215 mg/dl (11.9 mmol/l) decreased the infection rate but was associated with an increased frequency of hypoglycemia.

No prospective study has compared the effects of perioperative glycemic control in diabetic and non-diabetic patients. Subgroup analysis of the many studies on glycemic control in critically ill patients has yielded conflicting conclusions. Early work suggested that although intensive insulin therapy improved outcome in non-diabetic patients, it was of no benefit in diabetic patients. In contrast, a retrospective case-control study found no difference in mortality between diabetics and non-diabetics despite higher glucose values in the former group. It is possible that diabetic patients may tolerate a higher glucose than non-diabetics perioperatively as a result of their chronic hyperglycemia. Intraoperative glucose control in cardiac surgical patients has focused on diabetic patients with many studies showing improved outcomes (see above). A comparison of glycemic control in type 1 and type 2 diabetic patients has not been undertaken. It is likely that type 2 diabetics who already have marked insulin resistance will require more insulin to achieve glycemic control.

BENEFITS AND RISKS

The institution of glycemic control perioperatively has associated costs. It has been argued that such investment will lead to savings from improved clinical outcomes. There have been several reports that glycemic control programs have resulted in savings attributable to fewer complications, decrease in stay in ICU and hospital and lower laboratory costs. However, these studies relate to critically ill patients and cardiac surgical patients, particularly diabetics.

The risk of hypoglycemia is the major problem in trying to establish tight glycemic control (< 110 mg/dl, < 6.1 mmol/l) and has been found to occur commonly. Patients particularly at risk of hypoglycemia include the elderly, the malnourished and those with autonomic, renal, hepatic and cardiac failure. Hypoglycemia may also occur from the failure to monitor blood glucose frequently and from insulin dosage errors. The long term effects of hypoglycemia in surgical patients are unknown. In diabetic patients recurrent episodes of hypoglycemia have been shown to result in neuronal deficits, especially in children and the elderly.

Safe glycemic management is dependent totally on the frequent and accurate determination of blood glucose concentrations. The US Food and Drug Administration permits a ± 20% error for glucose meters, an inaccuracy that is a major handicap to glycemic control. Glucose values differ between whole blood and plasma although the terms are often used interchangeably. Most commercial glucose meters have a correction factor and report a plasma adjusted value. The assay strips used with glucose meters and arterial blood gas analysis tend to overestimate glucose values at low concentrations with the risk of missing hypoglycemia. Other factors that affect blood glucose measurements include peripheral hypoperfusion, anemia, increased circulating bilirubin and uric acid, mannitol, dopamine, dextrin and paracetamol.
There is debate about the best index of glycemic control perioperatively. It has been suggested that variability in circulating glucose may be more important than the absolute value. Indices of glycemic control include the admission glucose, maximum daily glucose, mean morning glucose, mean overall glucose or a hyperglycemic index.\textsuperscript{39} A recent study found that the simple measure of mean daily blood glucose was as informative as more complex metrics.\textsuperscript{39}

**CONCLUSIONS**

The initial enthusiasm for glycemic control during and after surgery has waned after the failure to replicate the findings of Van den Berghe and colleagues in critically ill patients. There is some evidence to suggest that glycemic control in cardiac surgical patients improves mortality, morbidity and infection rates, particularly in diabetic patients. There are no studies in general surgical patients to indicate whether blood glucose control improves outcome. Tight glucose control (bl. glucose < 110 mg/dL, 6.1 mmol/l) is associated with a large increase in the risk of hypoglycemia and cannot be supported. The Consensus Statement of the American Association of Clinical Endocrinologists and American Diabetes Association recommends that in critically ill patients blood glucose should be in the range of 140-180 mg/dL (7.8-10.0 mmol/l) and in non-critically ill patients should be less than 180 mg/dL (10.0 mmol/l).\textsuperscript{39} These limits apply to non-diabetic and diabetic patients. The inclusion of glucose targets as an indicator of quality of care is premature and should be reviewed.

**REFERENCES**

16. Lipshutz AKM, Grupper MA. Perioperative glycemic control. Anesthesiology 2008;109:408-21
17. Esposito K, Nappo F, Marfella R et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: Role of oxidative stress. Circulation 2002;106:2067-72
33. Montori VM, Bistrian BR, McMahon MM. Hyperglycemia in acutely ill patients. JAMA 2002;288:2167-69


Can Regional Anesthesia Coexist with DVT Prophylaxis?

Terese T. Horlocker, MD
Professor of Anesthesiology and Orthopedics
Mayo Clinic
Rochester, MN

The actual incidence of neurologic dysfunction resulting from hemorrhagic complications associated with neuraxial blockade is unknown; however, the incidence cited in the literature is estimated to be less than 1 in 150,000 epidural and less than 1 in 220,000 spinal anesthetics. In a review of the literature between 1906 and 1994, Vandermeulen et al. reported 61 cases of spinal hematoma associated with epidural or spinal anesthesia. In 87% of patients, a hemostatic abnormality or traumatic/difficult needle placement was present. More than one risk factor was present in 20 of 61 cases. Importantly, although only 38% of patients had partial or good neurologic recovery, spinal cord ischemia tended to be reversible in patients who underwent laminectomy within eight hours of onset of neurologic dysfunction.

The need for prompt diagnosis and intervention in the event of a spinal hematoma was also demonstrated in a recent review of the American Society of Anesthesiologists (ASA) Closed Claims database, which noted that spinal cord injuries were the leading cause of claims in the 1990s. Spinal hematomas accounted for nearly half of the spinal cord injuries. Risk factors for spinal hematoma included epidural anesthesia in the presence of intravenous heparin during a vascular surgical or diagnostic procedure. Importantly, the presence of postoperative numbness or weakness was typically attributed to local anesthetic effect rather than spinal cord ischemia, which delayed the diagnosis. Patient care was rarely judged to have met standards (1 of 13 cases) and the median payment was very high.

It is impossible to conclusively determine risk factors for the development of spinal hematoma in patients undergoing neuraxial blockade solely through review of the case series, which represent only patients with the complication and do not define those who underwent uneventful neuraxial analgesia. However, large inclusive surveys that evaluate the frequencies of complications (including spinal hematoma), as well as identify subgroups of patients with higher or lower risk, enhance risk stratification. Moen et al. investigated serious neurologic complications among 1,260,000 spinal and 450,000 epidural blocks performed in Sweden over a ten-year period. Among the 33 spinal hematomas, 24 occurred in females; 25 were associated with an epidural technique. The methodology allowed for calculation of frequency of spinal hematoma among patient populations. For example, the risk associated with epidural analgesia in women undergoing childbirth was significantly less (1 in 200,000) than that in elderly women undergoing knee arthroplasty (1 in 3600, p<0.0001). Likewise, women undergoing hip fracture surgery under spinal anesthesia had an increased risk of spinal hematoma (1 in 22,000) compared to all patients undergoing spinal anesthesia (1 in 480,000).

Overall, these series suggest that the risk of clinically significant bleeding varies with age (and associated abnormalities of the spinal cord or vertebral column), the presence of an underlying coagulopathy, difficulty during needle placement, and an indwelling neuraxial catheter during sustained anticoagulation (particularly with standard heparin or LMWH); perhaps in a multifactorial manner. They also consistently demonstrate the need for prompt diagnosis and intervention.

ORAL ANTICOAGULANTS

Few data exist regarding the risk of spinal hematoma in patients with indwelling epidural catheters who are anticoagulated with warfarin. The optimal duration of an indwelling catheter and the timing of its removal also remain controversial. To date, only three studies have evaluated the risk of spinal hematoma in patients with indwelling spinal or epidural catheters who receive oral anticoagulants perioperatively. Odoom and Sih performed 1000 continuous lumbar epidural anesthetics in vascular surgical patients who were receiving oral anticoagulants preoperatively. The thrombotest (a test measuring factor IX activity) was decreased in all patients prior to needle placement. Heparin was also administered intraoperatively. Epidural catheters remained in place for 48 hours postoperatively. There were no neurologic complications. While these results are reassuring, the obsolescence of the thrombotest as a measure of anticoagulation combined with the unknown coagulation status of the patients at the time of catheter removal limit the usefulness of these results. Therefore, except in extraordinary circumstances, spinal or epidural needle/catheter placement and removal should not be performed in fully anticoagulated patients.

There were also no symptomatic spinal hematomas in 192 patients receiving postoperative epidural analgesia in conjunction with low-dose warfarin after total knee arthroplasty. Patients received warfarin, starting on the postoperative day, to prolong the PT to 15.0-17.3 s (normal 10.9-12.8 s), corresponding to an INR of 2.0-3.0. Epidural catheters were left indwelling 37±15 h
Regional anesthetic management of the patient on oral anticoagulants*

Anesthetic management of patients anticoagulated perioperatively with warfarin is dependent on dosage and timing of initiation of therapy. Since factor VII has a relatively short half-life, prolongation of the PT and INR may occur in 24-36 hours after initiation of warfarin therapy. The PT will be prolonged (outside of normal range) when factor VII activity is reduced to approximately 55% of baseline. However, the therapeutic effect of warfarin anticoagulation is most dependent on reduction in factors II and X activity. Since these factors have circulating half-lives of 36-48 and 72-96 hours respectively, thromboprophylaxis is not adequate for 3-5 days after starting warfarin therapy.

Many orthopedic surgeons administer the first dose of warfarin the night before surgery. For these patients, the PT and INR should be checked prior to neuraxial block if the first dose was given more than 24 hours earlier, or a second dose of oral anticoagulant has been administered. Patients receiving low dose warfarin therapy during epidural analgesia should have their PT and INR monitored on a daily basis, and checked before catheter removal, if initial dose of warfarin was more than 36 hours beforehand. Reduced doses of warfarin should be given to patients who are likely to have an enhanced response to the drug. In general, is it recommended that indwelling neuraxial catheters be removed when the INR < 1.5 in order to assure adequate levels of all vitamin-K dependent factors. An INR > 3 should prompt the physician to withhold or reduce the warfarin dose in patients with indwelling neuraxial catheters. There is no definitive recommendation for removal of neuraxial catheters in patients with therapeutic levels of anticoagulation during a neuraxial catheter infusion.

The PT and INR of patients on chronic oral anticoagulation will require three to five days to normalize after warfarin discontinuation. Theoretically, since the PT and INR reflect predominantly factor VII activity, (and factor VII has only a six to eight hour half-life), there may be an interval during which the PT and INR approach normal values, yet factors II and X levels may not be adequate for normal hemostasis. Adequate levels of all vitamin K-dependent factors are typically present when the INR is in the normal range. Therefore, it is recommended that documentation of the patient's normal coagulation status be achieved prior to implementation of neuraxial block.

Intravenous and Subcutaneous Standard Heparin

Complete systemic heparinization is typically reserved for the most high-risk patients, typically patients with an acute thromboembolism. However, intraoperative administration of a modest intravenous dose is occasionally performed during vascular or orthopedic procedures. In a study involving over 4000 patients, Rao and El-Etr demonstrated the safety of indwelling spinal and epidural catheters during systemic heparinization. However, the heparin activity was closely monitored, the indwelling catheters were removed at a time when circulating heparin levels were relatively low, and patients with a preexisting coagulation disorder were excluded. A subsequent study in the neurologic literature by Ruff and Dougherty reported spinal hematomas in 7 of 342 patients (2%) who underwent a diagnostic lumbar puncture and subsequent heparinization. Traumatic needle placement, initiation of anticoagulation within 1 hour of lumbar puncture or concomitant aspirin therapy were identified as risk factors in the development of spinal hematoma in anticoagulated patients. Overall, large published series and extensive clinical experience suggests the use of regional techniques during systemic heparinization does not appear to represent a significant risk. However, the recent reports of paralysis relating to spinal hematoma in the ASA Closed Claims database suggests that these events may not be as rare as suspected and that extreme vigilance is necessary to diagnose and intervene as early as possible, should spinal hematoma be suspected.

The use of epidural and spinal anesthesia and analgesia in the presence of high dose intraoperative systemic heparin, specifically in cardiac surgery has gained recent popularity. In a recent survey of the membership of the Society of Cardiovascular Anesthesiologists, Goldstein et al surveyed 3974 cardiac anesthesiologists, and found 7% of their responders used spinal or epidural techniques for cardiac surgery. Interestingly, the majority of anesthesiologists would proceed if frank blood was noted in the spinal or epidural needle. To date there

*(Wu and Perkins)*

The authors recommended close monitoring of coagulation status to avoid excessive prolongation of the PT during epidural catheterization. They noted in the spinal or epidural needle. To date there may be no definitive recommendation for removal of neuraxial catheters in patients with therapeutic levels of anticoagulation during a neuraxial catheter infusion.
are no case reports of spinal hematomas associated with this technique published or within the Closed Claims Project. Ho et al calculated the risk of hematoma among these patients. In a complex mathematical analysis of the probability of predicting a rare event that has not occurred yet, they estimate the probability of an epidural hematoma (based on the totals of 4,583 epidural and 10,840 spinal anesthetics reported without complications) to be in the neighborhood of 1:1,528 for epidural injection, and 1:3,610 for spinal technique.

Low-dose subcutaneous standard (unfractionated) heparin is administered for thromboprophylaxis in patients undergoing major thoracoabdominal surgery and in patients at increased risk of hemorrhage with oral anticoagulant or LMWH therapy. As previously mentioned, subcutaneous heparin does not provide adequate prophylaxis following major orthopedic surgery, and is seldom utilized in this patient population. A review of the literature by Liu and Mulroy noted no spinal hematomas in over 9000 patients who received subcutaneous heparin in combination with spinal or epidural anesthesia. There are only three cases of spinal hematoma associated with neuraxial blockade in the presence of low-dose heparin, two of which involved a continuous epidural anesthetic technique. It is important to note that while the ACCP guidelines are more often recommending thrice daily dosing of subcutaneous heparin (due to patient co-morbidities and increased risk of thromboembolism), the safety of neuraxial block in these patients is unknown (Table 2).

REGIONAL ANESTHETIC MANAGEMENT OF THE PATIENT RECEIVING STANDARD HEPARIN*

The safety of neuraxial techniques in combination with intraoperative heparinization is well documented, providing no other coagulopathy is present. The concurrent use of medications that affect other components of the clotting mechanisms may increase the risk of bleeding complications for patients receiving standard heparin. These medications include antiplatelet medications, LMWH, and oral anticoagulants.

Intravenous heparin administration should be delayed for 1 hour after needle placement. Indwelling catheters should be removed 1 hour before a subsequent heparin administration or 2-4 hours after the last heparin dose. Evaluation of the coagulation status may be appropriate prior to catheter removal in patients who have demonstrated enhanced response or are on higher doses of heparin. Although the occurrence of a bloody or difficult needle placement may increase risk, there are no data to support mandatory cancellation of a case should this occur. If the decision is made to proceed, full discussion with the surgeon and careful postoperative monitoring are warranted.

Prolonged therapeutic anticoagulation appears to increase risk of spinal hematoma formation, especially if combined with other anticoagulants or thrombolytics. Therefore, neuraxial blocks should be avoided in this clinical setting. If systemic anticoagulation therapy is begun with an epidural catheter in place, it is recommended to delay catheter removal for 2-4 hours following heparin discontinuation and after evaluation of coagulation status.

There is no contradiction to use of neuraxial techniques during subcutaneous standard heparin ≤10,000 U/d. However, higher doses are associated with increased medical and surgical bleeding and may also increase the risk of spinal hematoma. Thus, the combination of neuraxial catheters with 5000 U TID or 7500 U BID dosing should be undertaken with care. The risk of neuraxial bleeding may be reduced by delay of the heparin injection until after the block, and may be increased in debilitated patients or after prolonged therapy. A platelet count is indicated for patients receiving subcutaneous heparin for greater than 5 days.

LOW MOLECULAR WEIGHT HEPARIN

Enoxaparin, the first LMWH to be approved by the Food and Drug Administration (FDA) in the United States, was distributed for general use in May 1993. Within one year, two cases of spinal hematoma had been voluntarily reported through the MedWatch system. Despite repeated efforts at relabeling and education, cases of spinal hematoma continued to occur. A total of 30 cases of spinal hematoma in patients undergoing spinal or epidural anesthesia while receiving LMWH perioperatively were reported between May 1993 and November 1997. An FDA Health Advisory was issued in December 1997. In addition, the manufacturers of all LMWH and heparinoids were requested to place a black “boxed warning”.

At the time of the Consensus Conference on Neuraxial Anesthesia and Anticoagulation on April 1998, there were 45 cases of spinal hematoma associated with LMWH, 40 involved a neuraxial anesthetic. Severe radicular back pain was not the presenting symptom; most patients complained of new onset numbness, weakness, or bowel and bladder dysfunction. Median time interval between initiation of LMWH therapy and neurologic dysfunction was three days, while median time to onset of symptoms and laminectomy was over 24 hours. Less than one third of the patients reported fair or good neurologic recovery.

The risk of spinal hematoma, based on LMWH sales, prevalence of neuraxial techniques and reported cases, was estimated to be approximately 1 in 3000 continuous epidural anesthetics compared to 1 in 40,000 spinal anesthetics. However, this is most likely an underestimation- in addition to the spinal hematomas that had been reported at the
time of the First Consensus Conference, there were approximately 20 more that had occurred, but were not yet reported to the MedWatch system. In total, nearly 60 spinal hematomas were tallied by the FDA between 1993 and 1998 (Table 3).

There have been only 13 cases of spinal hematoma following neuraxial block between 1998 and 2002 (the timing of the second consensus conference) reported through the MedWatch system or published as case reports. In addition to LMWH, five patients received ketorolac, one patient received ibuprofen, and one patient received intravenous unfractionated heparin during a vascular procedure. The regional technique was a spinal anesthetic in three cases. The remaining ten patients underwent epidural anesthesia in combination with LWMH therapy. Thus, the characteristics of the reported cases support the previous recommendations of epidural catheter removal prior to the initiation of LMWH thromboprophylaxis and avoidance of concomitant antiplatelet/anticoagulant medications. Although the number of cases voluntarily reported has markedly declined, this may be a result of decreased reporting, improved management, or simple avoidance of all neuraxial techniques in patients receiving LMWH. Continued monitoring is necessary.

The indications and labeled uses for LMWH continue to evolve. Indications for thromboprophylaxis as well as treatment of DVT/PE or MI have been introduced since the first Consensus Conference. These new applications and corresponding regional anesthetic management warrant discussion. Several off-label applications of LMWH are of special interest to the anesthesiologist. LMWH has been demonstrated to be efficacious as a “bridge therapy” for patients chronically anticoagulated with warfarin, including parturients, patients with prosthetic cardiac valves, a history of atrial fibrillation, or preexisting hypercoagulable condition. The doses of LMWH are those associated with DVT treatment, not prophylaxis, and are much higher. Needle placement should occur a minimum of 24 hours following this level of LMWH anticoagulation. The presence of blood during needle and catheter placement does not necessitate postponement of surgery.

Preoperative LMWH. Patients on preoperative LMWH can be assumed to have altered coagulation. A single-injection spinal anesthetic may be the safest neuraxial technique in patients receiving preoperative LMWH for thromboprophylaxis. In these patients needle placement should occur at least 10-12 hours after the LMWH dose. Patients receiving treatment doses of LMWH will require delays of at least 24 hours. Neuraxial techniques should be avoided in patients administered a dose of LMWH two hours preoperatively (general surgery patients), because needle placement would occur during peak anticoagulant activity.

Postoperative LMWH. Patients with postoperative initiation of LMWH thromboprophylaxis may safely undergo single-injection and continuous catheter techniques. Management is based on total daily dose, timing of the first postoperative dose and dosing schedule. The first dose of LMWH should be administered no earlier than 24 hours postoperatively, regardless of anesthetic technique, and only in the presence of adequate hemostasis. Indwelling catheters should be removed prior to initiation of LMWH thromboprophylaxis. If a continuous technique is selected, the epidural catheter may be left indwelling overnight and removed the following day, with the first dose of LMWH administered two hours after catheter removal.

ANTIPLATELET MEDICATIONS

Antiplatelet medications are seldom used as primary agents of thromboprophylaxis. However, many orthopedic patients report chronic use of one or more antiplatelet drugs (Horlocker, 1995). Although Vandermeulen et al implicated antiplatelet therapy in 3 of the 61 cases of spinal hematoma occurring after spinal or epidural anesthesia, several large studies have demonstrated the relative safety of neuraxial blockade in both obstetric, surgical and pain clinic patients receiving these medications. In a prospective study involving 1000 patients, Horlocker et al reported that preoperative antiplatelet therapy did not increase the incidence of blood present at the time of needle/catheter placement or removal, suggesting that trauma incurred during needle or catheter placement is neither increased nor sustained by these medications. Therefore, antiplatelet therapy should be considered if the patient is likely to be at risk for thromboembolic events and if the risk is deemed to outweigh the potential benefit of LMWH.
medications have not been tested in combination. Platelet dysfunction is present for 5-7 days after discontinuation of clopidogrel and 10-14 days with ticlopidine. Platelet glycoprotein IIb/IIIa receptor antagonists, including abciximab (Reopro®), epifibatide (Integrilin®) and tirofiban (Aggrastat®), inhibit platelet aggregation by interfering with platelet-fibrinogen binding and subsequent platelet-platelet interactions. Time to normal platelet aggregation following discontinuation of therapy ranges from eight hours (epifibatide, tirofiban) to 48 hours (abciximab). Increased perioperative bleeding in patients undergoing cardiac and vascular surgery after receiving ticlopidine, clopidogrel and glycoprotein IIb/IIIa antagonists warrants concern regarding the risk of anesthesia-related hemorrhagic complications.

REGIONAL ANESTHETIC MANAGEMENT OF THE PATIENT RECEIVING ANTIPLATELET MEDICATIONS*

Antiplatelet drugs, by themselves, appear to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anesthesia. However, the concurrent use of medications that affect other components of the clotting mechanisms, such as oral anticoagulants, standard heparin, and LMWH, may increase the risk of bleeding complications for patients receiving antiplatelet agents. Assessment of platelet function prior to performance of neuraxial block is not recommended. However, careful preoperative assessment of the patient to identify alterations of health that might contribute to bleeding is crucial.

The increase in perioperative bleeding in patients undergoing cardiac and vascular surgery after receiving ticlopidine, clopidogrel and platelet GP IIb/IIIa antagonists warrants concern regarding the risk of spinal hematoma. The recommended time interval between discontinuation of thienopyridine therapy and neuraxial block is 14 days for ticlopidine and 7 days for clopidogrel. For the platelet GP IIb/IIIa inhibitors, the duration ranges from eight hours for epifibatide and tirofiban, to 48 hours following abciximab administration.

HERBAL MEDICATIONS

There is a widespread use of herbal medications in surgical patients. Morbidity and mortality associated with herbal use may be more likely in the perioperative period because of the polypharmacy and physiological alterations that occur. Such complications include bleeding from garlic, gingko and ginseng, and potential interaction between ginseng-warfarin. Because the current regulatory mechanism for commercial herbal preparations sold in the United States does not adequately protect against unpredictable or undesirable pharmacological effects, it is especially important for anesthesiologists to be familiar with related literature on herbal medications when caring for patients in the perioperative period.23

REGIONAL ANESTHETIC MANAGEMENT OF THE PATIENT RECEIVING HERBAL THERAPY*

Herbal drugs, by themselves, appear to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anesthesia. This is an important observation since it is likely that a significant number of our surgical patients utilize alternative medications preoperatively and perhaps during their postoperative course. There is no wholly accepted test to assess adequacy of hemostasis in the patient reporting preoperative herbal medications. Careful preoperative assessment of the patient to identify alterations of health that might contribute to bleeding is crucial. Data on the combination of herbal therapy with other forms of anticoagulation are lacking. However, the concurrent use of other medications affecting clotting mechanisms may increase the risk of bleeding complications in these patients.

*ALL MANAGEMENT RECOMMENDATIONS

REFERENCES


Table 1. Risk factors and estimated incidence for spinal hematoma and central neuraxial anesthesia

<table>
<thead>
<tr>
<th>No heparin</th>
<th>Relative Risk of spinal hematoma</th>
<th>Estimated incidence for epidural anesthesia</th>
<th>Estimated incidence for spinal anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atraumatic</td>
<td>1.00</td>
<td>1:220,000</td>
<td>1:320,000</td>
</tr>
<tr>
<td>Traumatic</td>
<td>11.2</td>
<td>1:20,000</td>
<td>1:29,000</td>
</tr>
<tr>
<td>With aspirin</td>
<td>2.54</td>
<td>1:150,000</td>
<td>1:220,000</td>
</tr>
<tr>
<td>Heparin following neuraxial procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atraumatic</td>
<td>3.16</td>
<td>1:70,000</td>
<td>1:100,000</td>
</tr>
<tr>
<td>Traumatic</td>
<td>11.2</td>
<td>1:2,000</td>
<td>1:2,900</td>
</tr>
<tr>
<td>Heparin &gt; 1 hr after puncture</td>
<td>2.18</td>
<td>1:100,000</td>
<td>1:150,000</td>
</tr>
<tr>
<td>Heparin &lt; 1 hr after puncture</td>
<td>25.2</td>
<td>1:8,700</td>
<td>1:13,000</td>
</tr>
<tr>
<td>With aspirin</td>
<td>26</td>
<td>1:8,500</td>
<td>1:12,000</td>
</tr>
</tbody>
</table>

OBJECTIVES:
The objective of this session is for the participant to recognize the association between red cell transfusion and adverse outcomes in patients with cardiovascular disease undergoing cardiac surgery. In addition, the participant will become aware of structural and functional changes in red cell products with increasing storage duration and implications of these changes on patient outcome.

While life saving, red cell transfusion has been associated with increased morbidity, higher inhospital mortality and reduced long-term survival in patients undergoing surgery. A higher prevalence of cardiac, neurologic and pulmonary morbidities have been reported for patients transfused in the perioperative period. Transfusion of RBC has also been attributed to more infectious complications such as pneumonia, sepsis and bacteremia and deep and superficial wound infections compared to those not receiving a red cell transfusion. A recent investigation of patients undergoing elective major vascular surgery noted that perioperative transfusion in patients who were not anemic and who were clinically stable were at significant risk for myocardial infarction and death. An investigation examining the role of transfusion in perioperative lung injury reported more pulmonary complications in patients transfused red cells and fresh frozen plasma. Pulmonary complications included respiratory distress, longer intubation times, and reintubation for pulmonary reasons. Interestingly, a majority of patients both transfused and not transfused had lung injury following cardiopulmonary bypass manifested by a PaO2/FiO2 ratio less than 300. Differentiation of transfusion associated circulatory overload, and transfusion related lung injury is particularly problematic in this patient population. Excess morbidity associated with transfusion often translates to longer intensive care unit and hospital length of stay.

There are a number of structural and functional changes that occur with red cell storage that may in part be related to a number of adverse outcomes associated with transfusion. Following donation blood is routinely stored for up to 42 days. The influence of prolonged storage on impairment of oxygen delivery and clinical outcomes is controversial. An analysis of changes occurring during red cell storage suggests that storage induced defects in RBC units could be related to transfusion associated adverse outcomes. The authors noted RBC deformability gradually decreased with increasing storage duration in addition to decreases in 2, 3 DPG, and increases in potassium, lactate, and free hemoglobin with increasing duration of storage. Reynolds et al reported that loss of nitric oxide bioactivity with routine blood storage adversely impacted red blood cell hypoxic vasodilatory activity with associated impairment in blood flow. Interestingly, they reported that repletion of nitric oxide bioactivity could restore red blood cell vasodilatory activity and improve tissue blood flow. A recent laboratory investigation by Sweeney et al commented on a mechanism whereby stored red blood cells could contribute to excess thrombotic complications. In their investigation red cell storage duration was associated with improved cerebral oxygenation versus older blood. The authors noted that some stored red blood cells released microvesicles which expressed phosphatidylserine and were capable of facilitating thrombin generation. Relevy and colleagues suggested the potential risk with transfusion may be related to impaired red blood cell rheology. The authors examined the effect of cold storage on RBC adherence and deformability noting that red blood cell flow properties were affected by cold storage. Cold storage increased the number of adherent red blood cells and strength of their interaction with endothelial cells. A marked decrease in RBC deformability was reported as early as 2 weeks into the storage period. In a laboratory investigation Rigamonti et al demonstrated that red cell storage limits the ability of red blood cells to deliver oxygen to brain tissue. They noted fresh blood demonstrated greater increases in regional cerebral blood flow and tissue oxygen tension compared to stored blood.

There are a number of clinical investigations that report an increase risk for adverse outcomes associated with storage duration. In cardiac surgery, administration of red cells older than 14 days storage duration was associated with reduced survival and an increase in complications following surgery. In trauma patients, Zallen et al reported a risk adjusted increase in multisystem organ failure with increasing number of RBC transfused and with red cell units of older storage duration, beyond 14 and 21 days storage. Leal-Noval et al examined transfusion on cerebral oxygenation in patients with traumatic brain injury. Younger blood stored less than 19 days storage duration was associated with improved cerebral oxygenation versus older blood. In a separate investigation Leal-Noval S et al suggested storage duration longer than 28 days may be a risk factor for nosocomial pneumonia. Of note, there are investigations that do not find an association...
between prolonged red cell storage and adverse outcomes.\textsuperscript{17,18}

While transfusion is necessary for some patients, it has a strong reported association with adverse morbid outcomes. Whether morbidity is due intrinsic properties of allogenic red cells or to the biochemical and mechanical properties that occur with increasing storage duration is unsettled. Furthermore, the optimal hematocrit to initiate a transfusion in an individual patient is unknown in part because of our inability to measure tissue oxygenation at the bedside.

REFERENCES

The preoperative work up of the neurosurgical patient obviously involves the “routine” history, physical and appropriate laboratory tests. However there are a few additional questions which will make planning the intraoperative care easier. These are:

- What position will the patient be in?
- How much bleeding will there be?
- Do you anticipate any ischemia?
- Will there be any neuromonitoring?
- Is the ICP elevated?
- Where will the patient go afterwards?

What’s the diagnosis and what operation will you do?

Acute subdural.

These are usually associated with acute head trauma so that the underlying brain is injured as well. The extent of the underlying injury to the brain and other organs will determine whether the patient can be extubated at the end of the procedure. Management is focused on the associated elevated intracranial pressure (ICP) and the other injuries. Surgery is usually a craniotomy.

Chronic subdural.

These usually occur in older patients who fell in the recent past and then developed slowly progressive neurological deterioration. Many are on anticoagulants for cardiovascular disease. The neurological deterioration is slow because of cortical atrophy which results in a lot of space for the hematoma to accumulate in before ICP starts increasing. The underlying brain is usually not injured. Initial anesthetic management may involve managing the elevated ICP but once the hematoma has been removed, the brain should be allowed to fill the space i.e. PaC02 should be normal or slightly elevated.

Intracerebral Hemorrhage (ICH).

Intracerebral hemorrhage is usually associated with trauma or hypertension. An aneurysm or AVM may also be the cause of the bleed and if not diagnosed preoperatively may result in torrential intraoperative bleeding.

Tumor

These usually present with features of elevated intracranial pressure and/or seizures. Intraparenchymal tumors are usually not very vascular but meningiomas can be exceedingly vascular. In patients with the latter tumor preoperative angiography and embolization should be considered. Anesthetic management is focused on preventing increases in ICP and preferably lowering it.

What position will the patient be in?

Supine

Lateral

Modified Lateral (Park Bench) – The patient is placed lateral and then leaned forward with the head turned towards the floor. It is used by some for posterior fossa and cervical procedures.

Prone – used for posterior fossa and spinal procedures.

Sitting – infrequently used these days because of concerns about air embolism.

How much bleeding will there be?

Performing a craniotomy i.e. “the opening” should usually result in <250 ml blood loss. Most intraparenchymal tumors are not very vascular and should not result in significant hemorrhage. Conversely meningiomas can be very vascular and adherent. Preoperative angiography and embolization can often substantially reduce blood loss.

Cerebral aneurysms have the potential to bleed significantly although this is uncommon with experienced, competent aneurysm surgeons. Arteriovenous malformations are usually embolized in advance of surgery thus reducing intraoperative bleeding.

Blood loss from spine surgery ranges from 50ml to 15 liters depending on the lesion and extent of surgery. Ask the surgeon for an estimate and then multiply by an appropriate factor.

Do you anticipate any ischemia?

The potential for neural ischemia may be an indication for neuromonitoring and the surgeon may request some (purported) neuroprotective drugs. There is abundant experimental evidence that currently used anesthetics e.g. sevofoflure, propofol, thiopentone, produce cerebral protection as assessed by multiple surrogate endpoints. However, in the context of neurosurgery there are no prospective randomized trials showing a benefit to any of the commonly used techniques including drugs, shunts and physiological manipulation.
WILL THERE BE ANY NEUROMONITORING?

Evoked potential monitoring is frequently used during intracranial, neurovascular and spinal procedures. The purpose of the monitoring is to prevent ischemic injury. Sensory and/or motor pathways are selectively stimulated resulting in very small evoked responses that require rapid repeated stimuli which are summated in order to produce an interpretable signal. Prospective randomized trials of all the neuromonitoring modalities are lacking and the best available studies are cohort studies and historical controls.

Somatosensory Evoked Potentials (SSEP)

Most commonly the median and/or the posterior tibial nerves are stimulated and the responses collected at the cervical and cortical levels. The SSEP indicates the integrity of the specific sensory neural pathway stimulated and injury to areas of the nervous system outside these tracts may not be detected. SSEPs are sensitive to inhalational anesthetics and become progressively suppressed as concentration increases. SSEPs are very much less influenced by intravenous agents such as propofol, opioids, thiopental. Thus suitable anesthetic choices are a TIVA anesthetic or low dose inhalational agent with an opioid e.g. <1 MAC without N2O.

Motor Evoked Potentials (MEP)

Clinical use of MEPs is relatively new and utilizes multiple transcranial electrical stimulations to stimulate a motor response in the upper and lower limbs. MEPs are very much more sensitive to anesthetic suppression than SSEP and are progressively suppressed by >0.3MAC of the volatile agents. Thiopental, propofol and midazolam can also suppress the signals but the inhalational agents are much more suppressive than the IV. In contrast ketamine and etomidate may actually increase the amplitude making them useful adjuvants when good quality signals are not being obtained. Early experience with dexmedetomidine suggests that it may be suitable. Muscle relaxants should be avoided or kept to a minimum with constant TOF. Suitable techniques include propofol-opioid TIVA, low dose vapor together with opioid, low doses of propofol, vapor with opioid and any technique may be supplemented with a low dose ketamine infusion. Newer stimulation paradigms are increasingly less anesthetic sensitive.

IS THE ICP ELEVATED?

Elevated ICP is most easily determined when it is directly measured although the majority of patients will not have intracranial monitors in place and a clinical estimate should be made from clinical signs e.g. headache, drowsiness, pupillary dilation, hemiparesis, and from CT/MRI e.g. midline shift and ventricular compression. It is also important to determine if the increase in ICP is sudden e.g. acute subdural or more gradual e.g. tumor. Patients with acute coma producing elevated ICP or very large lesions will have exhausted endogenous compensatory mechanisms and will be less tolerant of anesthetic techniques that may increase ICP. In such patients a prudent option may be a propofol-opioid infusion or sevoflurane-opioid at least until the dura is opened and the mass decompressed. In patients with very small masses the actual choice is likely less important, at least in relation to ICP and no prospective randomized trials have yet shown a difference in patient outcome.

Propofol and thiopental have been shown to reduce elevated ICP. Of the vapors, sevoflurane is the least vasodilatory and does not seem to increase ICP until well above 1 MAC. No inhalational agent actually decreases ICP.

Hyperventilation has been a “tradition” in neuroanaesthesia but has fallen into disfavor as there is evidence, at least with prolonged use in head trauma, that it produces ischemia and potentially a worse neurological outcome. The current recommendation is to keep the PaCO2 in the mid 30’s and to reduce it further only if needed and preferably for short periods. Our recent multicenter randomized blinded trial found that hyperventilation (PaCO2 28) improved operating conditions and ICP in patients with supratentorial tumors.

Other techniques to reduce ICP or a bulging brain include a head-up position, avoidance of venous outflow obstruction and mannitol. There is also current interest in the use of hypertonic saline for this purpose. One should also eliminate or reduce the amount of cerebral vasodilators being used including (high dose) inhaled anesthetics and vasoactive drugs such as nitroprusside & nitroglycerine.

WHERE WILL THE PATIENT GO AFTERWARDS?

The disposition of the patient to the ICU or the PACU may influence the anesthetic choice and may also be reflective of the severity of the neurologic impairment or the extent of the planned surgery.

REFERENCES:


BOISSEAU N, MADANY M, STACCINI P, ARMANDO G, MARTIN F, GRIMAUD D, RAOUCOLES-AIME M. Comparison of the effects of


http://www.braintrauma.org [provides guidelines for the anesthetic and surgical management of the patient with traumatic brain injury]


PATEL P. No magic bullets: the ephemeral nature of anesthetic-mediated neuroprotection. Anesthesiology 2004 May;100:1049-51.


In the United States, approximately 72 million people suffer from hypertension (that equates to about 30% of the population aged over 20 years-old). It is one of the most common chronic medical conditions worldwide (US National Center for Health Statistics, 2005), and occurs almost twice as often in the African-American population as those of Caucasian origin. The incidence of hypertension increases with age, and affects men with a slightly greater incidence than women. In the USA, hypertension affects about 255 of all adults over the age of 40 years. More importantly, the prevalence of undiagnosed hypertension is about 1 in 15 (ie. about 15 million patients). In the UK, there are about 7.5 million patients suffering from raised blood pressure; but importantly 80-85% of these patients are either not treated or are poorly treated. Based on these two reported prevalences, the worldwide incidences of patients suffering from hypertension is about 600 million people, and hence the likelihood of a hypertensive patient undergoing elective non-cardiac surgery is high. Is there any evidence that hypertension affects perioperative outcome?

The following questions summarize some of the present controversies in the management of these patients:

1. Are all therapies equally effective at controlling the exaggerated hemodynamic responses; should drugs be continued until surgery; are there any important interactions with anesthesia?
2. Does drug therapy affect peri-operative outcome?
3. Does hypertension contribute to post-operative adverse cardiovascular events in surgical patients?
4. What should the clinician do for the surgical patient with isolated systolic hypertension or 'white-coat' hypertension?
5. Which patients (if any) should the anesthetist consider cancelling?

Blood pressure can be classified into 4 categories, as described in the JNC VII Report (2003):  

<table>
<thead>
<tr>
<th>Classification</th>
<th>Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotension</td>
<td>&lt;120 and &lt;80 mmHg</td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>120-139 or 80-89</td>
</tr>
<tr>
<td>Stage I</td>
<td>140-159 or 90-99</td>
</tr>
<tr>
<td>Stage II</td>
<td>&gt;160 or &gt; 100</td>
</tr>
</tbody>
</table>

In primary care practice, both the WHO and British Hypertension Society guidelines target a blood pressure of <140/85 in non-diabetic patients and <140/80 in hypertensive diabetics.

1. **DRUG THERAPIES, ANESTHESIA AND HYPERTENSION**

For much of the last two decades, β-blockers have been the mainstay of the treatment of arterial hypertension in the United Kingdom and many other countries. However they are no longer the initial therapy for hypertension in many patients. Why is this? The change in treatment modality relates to the adverse and side-effects of the drugs. All β-blockers have a pre-diabetic potential. Is this new form of 'type 2 diabetes' significant for patients? Based on the VALUE trial, Aksnes et al suggest that the cardiac risk profile with β-blockers is about 50% that seen in patients of established diabetes mellitus. If the results of the ASCOT study (Anglo-Scandinavian Outcome Trial) are included in any meta-analysis, nearly all outcomes are more favourably influenced by a regimen based on a calcium entry blocking drug when compared with atenolol.

Treatment with β-blockers results in a decrease in aortic pressure that is less than that seen with calcium entry blocking drugs. There is a lack of data for the capacity of β-blockade to achieve adequate regression of target organ damage such as left ventricular hypertrophy or endothelial dysfunction. The cardiac protective effects of β-blockers are often over-stated; there is only one study investigating blood pressure management in patients with both hypertension and coronary artery disease (INVEST). Hence, treatment with β-blockers is the least cost effective of all the standard therapies with regard to hospitalization; clinical events and therapy of new diabetes. Although they are no longer the first line drug for primary care treatment of hypertension, patients with the combination hypertension and coronary artery disease should continue to receive these agents. Interactions with both general and regional anesthetic techniques show them to be well tolerated, and to confer hemodynamic stability.

Do the changes in drug therapies for management of hypertension in primary care have implications for the preoperative surgical patient with hypertension? Are all therapies equally effective at controlling exaggerated hemodynamic responses? Should all drugs be continued up until surgery? Are there any important interactions with anaesthesia?
Anesthesia and hypertensive therapies

Diuretic-treated patients can present with hypokalemia, raising the issue of preoperative potassium supplementation. However the studies of Wong et al showed that rapid normalization of the plasma potassium concentration may worsen the trans-membrane potassium gradient, thereby increasing the risk of arrhythmias.9 The electrophysiological indicators of hypokalemia therefore make slow replacement of potassium over 24-48 hours the optimum approach. Current policy is that anti-hypertensive therapies are continued up to the morning of surgery, with the possible exceptions of ACEIs and ARAs. Our studies found no significant differences in blood pressure and heart rate responses between agents, with no excessive hypotension on induction of anesthesia in patients receiving monotherapy of ACE inhibitors, β-blockers, calcium channel entry blockers or diuretics. Only β-adrenoceptor blockers protect against the noxious pressor and chronotropic responses to laryngoscopy and intubation, thereby reducing the risk of myocardial ischemia.10,11

Interactions between anesthesia and angiotensin converting enzyme inhibitors (ACEIs) and angiotension II receptor antagonists (ARAs) are controversial. High doses of ACEIs and ARAs may accentuate the hypotension caused by anesthesia, and patients on ARA are less responsive to ephedrine and phenylephrine. Although some authors suggest that these drugs are stopped 24 hours before surgery,12-14 this may increase the need for active postoperative management of hypertensive episodes.15 The doses of ACEIs and ARAs prescribed in the UK and many other countries tend to be lower than in the studies of Coriat and Brabant;12,13 and hence maintaining these drugs (as for all other therapies) up to and including the morning of surgery may be practised. To date (January 2010), there are no data on the interaction between anesthesia and surgery for a new class of drugs (direct renin inhibitors - eg. aliskiren).

α1 agonists achieve hemodynamic stability by reducing sympathetic activity. Clonidine also causes anxiolysis and sedation; so decreasing the requirements for volatile and intravenous anesthetic agents, and may also reduce the risk of postoperative adverse cardiac events in both cardiac and noncardiac surgical patients.16 The meta-analysis by Wijeysundera et al17 reported a reduction in morbidity (myocardial infarction) and mortality in vascular surgical patients receiving an α1 agonist, and a reduction in myocardial ischemia in cardiac surgical patients. However the heterogeneity of the studies in this analysis stresses the need for further large randomized clinical trials. With β-blockers, the numbers-needed-to-treat (NNT) to prevent cardiovascular complications range between 2.5-3.8 compared with NNTs of 19-38 for α1 agonists. A meta-analysis of studies with dexametomidine (DMD) including 840 patients from 20 trials has reported TRENDS towards improved cardiac outcomes (myocardial infarction, myocardial ischemia) but an increased incidence of hypotension and bradycardia.18

All anti-hypertensive therapies show no major effect on cardiovascular disease risk in hypertensive patients that is independent of their effect on blood pressure. The effect of lowering on risk of blood pressure is independent of the pre-treatment blood pressure; different drugs differ little in their efficacy; and there is a halving of the risk of coronary heart disease events and strokes for each 10 mmHg reduction in diastolic blood pressure.19

Recent data suggest that aspirin may antagonise the hypotensive effects of spironolactone, ACEIs and ARAs. Although statins have been shown to be beneficial in cardiovascular at-risk patients, this benefit is lost by acute pre-operative withdrawal. Another important issue in the hypertensive patient is the change in organ autoregulation with disease and treatment. Does anesthesia affect these autoregulatory mechanisms? Kadoi et al have demonstrated there is better preservation of cerebral blood flow control in the presence of changes in PaCO2 during isoflurane anesthesia when compared with sevoflurane anesthesia.20 If similar results are demonstrated by other research groups, this may influence our choice of anesthetic technique in the hypertensive patient.

2. β-BLOCKERS, MYOCARDIAL ISCHEMIA AND ADVERSE CARDIAC OUTCOMES

Besides their effects on heart rate and blood pressure, β-blockers have other useful perioperative properties including reduction of myocardial ischemia and adverse cardiac events.22,23 The studies of Mangano et al22 and Poldermans et al23 in which more than 60% of the patients were described as being ‘hypertensive’, both show improvements in 2 and 1 year outcomes respectively in patients with or at high-risk for coronary artery disease undergoing non-cardiac surgery and who were treated with perioperative β-blockers. In the study of Mangano et al, atenolol started preoperatively and continued for 1 week after surgery increased event-free survival from 81% to 91%.24 Despite some limitations of the study design (analysis did not include cardiac events occurring during hospitalization; and β-blockers were withdrawn preoperatively in some patients prior to randomization), the American College of Medicine proposed in 1997 that atenolol be given before operation to all patients with coronary artery disease or with associated risk factors. This approach was supported by the data available at that time relating to the efficacy of β-blockers in the treatment of myocardial infarction, hypertension, and later in the management of patients with cardiac failure.

In 1999, Poldermans and colleagues reported a randomized control trial (RCT) in patients with reversible cardiac ischemia presenting for major elective vascular surgery.23 The results showed a
100% reduction in the incidence of myocardial infarction and an 80% reduction in cardiac deaths in those patients treated with bisoprolol before and for 28 days post-surgery. Again the study presents difficulties for the clinician - as it was an unblinded study, and was stopped at the first interim analysis. However, it appeared to strengthen the case for β-blockade in patients with coronary artery disease or with significant risk factors (including hypertension), such that the American College of Cardiology/ American Heart Association (ACC/AHA) 2002 guidelines state ‘that current studies suggest that appropriately administered β-blockers reduce perioperative ischemia and MAY (emphasis added) reduce the risk of myocardial infarction and death in high-risk cases’. These guidelines categorized the use of β-blockers in patients undergoing vascular surgery with ischemia detected during preoperative testing as a class I recommendation, and the use of preoperative β-blockers in patients with preoperative untreated hypertension, known coronary artery disease, or major risk factors for coronary artery disease as class IIa recommendations.

Subsequent studies, meta-analyses and systematic reviews have questioned these data, such that the 2006 and 2007 ACC/AHA guidelines stated that ‘current studies SUGGEST (emphasis added) that β-blockers reduce perioperative ischemia and MAY (emphasis added) reduce the risk of myocardial infarction and death in patients with known coronary disease’.

In summary, our knowledge about the efficacy of β-blockers in medical settings has changed with regard to hypertension (due to the findings of the ASCOT and ALLHAT studies); in the management of acute myocardial infarction (with publication of the COMMIT trial); and because of doubts over their efficacy of β-blockade in the perioperative period. Although the studies of Mangano et al. and Poldermans et al. support the advantages of perioperative β-blockade, subsequent RCTs (including DIPOM; MaVS; POBBLE; BBSA) fail to show similar results.

Because of this uncertainty, there was need for a large multinational RCT of β-blockers versus placebo in patients at risk of perioperative cardiac events. This has recently reported as the PeriOperative Ischemia Study Evaluation [POISE], a multicenter study recruiting 8351 patients. POISE compared the study drug (metoprolol succinate extended-release) and placebo. Treatments were started 2-4 hours before surgery and continued for 30 days. The primary 30 day outcome was a combined one of cardiovascular death, non-fatal myocardial infarction, and non-fatal cardiac arrest. Secondary outcomes included total all-cause mortality, stroke, myocardial infarction, need for coronary revascularization, new atrial fibrillation, congestive cardiac failure, hypotension and bradycardia. 63% of the 8351 patients were classified as ‘hypertensive’. Thirty day results show a significant reduction in ALL myocardial infarction [4.2% in the metoprolol group vs. 5.7% in the placebo arm]; a reduced need for coronary revascularization; and a reduction in the number of patients developing atrial fibrillation. However there were significant increases in total mortality [3.1% vs. 2.3%]; stroke [1% vs. 0.5%]; and clinically significant hypotension and bradycardia in the metoprolol group.

As a result of all these studies, the utility of β-blockade in the medical and perioperative management of the hypertensive patient is presently debated, and best practice remains to be defined.

3. HYPERTENSION AND PERIOPERATIVE OUTCOMES

Does hypertension contribute to post-operative adverse cardiovascular events in surgical patients? Until recently, there were few data on the influence of hypertension on postoperative outcomes, although Sprague in 1929 reported a 32% incidence of perioperative cardiac death in patients with hypertensive heart disease. But what is the effect of hypertension on cardiovascular morbidity? In 1973-75, Prys-Roberts and colleagues examined the influence of anesthesia and hypertension, and showed that induction of anesthesia, laryngoscopy and intubation were associated with development of hypotension, ventricular arrhythmias and cardiac ischemia in untreated or poorly treated hypertensive patients, but that the effects can be obtunded by pre-operative β-blockade. However Goldman and Caldera found no relationship between preoperative blood pressure and development of cardiac arrhythmias, ischemia, failure or postoperative renal failure in patients with mild hypertension.

Results from examination of the influence of hypertension as a determinant of cardiovascular complications give a confused picture. The study of Forrest et al. including more than 17000 patients showed no difference in incidence of complications between the whole group and a sub-group of hypertensive patients (3.5% vs. 7.0%). More recently, Davenport et al. reported on 183069 patients from 128 VA and 14 academic medical centers who underwent surgery during the years 2002-2004. The main outcome measures were the incidence of serious cardiac adverse events (namely acute myocardial infarction and cardiac arrest needing resuscitation within 30 days of surgery). The authors reported that 2362 patients (1.29%) suffered one or other of these adverse events, with 59.44% dying. This compared with a death rate of 1.85% in patients not undergoing a serious cardiac adverse event. Using univariate modeling, they identified 31 preoperative risk factors, and 10 preoperative tests as significant markers. These data were then subjected to forward stepwise logistic regression analysis. After adjusting for confounding variables, the authors showed that hypertension was not a significant risk factor.

Because the incidence of perioperative complications in noncardiac surgical patients is low,
surrogate end-points that occur more frequently are often used to assess perioperative outcome (these include hemodynamic instability; cardiac ischemia; major cardiac complications as well as cardiac death).

**Cardiac ischemia and biomarkers**

We have previously reported a greater incidence of preoperative silent myocardial ischemia (SMI) in hypertensive compared with normotensive patients; and in untreated and poorly treated hypertensive patients compared with normotensive patients and treated hypertensive patients with blood pressure <160/90. Different intercurrent treatments appear to have no effect on the occurrence of preoperative SMI in these at-risk patients. Conflicting evidence exists for an association between hypertension, postoperative SMI and outcome. Howell et al found univariate associations between diagnosed and treated arterial hypertension, admission systolic and diastolic blood pressures and post-operative SMI. Only hypertension per se and systolic blood pressure remained following multivariate analysis with the odds ratio for post-SMI being 1.2 per 10 mmHg increase in systolic pressure. This finding agreed with the work of Stamler et al who showed systolic hypertension to be the more potent risk factor for the complications of hypertensive disease.

Most studies addressing the question of hypertension in surgical patients have examined the association between hypertension and outcome without paying any attention to either the level of blood pressure, or the presence of absence of treatment. We found no association between hypertension and perioperative myocardial ischemia when the data are adjusted for the presence of confounders (β-blockade, calcium channel entry blockade and vascular surgery).

Although hypertension is associated with increased perioperative SMI, which may in turn be associated with an increased incidence of adverse cardiovascular complications including death, we still need firm data against which to use these results for cancellation of elective surgical patients.

A recent study from Switzerland has reported the effects of anaesthesia and surgery on a composite cardiovascular endpoint (hypov- or hypertension [< or > 30% MAP for > 5 minutes; occurrence of new arrhythmias; angina pectoris or ECG changes compatible with ischemia; or related death] in 124939 patients undergoing elective surgery under either general or regional anesthesia. 27881 patients were hypertensive on treatment or had a preoperative blood pressure > 160/100. In 7549 patients, at least one cardiac adverse event was observed in the 24 hours following surgery (6% [CI 5.9-6.2]). The incidence in hypertensive patients was 11.2% compared with 4.6% in normotensive patients [crude relative risk (RR) ratio 2.64; adjusted RR 1.38 (1.27-1.49)]. In the patient with hypertension AND OTHER CARDIOVASCULAR DISEASE, the RR ratio was 1.62.

Another surrogate marker is myocardial necrosis measured either using monoclonal antmyosin antibodies or serum troponins. Cardiac ischemia causes release of troponins. Pons-Llado et al showed a greater degree of underlying myocardial damage in symptomatic hypertensive patients compared with both asymptomatic hypertensive and normotensive patients; whereas Reddy et al found elevated serum troponin T concentrations in hypertensive medical patients compared with controls. In an unpublished meta-analysis of 22 studies, Biccard and Sear have found a relative risk ratio of 1.36 [1.21-1.53] for the relationship between hypertension and elevated postoperative cardiac troponins. These data indicate that hypertension may be associated with an increased risk of myocardial damage in the perioperative period.

4. **MAJOR CARDIAC COMPLICATIONS AND HYPERTENSION**

In 2004, Howell et al published a meta-analysis of 30 studies examining hypertensive disease as a univariate marker for adverse cardiac outcome. There was a significant association with cardiac death and cardiac complications (odds ratio 1.25 [1.07-1.47]); however this analysis did not take account of any confounding factors, or heterogeneity between the different studies included in the paper.

Nevertheless again the results suggest a small but significant influence of a preoperative diagnosis of arterial hypertension on cardiac outcome.

Does the admission blood pressure influence perioperative outcome? Goldman and Caldera found no association between admission blood pressure and perioperative cardiac death and the data of Howell et al were insufficient to allow comment on an association between level of blood pressure elevation and outcome. However two other recent studies suggest there may be an association between admission blood pressure and adverse outcomes.

Further support for hypertension as a predictor of cardiac adverse events has been found in a prospective observational study of 7740 (general, vascular and urologic surgery) operations. 83 patients experienced a perioperative cardiac adverse event (cardiac arrest; non-STEMI; Q wave myocardial infarction; or new cardiac arrhythmia) within 30 days of surgery. Using univariate analysis, nine independent predictors of adverse outcome were identified (age > 68 years; BMI > 30; emergency surgery; previous PCI or cardiac surgery; active CCF; cerebrovascular disease; operation lasting >3.8 hours; blood requirement of >1 unit intraoperatively; and hypertension). When logistic regression was used to include both pre- and intra-operative variables, there was a significant adjusted hazard ratio associated with pre-existing hypertension [HR: 1.7 (1.0-2.9)] –
the magnitude of the increased risk being similar to that reported by Howell et al.\textsuperscript{46}

Another recent study examined the predictors of acute renal failure after noncardiac surgery in patients with pre-existing normal renal function,\textsuperscript{59} again based on a prospective observational study of 65043 patients. 15102 of these patients fulfilled inclusion criteria. Outcome measures were acute renal failure in the first seven postoperative days; and 30-, 60- and 365-day all-cause mortality. Hypertension was a comorbidity factor in 30\% of all patients; and in 40\% of those developing postoperative renal dysfunction. However, logistic regression modeling did not show hypertension to be an independent predictor of adverse outcome; although both coronary artery disease and peripheral vascular disease (both of which may be associated with hypertension) were predictive markers.

5. CARDIAC DEATH AND HYPERTENSION

There are fewer data examining the association between hypertensive disease and postoperative mortality.\textsuperscript{51,52} We have shown both univariate and multivariate associations between 30-day postoperative cardiac mortality and a history of hypertension in elective surgery using a case-control analysis of data from the Oxford Record Linkage Study. An analysis involving over 22000 patients shows a relative risk ratio for cardiac death in the perioperative period of 1.40 [1.11-1.75] in hypertensive patients.

6. ISOLATED SYSTOLIC HYPERTENSION AND ELECTIVE SURGERY

Isolated systolic hypertension (ISH: SBP >140mmHg; DBP <90mmHg in the absence of any other secondary disease input in patients aged > 18-years) is the most common subtype of raised blood pressure. Diagnosis is based on the average of 2 or more seated blood pressure readings on 2 or more occasions. It affects 2/3 of all patients aged >50 years, and is more prevalent than diastolic hypertension. ISH is associated with greater risk of patients developing fatal and non-fatal strokes, and coronary heart disease, congestive cardiac failure, renal insufficiency and cardiac death. ISH occurs because of increased conduit vessel stiffness and decreased distensibility of the aorta and large arteries. The heart responds to the increase in wall tension by LV hypertrophy and an increased myocardial contraction time, and in turn secondary diastolic dysfunction. There is also an impairment of endothelial function. Effective treatments in non-surgical patients (thiazides, calcium channel blockade or \( \beta \)-adrenoceptor antagonists with vasodilating properties eg. dilevalol) decrease overall mortality, as well as decreasing the incidence of CVA, myocardial infarction and congestive cardiac failure. Many ISH patients also have pulse pressure hypertension (PP > 80 mmHg).\textsuperscript{53}

To date, there are few observations on anesthetic interactions in these patients.\textsuperscript{54} In the presence of uncontrolled systolic hypertension, induction of anesthesia causes decreases in blood pressure and stroke volume. This is difficult to prevent. Useful approaches may include head-down tilt to increase venous return and increments of metaraminol (with its predominant vasoconstrictor properties) titrated to response. Use of vagotonic drugs (especially the combination propofol and opioids) is best avoided, and pre-treatment with glycopyrrolate may be advantageous. These patients also suffer marked vasopressor responses to noxious stimulation. Tamborini and colleagues have also shown there to be a reduction in coronary flow during induction of anesthesia.\textsuperscript{55}

Hence it is relevant to ask whether we need to do anything special for the patient with isolated systolic hypertension who is scheduled for surgery?

Other than a possible association with postoperative silent myocardial ischemia (SMI), there are few data suggesting that ISH is a risk factor per se in relation to anesthesia. There is, however, evidence that patients with ISH may show a greater ‘white-coat’ effect than those with systo-diastolic hypertension, with the blood pressure settling with time;\textsuperscript{56} but the relevance of this to the surgical patient is unclear. The data of Howell et al\textsuperscript{46} showed that only systolic arterial pressure (not diastolic pressure) was a risk factor for the development of postoperative SMI - with an odds ratio of 1.20 for increasing the risk for each 10 mmHg increase in systolic pressure. There are few other outcome data for patients with ISH. One such set of data showing an association between ISH and adverse cardiovascular outcome is that of Aronson et al using a prospective analysis of 2417 patients undergoing coronary artery bypass surgery.\textsuperscript{57} The unadjusted odds ratio for the association between ISH and adverse outcome was 1.4; and after adjusting for confounders, this was still an increased OR of 30\% over controls. Other data from Benjo et al have confirmed that pulse pressure is an age-independent predictor of stroke development after cardiac surgery.\textsuperscript{58}

Whether cancellation of the surgical patient with ISH in order to initiate treatment is only justified if this can be shown to improve outcome; these data are awaited.

7. WHITE-COAT HYPERTENSION AND ANESTHESIA

White-coat hypertension (WCHT) is defined as a nurse-taken blood pressure of <140/90 when compared with a physician-taken value of >160/95. It is thought that the blood pressure increase is associated with stress.\textsuperscript{59} An increased incidence of SMI is seen in patients with white-coat hypertension.\textsuperscript{60} Because of this association, treatment may be justified. Diagnosis depends on use of 4 hourly BP chart for 12 hours - does it settle?
8. HYPERTENSION AND PATIENT CANCELLATION

Which groups of patients (if any) should the anesthetist consider cancelling? The 2007 ACC/AHA guidelines offer few substantive recommendations as to which hypertensive patients should be cancelled to allow treatment prior to surgery, or how long such treatment should be continued before surgery. Indeed the ACC/ AHA Guidelines list ‘uncontrolled systemic hypertension’ as a low-risk factor for cardiac complications.

Observational data agree that stage 1 and 2 hypertension is not an independent risk factor for peri-operative cardiovascular complications, and hence there is no scientific evidence to support postponing these patients IN THE ABSENCE of target organ damage. However, the case for stage 3 (SAP >180 and/or DAP >110 mmHg) hypertension is less clear; the ACC/AHA recommend control of blood pressure before surgery, but this is not supported by a large body of data relating exclusively to patients with these levels of blood pressure.

Our recommendation and practice is only to cancel and treat in those with documented target-organ damage. Blood pressure control should be optimized pre-surgery in patients in whom hypertension is associated with accompanying significant risk factors such as diabetes mellitus, coronary artery disease, peripheral vascular disease, impaired renal function, smoking or hypercholesterolemia. In patients with ISH, there is a clear association with an increased prevalence of SMIs; but the influence of ISH on perioperative outcomes has not been studied. In patients with ‘white-coat’ hypertension, as many repeat blood pressures as possible should be obtained to inform clinical decisions. Starting a normally normotensive patient with white-coat hypertension on inappropriate therapy is dangerous. If surgery is to be deferred to allow white-coat hypertension to be treated, it is unclear how long treatment be given before the patient is subjected to surgery.

CONCLUSIONS:

Patients with hypertension are frequently encountered in noncardiac surgical practice. They require careful assessment by the anesthetist with regard to adequacy of treatment and identification of accompanying target-organ damage. In managing preoperative hypertension, cosmetic control of blood pressure is not recommended because both vascular and cerebrovascular autoregulation remain abnormal for several weeks, whereas it may take 2-18 months for treatment of hypertension to influence diastolic dysfunction. There is no doubt that severe perioperative hypertension is a major threat to hypertensive patients especially in the presence of increases in blood pressure in excess of about 20% of the preoperative value. The consequences of these pressure surges include bleeding from vascular suture lines, cerebrovascular haemorrhage and myocardial ischemia/ infarction. The mortality from such events may be as high as 50%. Such perioperative hypertensive crises are generally sympathetically mediated, and are associated with increases in peripheral vascular resistance.

REFERENCES:

IARS 2010 REVIEW COURSE LECTURES


30. Sprague HB. The heart in surgery. An analysis of the results of surgery on cardiac patients during the past ten years at the Massachusetts General Hospital. Surg Gynecol Obst 1929: 49: 54-58.


Learning Objectives:
1) Review Functional Factors Contributing to Increased Respiratory Morbidity. 2) Examine Role and Efficacy of Measures to Improve Pulmonary Function. 3) Identify Benefits/Disadvantages of Various Anesthetic Drugs and Techniques.

Perioperative concerns in patients with respiratory disease have largely focused on risk assessment for development of postoperative pulmonary complications. The latter arise from two major causes. The first is the site of surgery such that upper abdominal procedures are associated with the greatest reduction in lung volumes with shallow breathing and abnormal gas exchange. These are intensified with thoracic surgery and its accompanying trauma to lung tissue. All of the surgical effects are multiplied in the presence of the other major factor, underlying lung dysfunction.

Although initial identification of patients with abnormal lung function is readily achievable with subjective information obtained from history and physical exam, objective estimation of disease severity requires some form of pulmonary function testing. The benefits from such evaluation are not confined to predicting and reducing postoperative complications. They also extend to reducing intraoperative morbidity by providing insight into choice of anesthetic drugs and techniques. This is particularly the case in patients with chronic obstructive disease (COPD).

CANDIDATES FOR PER OPERATIVE PULMONARY EVALUATION
For pulmonary function data to be of any value preoperative selection of patient for testing is of paramount importance. Essentially the prime candidates should be those in whom there is a reasonable expectation of abnormality and risk. A broad list was initially provided by Tisi 3 decades ago and included the following factors:

- Age > 70
- Morbid Obesity
- Thoracic Surgery
- Upper Abdominal Surgery
- History of Smoking, Cough
- Any Pulmonary Disease

This list was later refined by the American college of Chest Physicians. More recent adherence to the guidelines below have served to limit widespread costly and unnecessary testing.

- Lung Resection
- Smoking History, Dyspnea
- Cardiac Surgery
- Upper and Lower Abdominal Surgery
- Uncharacterized Respiratory Symptoms

PREDICTION OF PERIOPERATIVE RISK
Unfortunately no test result is an optimum predictor of perioperative respiratory morbidity because of limitations in identifying all of the important factors. A summary of pulmonary functional criteria suggestive of increased risk is outlined in TABLE 1.

One of the more valuable and easily obtained measurements is that of the peak expiratory flow (PEF). This is the maximal flow rate attained at the onset of a forced expiration. Although PEF can be estimated from the initial portion of the spirogram, it can be more conveniently measured with a host of inexpensive hand held flow meters. The PEF is highly dependent on effort and highly sensitive to the caliber of the large airways. The latter makes it useful for assessing bronchodilator therapy. Values less than 200 L/min (3.3 L/s) are indicative of impaired cough efficiency and a corresponding high risk of postoperative pulmonary difficulties. The PEF is also quite useful in differentiating between pulmonary and cardiac origins of dyspnea. Ailani, et al have devised the Dyspnea Differentiation Index (DDI) which is calculated as PEF X PaO2 / 1000. The DDI is superior to PEF reductions alone which themselves suggest a pulmonary cause of dyspnea. The latter group had DDI values less than one half those of patients with dyspnea due to cardiac causes (TABLE 2).

Of the indicators on Table 1 one of the more underappreciated factors is the chest x-ray. The presence of hyperaeration is a marker for clinically severe disease which has been associated with a significant (~33%) incidence of postoperative pulmonary problems. It usually identifies hyperinflation associated with airway obstruction and the loss of elastic recoil from destruction of lung parenchyma. This dynamic hyperinflation may also present problems intraoperatively with controlled ventilation.

The presence of resting hypercapnia (PaCO2 > 46 mmHg) in the absence of drug therapy (e.g. opioids) suggests some inadequacy of the respiratory apparatus due to advanced disease and portends the likelihood of problems regardless of the nature of the surgery. The chronic hypercapnia of COPD is
associated with increased alveolar dead space (VD alv) which incurs the need for increased minute ventilation. Although simplistically attributed to respiratory muscle fatigue and diminished neural drive, the increased CO2 levels are actually a variant of “permissive hypercapnia” due to an economic breathing strategy of low tidal volumes (VT) and increased respiratory frequency (f). As such the respiratory muscles operate with a breathing pattern which offsets fatigue and lessens the sense of effort while producing less than optimal CO2 excretion because of the increased VD alv.

PREOPERATIVE MEASURES TO IMPROVE LUNG FUNCTION AND RISK

Identifying lung dysfunction is not devoted simply to assessing risk but also to alter morbidity by employing measures to improve lung function. Some of these modalities are listed in Table 3. Unfortunately today's custom of same day surgical admission limits their application. Nevertheless, 2 of the most important and effective maneuvers are cessation of smoking and bronchodilator therapy. There is roughly a 6 fold increase in peri operative complications (most notably bronchospasm) in smokers with spirometric evidence of airway obstruction. Smokers in general demonstrate an increase in adverse events especially during induction of anesthesia regardless of functional state. The obvious benefits of smoking cessation include a decrease in the volume of secretion and airway reactivity as well as improved mucociliary transport. Unfortunately, the benefits and the associated risk reduction are not achieved in less than a month of abstinence. Shorter periods (< 1 week) may actually be associated with increased secretions and heightened airway reactivity. The only benefit which accrues then is a reduction in carboxyhemoglobin content.

A common feature of patients with respiratory disease, especially those presenting for thoracic surgery, is a combination of airway hyper responsiveness and potentially reversible airway obstruction. Therefore, medications which establish and maintain patency of the airways are particularly valuable. Unfortunately, some clinicians assume that because a patient exhibits little or no response to bronchodilators during spirometric testing, the airway obstruction is not “reversible”. It is important, however, to realize that the response to bronchodilators tends to be bell shaped in that it is maximal with moderate disease and diminished in patients with both mild and severe disease. This is partly because usual reliance on FEV1 increase tends to underestimate therapeutic efficacy of bronchodilators. Spirometric inspiratory capacity (IC) and derived measures such as the ratio of VT / IC or inspiratory reserve volume itself may provide a better estimate of reduced hyperinflation associated with the bronchodilating effect.

Long acting beta 2 sympathetic aerosols such as salbutamol or salmeterol are the mainstays for treatment and prevention of perioperative bronchospasm. Their use and efficacy is often limited by occurrence of tachycardia. The latter can be avoided by the use of quatermary anticholinergic compounds such as atropine and even more so tiotropium (SPIRIVA). The latter compound lacks the problematic inhibitory effects on M2 muscarinic receptors and has a very long (~24 hr) duration of action. As such it can be conveniently administered preoperatively by means of a convenient aerosol-free inhaler.

IMPLICATIONS FOR ANESTHETIC MANAGEMENT

When possible regional anesthesia represents an ideal choice for patients with pulmonary disease because it obviates the need for airway instrumentation and possibility of adverse airway responses. This is not feasible if patients refuse or the site of surgery does not permit. Management of a general anesthetic in a patient with lung disease, in particular airway obstruction, revolves around prevention of airway constriction. The latter is best accomplished by avoiding airway stimulation in the presence of inadequate anesthetic depth. The choice of induction agents is vital in dealing with this potential problem. The limited clinical observations suggest that propofol may offer the best option for avoiding airway reactivity with induction and intubation. The advantages appear to be greatest in smokers.

The choice of inhalation anesthetics in such patients has historically placed emphasis on halothane largely because of its well recognized bronchodilating properties. The bronchodilating efficacy of sevoflurane, however, appears to be better in a population of VA patients, most of whom were smokers. Desflurane, on the other hand, is devoid of any bronchodilating actions and appears to have disadvantages related to its physical properties, most notably its high density and propensity for airway irritation.

Adequate anesthetic depth (>1 MAC) is obviously important to minimize likelihood of bronchospasm. When considering the mode of ventilation (i.e. spontaneous vs. controlled), it is important to consider the reduction in the ventilatory response to CO2 that accompanies inhalation anesthesia. With the mechanical impairment in patients with airway obstruction (e.g. decreased FEV1) one might expect CO2 removal to be further impaired. Indeed Pietak et al reported alarming degrees of hypercapnia in such patients allowed to breathe spontaneously in the presence of 1 % halothane. The low tidal volumes and high respiratory rates resulted in a high amount of “wasted” ventilation, more specifically increased alveolar dead space, despite the fact that overall minute ventilations were the same as normal patients. Although no data exist with newer agents...

©International Anesthesia Research Society. Unauthorized Use Prohibited.
such as sevoflurane in patients with obstructive lung disease, greater elevations of resting CO2 compared with halothane in normals would suggest that the effects in the presence of obstructive airway disease are also likely to be more severe.

MANAGEMENT OF VENTILATION

The need for positive pressure ventilation is unavoidable with general anesthesia in patients with variations of obstructive airway disease, but the approaches to mechanical ventilation are controversial. Traditional objectives have focused on the need to avoid excessive peak airway pressure (Ppk) based on the rather naïve perception that the latter is the major cause of lung parenchymal disruption usually referred to as “barotrauma” The limitation of Ppk is simplistically achieved by low rates of inspiratory flow (VI). The importance of reducing VI was long ago disputed by Tuxen and Lane18 who demonstrated that plateau pressure (Pplat) and not Ppk was related to lung hyperinflation, barotrauma, and circulatory depression. These are all the result of end expiratory and end inspiratory volume increases which can be reduced by the 3 following basic ventilatory strategies19:

- Reduced Respiratory Frequency (f)
- Reduced Tidal Volume (VT)
- Shortened Inspiratory Time (Ti)

Reductions in f have the the greatest impact on reducing hyperinflation and are far more effective than reducing VT since the latter progressively increases the alveolar dead space fraction. Perhaps more benefits are derived from reductions in Ti to allow more time for passive exhalation. In order to maintain delivered VT, inspiratory flow rate must be increased. This is best accomplished with the square wave flow pattern of volume control ventilation. As surrogate markers of lung hyperinflation the plateau pressure during an inspiratory pause and “auto PEEP” are relatively easy to measure guides to adjusting ventilator settings. The former estimates the average end inspiratory alveolar pressure while the latter indicates that inspiration is beginning prior to the cessation of expiratory flow.

MANAGEMENT IN THE IMMEDIATE POSTOPERATIVE PERIOD

One major concern in theses patients is the appropriate time to extubate. While the endotracheal tube may be removed early to minimize reactive bronchospasm, this is often not safe. Because of residual anesthetic effects, patients often require ventilatory support in the post anesthesia recovery unit. Reduced lung volumes and abnormal gas exchange persist for as long as 48 hours and patients whose respiratory dysfunction is obvious preoperatively require enhanced vigilance. However, it does seem reasonable to extubate some patients early on awakening and observe them closely for signs of deteriorating gas exchange before considering reintubation.

POSTOPERATIVE ANALGESIA

Analgesia, of course, is a vital component of postoperative therapy. In patients with lung disease there is a narrow therapeutic window because of respiratory depression associated with systemic opioids. Neuraxial blockade (e.g. epidural) with local anesthetics and opioids can avoid the problem somewhat. Although there are no objective data indicating improved spirometric performance, the benefits of mobility and deep breathing without discomfort render epidural analgesia an ideal choice. Much of its benefit accrues from a reduced need for systemic opioid analgesia.

OXYGEN ADMINISTRATION.

The need to administer supplemental oxygen to patients in the post anesthesia care unit is well recognized. There has been some unwarranted concern that oxygen administration will cause certain patients with obstructive lung disease and resting hypercapnia to stop breathing by eliminating their ventilatory response to hypoxia. While it may not be desirable to administer 100% oxygen to such patients, it is not appropriate to deny supplemental oxygen. The PaCO2 will increase and have long been recognized as due to a number of factors, the least of which is a major decrease in minute ventilation. These include the Haldane Effect and most notably an increase in V/Q mismatch because of the vasodilating actions of oxygen on the pulmonary vasculature.

SUMMARY

The peri-operative management of patients with lung disease begins with identifying such patients and determining the severity of their respiratory function. The latter may not require extensive spirometric evaluation and can be accomplished to a great extent by simple evaluations such as peak Flow, arterial blood gases, chest x-ray, etc. The evaluation serves to identify a group of patients at risk for postoperative pulmonary complications but also alerts to individuals who may experience a stormy anesthetic because of increased airway reactivity. In most instances therefore, the efforts are directed at minimizing airway responses during light anesthesia and periods of airway instrumentation. In other patients with lung dyfunction not associated with airway obstruction, the efforts must simply be directed at minimizing the further decrements in lung volume and deterioration of gas exchange so characteristic of the intra and post operative periods.

REFERENCES


---

**TABLE 1: INDICATORS OF INCREASED PERIOPERATIVE PULMONARY MORBIDITY**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Cardiac (n=24)</th>
<th>Pulmonary (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 &lt; 2.0 L</td>
<td>68 +/- 12 (44-92)</td>
<td>59 +/- 13 (32-85)</td>
</tr>
<tr>
<td>FEF 25-75 &lt; 40 % of Predicted</td>
<td>267 +/- 97 (73-461)</td>
<td>144 +/- 66 (12-276)</td>
</tr>
<tr>
<td>Maximum Voluntary Ventilation &lt; 50% of Predicted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Expiratory Flow &lt; 200L/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaCO2 &gt; 46 mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest X-ray Evidence of Hyperinflation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2: PULMONARY VS. CARDIAC CAUSES OF DYSPNEA**

<table>
<thead>
<tr>
<th></th>
<th>Cardiac (n=24)</th>
<th>Pulmonary (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2 (mmHg)</td>
<td>68 +/- 12 (44-92)</td>
<td>59 +/- 13 (32-85)</td>
</tr>
<tr>
<td>Peak Flow (L/min)</td>
<td>267 +/- 97 (73-461)</td>
<td>144 +/- 66 (12-276)</td>
</tr>
<tr>
<td>DDI</td>
<td>18 +/- 8 (2.6-34.2)</td>
<td>8 +/- 4 (0.4-16.4)</td>
</tr>
</tbody>
</table>

**TABLE 3: PREOPERATIVE PULMONARY THERAPY**

- Smoking Cessation
- Bronchodilators
- Incentive Spirometry (Sustained Deep Inspirations)
- Chest Physiotherapy
- Fluid Intake (>3L/day)
- Expectorants (Historically Glycerol Guaiacolate)
Vexing Pediatric Anesthesia Issues for the Generalist Anesthesiologist

Peter J. Davis, MD
Anesthesiologist-in-Chief, Children’s Hospital of Pittsburgh
Professor of Anesthesiology & Pediatrics
University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Learning Objectives:
I. Are parents useful (in the operating room)?
   a. To discuss the developmental differences in child development
   b. To review the incidence of postanesthesia behavioral disturbances
   c. To determine the benefit of parental presence in the operating room

II. Will anesthesia make my child stupid?
   a. To determine the incidence of cognitive impairment following anesthesia in adults
   b. To review the animal data of neonatal neurotoxicity
   c. To review the human data of neonatal anesthesia exposure on learning disabilities

This lecture has a myriad of possible topics, but I have chosen to focus on 2 current issues
1. Anesthesia neurotoxicity in the developing brain: Do anesthetic agents make your child stupid
   2. Parental presence in the OR and premedication agents: Their role in pediatric anesthesia

1. ANESTHESIA NEUROTOXICITY IN THE DEVELOPING BRAIN: DO ANESTHETIC AGENTS MAKE YOUR CHILD STUPID

An area of intense interest in both the scientific community and lay press involves the findings of anesthetic associated toxicity in the developing central nervous system. Early work in the 1980s by Uemura and colleagues noted that rats exposed to varying concentrations of halothane from the time of conception to PND28 had a decrease in synaptic density and that these exposed animals also demonstrated behavioral disturbances (1). More recent investigations with newborn animal models have reported apoptosis in multiple areas of the central nervous system during this period of rapid synaptogenesis when these animals are exposed to drugs that work via N-methyl D aspartate antagonists (NMDA) or Gamma-aminobutyric acid (GABA) agonists (2-11). These findings have been reported in both rodent and non human primate models. Ketamine, sevoflurane and isoflurane have all been shown to have dose-dependent and time-exposure effects on neuroapoptosis in the developing brain. When these agents are combined, these drugs act synergistically with regards to both their anesthetic and neuroapoptotic effect. In addition to a dose effect, these animals have a period, or window of vulnerability, in which these agents act in the developing brain. This window of vulnerability differs among species, and though there are no specific studies on the vulnerability period in humans, these animal models suggest that the vulnerable period in humans correlate to a human period of late pregnancy to early childhood. Although the data is mixed with respect to the behavioral/neurocognitive outcomes in rodents, there is no data on the neurocognitive function following anesthetic exposures in the nonhuman primate.

To complicate the situation, rodent studies have shown that ketamine exposure during this period of rapid synaptogenesis can increase neuroapoptosis and alter behavior in exposed rat pups; however, if rat pups are exposed to chronic pain (in the absence of the drug), chronic pain can also cause an increase in neuroapoptosis. If these animals are exposed to chronic pain and ketamine, neuroapoptosis is markedly attenuated (12). Stratman and colleagues have shown in rat pups that exposure to increased levels of carbon dioxide results in an increase in neuroapoptosis to a level that is similar to that observed with exposure to isoflurane. However, neurocognitive performance in the carbon dioxide exposed group was similar to control animals, while animals exposed to isoflurane had neurocognitive impairment (7). Stratman et al has challenged the view of neuroapoptosis and has suggested that anesthetic agents may effect neurogenesis. Recent animal work suggests that magnesium administration can cause neuroapoptosis (13). Thus, women receiving magnesium infusions to suppress labor or treat preeclampsia may create a risk factor for neurocognitive behavior disorders. How do these findings translate to the human experience? The answers are less clear. Two studies suggest a possible association with neurocognitive impairment and one does not. Wilder and others, looking at databases and county registries in the Rochester Minnesota area, suggest that exposure to anesthesia may have a detrimental effect with regards to learning disabilities. In this study, the investigators reported on a cohort of 5357 births in Rochester Minnesota between 1976 and 1982. The incidence of learning disabilities and its relationship to anesthetic exposure was determined while adjusting for other possibly relevant covariables (14). In this study, the authors concluded that 2 or more anesthetic exposures increased the odds of a learning disability. Though this paper has a significant number of strengths (sample size, inclusion of covariates, a wide range of surgical procedures, varying anesthetic exposures, no preconceived outcome results (i.e. no selection or
observational bias), there are a few limitations that raise caution in interpreting the results. Namely, the study population had anesthesia performed before pulse oximetry and end-tidal monitoring were standard of care or available. In addition, because of the retrospective nature of the study, learning disability evaluations may have been self-selective. Another study to suggest an association between anesthetic exposure and neurobehavioral outcome is the report of Kalkman and colleagues (15) on 249 children following exposure to anesthesia between 0-6 years of age during years 1987, 1991, 1993 and 1995). In a cross-sectional study, these investigators surveyed parents of children from the Netherlands who had undergone GU surgery with a questionnaire on behavioral development. The behavioral development measurement involved the Dutch translation of the Child Behavior Check List developed and validated in the United States. This test completed by the parents, reports their child's competencies and behavior/emotional problems based on the child's activities, social relations and school performance. The parents reported a higher trend in learning deficits. However, based on their findings, a cohort of over 6,000 patients would be needed to confirm or refute their findings.

However, in a study of twin cohorts from the Netherlands, Bartels and others reported no causal relationship between anesthesia and learning deficits. In their study of 1143 monozygotic twin pairs, Bartels noted that twins exposed to anesthesia before age 3 had significantly more cognitive problems and lower educational achievement scores than did twins not exposed to anesthesia. However, in twin pairs that were discordant for anesthesia (i.e. one twin exposed and one twin not exposed), these twins were not different from each other (16).

WHAT IS THE CLINICIAN TO DO WITH ALL THIS INFORMATION?

At this time, no studies demonstrate that anesthetic drugs cause harmful effects to the nervous systems of children. There is no phenotype for this anesthetic-associated neurocognitive disorder. The retrospective studies to date suggest that multiple exposures might entail risk. However, these studies suffer from all the weaknesses inherent in retrospective designs. Specifically, they cannot control for the multiple confounding variables that exist with normal growth and development. However, the existing scant human data and the clinical impression all suggest that anesthetic exposures up to several hours are not associated with risk. This is similar to the findings in animal models. The bottom line for the practicing anesthesiologist, and concerned parents, is that at present there is no direct evidence that exposure to anesthetic drugs, per se, is unsafe for children. Of course, there are real risks of anesthesia in children, including hypoxia and cardiovascular compromise. The available data suggest that discussions about anesthetic risks in young children continue to focus primarily on the very real risks of airway compromise, hypoxia, and cardiovascular instability, and not on the hypothetical risk of neurologic injury from anesthetic drugs. The present data do not support postponing necessary surgery in children until a later age to avoid hypothetical dangers of exposure to anesthetic drugs.

2. PARENTAL PRESENCE IN THE OR AND PREMEDICATION AGENTS: THEIR ROLE IN PEDIATRIC ANESTHESIA

This aspect of the lecture will focus on premedication and the induction of pediatric patients presenting for surgery. In order to better assess the role of premedications and induction techniques, it is imperative to understand the psychological needs of children and how they differ during development. Also important in this process of preparing children and their parents for surgery is to understand what the risk factors are for both patient and parent with regard to preoperative anxiety (18-23). The role of premedications and induction techniques are truly dependent on the perioperative environment and the philosophy of the institution. The endpoints of success to reduce preoperative anxiety need to be defined. Mask acceptance and ease of induction are classically measured, but in fact may be surrogate endpoints. Postoperative behavioral changes may be more significant findings, but postoperative behavioral changes may also be related to other factors in the child's hospitalization/care. Studies have shown that 54% of children undergoing outpatient surgery exhibit postoperative behavioral changes (24-27). These changes include nightmares, disruptive sleep, enuresis, separation anxiety and temper tantrums. Though difficult to assess, the incidence of preoperative anxiety in children is estimated to be up to 75%. Anxiety is that feeling of tension, nervousness and worry associated with increased autonomic nervous system activity. Age-related concerns involve stranger anxiety, parental separation, pain discomfort, disfigurement, and loss of control, fear of awareness, fear of not waking up and fear of being put to sleep. Risk factors for increased preoperative anxiety in children include age (coping strategies), children with high trait anxiety, shyness, inhibited temperament and increased parental anxieties. In the US, the three most common interventions for children with preoperative anxieties include:

1. Preoperative preparation programs
2. Parental presence at induction of anesthesia
3. Preanesthetic medication

PREOPERATIVE PREPARATION

Most studies have suggested that preoperative preparation programs reduce anxiety and enhance coping in children. Institutional programs have
evolved to include play therapy, music therapy, child-life preparation and the teaching of coping skills (28-30).

**PARENTAL PRESENCE**

Parental presence at induction of anesthesia has increased in frequency (31). The advantages of parental presence include the decreased need for premedications and avoidance of separation anxiety. Concerns regarding parental safety, effectiveness, the child's well being, increased parental anxiety, and consequently, increased patient anxiety, have been cited as the down side to parental presence (31-36). When parental presence is compared to the use of oral midazolam, children who were premedicated with oral midazolam had less anxiety than the children in the parental presence group. In addition, in studies of children where parental presence is combined with oral midazolam and compared to children who only received oral midazolam, there was no further reduction in patient anxiety.

**PREANESTHETIC MEDICATION**

Which agent is best and through which orifice it should be administered have been the subjects of numerous papers in the history of pediatric anesthesia. The various drugs, routes of administration, and dosages are well reviewed in the textbooks of pediatric anesthesia (Krane & Davis, Chapt 8, Smith's Anesthesia for Infants and Children, 8th edition) (20). In the past, most preanesthetic medications have been dictated by tradition. However, more recently, Kain has reported that sedative premedications were used in approximately 50% of all children and adults undergoing surgery, and that in children, midazolam was the most commonly used premedication (>96%) followed by fentanyl and ketamine. For purposes of discussion, the agents midazolam, OTFC, and the -2 agonists clonidine and dexmedetomidine will be reviewed (36-44).

Recently, the use of -2 agonists has come into wider use in pediatric anesthesia. The use of clonidine has been well studied, and more recently the role of dexmedetomidine is being evaluated. Dexmedetomidine bioavailability following per oral, buccal and intramuscular administration were 16, 82 and 104% respectively (42). Studies in adults by Yuen et al. using crossover design have shown that nasal administration of dexmedetomidine has a peak sedative effect in 90-105 minutes and significant sedation occurring in 45-60 minutes. In addition, 75% and 92% of adult volunteers receiving 1.0 and 1.5 µ/kg respectively had OAA/S scores of 3 or less. In a blinded study involving children premedicated with both oral midazolam (0.5 mg/ kg), nasal dexmedetomidine (0.5 µg/kg) or nasal dexmedetomidine (1.0 µg/kg), Yuen et al. noted that intranasal dexmedetomidine produced more sedation than midazolam, but patient cooperation at the time of induction was similar to the group receiving midazolam (43,44).

**REFERENCES:**


Valvular heart disease is becoming more common in our aging population. An estimate of the prevalence of moderate to severe disease in patients > 75 years old is 13.3%. Maintenance of hemodynamic stability in these patients can be quite challenging. This review will focus on anesthetic management of the classic lesions: aortic stenosis (AS), aortic regurgitation (AR), mitral stenosis (MS), and mitral regurgitation (MR).

General guidelines for hemodynamic management (heart rhythm, heart rate, preload, afterload, and contractility) will be presented for each valvular lesion. However, the anesthesiologist should bear in mind that “mixed” valvular lesions are more common than “pure” valvular lesions. Thus, the clinician will need to determine which is the most severe (hemodynamically significant) lesion and/or will need to “split the difference” between management goals for multiple valve lesions.

AORTIC STENOSIS

Aortic stenosis (AS) is a commonly encountered cardiac valve lesion in the U.S. Acquired AS is due to idiopathic senile degeneration with sclerosis and calcification of the valve. There is a clear association between clinical risk factors for atherosclerotic disease and the development of AS, including the process of chronic inflammation. An increased incidence with aging occurs due to greater mechanical stress over time and longer exposure to risk factors such as hypertension, smoking, diabetes, and hypercholesterolemia. Aortic stenosis is now seen in 2%-4% of adults greater than 65 years of age, and this prevalence is expected to increase.

Another common etiology of aortic stenosis is a congenital defect in the valve, because 1%-2% of the population are born with a bicuspid aortic valve. Inheritance has been found to play a role, with an autosomal dominant pattern and a variable penetrance. A bicuspid aortic valve that does not yet show any signs of damage nevertheless tends to open and close with abnormal folding and creasing, leading to scarring and calcification. Although patients with a bicuspid aortic valve are asymptomatic until late in the disease process, severe, symptomatic AS with or without aortic regurgitation (AR) may develop in mid-life? In undeveloped countries, rheumatic disease is a fairly common cause of AS, and it is usually associated with concomitant AR.

Aortic stenosis is an important clinical entity because of the potential for sudden death and because of the relative ineffectiveness of external cardiac massage during a cardiac arrest. The diagnosis of AS is made from a detailed history and physical examination, supplemented by echocardiography. Symptoms of AS can range from decreased exercise tolerance and exertional dyspnea to angina, CHF, and syncope. On physical examination, a systolic ejection murmur with radiation to the carotids is strongly suggestive of AS.

Echocardiography can be used to determine multiple aspects of the pathophysiology of the lesion including the severity of AS, any structural abnormalities of the valve causing left ventricular outflow tract (LVOT) obstruction, and any accompanying disease that can be found in the other heart valves. A commonly used parameter of severity is the aortic valve area (AVA), with normal AVA being 3-4 cm². In severe AS, AVA is ≤ 1 cm². Another parameter commonly used to determine the severity of AS is the gradient across the aortic valve, whereby AS is considered severe if the mean gradient is ≥ 40 mmHg.

In the presence of AS, the obstruction of left ventricular outflow results in increased peak systolic wall stress. This chronic pressure overload directly stimulates parallel replication of sarcomeres in the left ventricle, with consequent development of concentric hypertrophy. Figure 1 shows a typical pressure-volume loop for a patient with AS. The peak pressure generated by the left ventricle during systole is much higher because of the high transvalvular pressure gradient. Concentric hypertrophy decreases systolic myocardial wall stress from the increasing afterload. However, it also leads to diastolic dysfunction with an increase in left ventricular end-diastolic pressure (LVEDP) and subendocardial ischemia. Eventually, the ejection fraction is somewhat decreased, indicating reduced

![Figure 1: Pressure-volume loop in aortic stenosis.](image-url)
left ventricular contractility. The evaluation of the severity of AS can be complicated in the patient who presents with impaired systolic left ventricular function since compromised left ventricular function results in low flow across the LVOT and aortic valve, thus decreasing the gradients in these areas.2

ANESTHETIC MANAGEMENT

Operative risk depends upon the severity of the AS, whether the patient has concomitant coronary disease, and the risks of the surgical procedure. Also, it is important to realize that the presence of severe AS reduces the usefulness of CPR for maintaining a cardiac output sufficient to meet the patient's physiologic needs. Anesthetic management of patients with AS revolves around avoiding fluctuations in the patient's hemodynamics, while achieving adequate anesthetic depth.

Every effort should be made to ensure that the patient with AS stays in sinus rhythm. Due to diastolic dysfunction and impaired relaxation, the "atrial kick" may contribute as much as 40% of the total cardiac output.9 Anything interfering with atrial function (e.g., junctional rhythm or atrial fibrillation) can lead to severe hypotension. Therefore, in order to treat any possible arrhythmia, external cardioversion pads should be considered, preferably before induction of anesthesia.

It is also important to avoid either tachycardia or bradycardia.10,11 Bradycardia is undesirable because the stroke volume is already limited by the stenotic valve itself; therefore, cardiac output is unacceptably low in the presence of bradycardia. Tachycardia can usually be tolerated for short periods, but can further jeopardize an already compromised coronary supply/demand relationship in the presence of ventricular hypertrophy and concomitant coronary disease.

Preload should be maintained or increased in order to adequately fill the noncompliant left ventricle. Afterload should be maintained or increased. Systemic hypotension causes reduced coronary perfusion pressure and should be managed with the early use of α-adrenergic agonists. Contractility should be maintained.

Premedication may help to prevent perioperative tachycardia in patients with AS. Monitoring includes standard noninvasive modalities. Usually, an arterial line is placed in the preoperative period. Invasive monitoring of central venous pressure is considered, if the surgical procedure involves the potential for blood loss and volume shifts. TEE monitoring is nearly always desirable if there are no contraindications to its placement.

AORTIC REGURGITATION

Aortic regurgitation (AR) is the flow of blood from the aorta backwards into the left ventricle during the diastolic phase of the cardiac cycle. Chronic AR is more prevalent and carries a much better prognosis than acute AR. Causes of chronic AR include congenital lesions, connective tissue disorders, inflammatory diseases, appetite suppressant medications, rheumatic disease, and annular dilation from aging and chronic hypertension. These processes cause malcoaptation of the AV leaflets by causing abnormalities in the leaflets themselves or dilation of the AV annulus, the aortic root, or both.12

Progressive volume loading in chronic AR increases end-diastolic wall tension. The left ventricle undergoes a process of remodeling due to series replication of sarcomeres and myofibril elongation, with development of eccentric ventricular hypertrophy and chamber enlargement.13 Figure 2 shows that the pressure-volume loop is shifted far to the right in patients with chronic AR. Notably, left ventricular end-diastolic pressure (LVEDP) remains relatively normal because left ventricular end-diastolic volume (LVEDV) increases slowly. Therefore, patients with chronic AR may remain asymptomatic for years or even decades. However, patients with chronic AR eventually present with symptoms of left heart failure, e.g., exercise intolerance, dyspnea, and paroxysmal nocturnal dyspnea or orthopnea. Even when these patients have normal coronary arteries, a few nevertheless present with angina due to poor coronary perfusion resulting from low diastolic aortic pressure.

In patients with AR, forward flow is improved by peripheral vasodilation. Typically, a normal ejection fraction is maintained by a large stroke volume. However, over time, increases in the left ventricular wall stress and afterload result.14 Eventually, as left ventricular dilation and hypertrophy progress, irreversible left ventricular dysfunction develops, and patients become symptomatic. Further impairment of systolic function occurs secondary to oxidative stress, collagen degradation, and matrix metalloproteinase activation.15 As a compensatory mechanism for poor cardiac output, sympathetic constriction of the peripheral vasculature occurs to maintain blood pressure, although this worsens regurgitation and cardiac output.

Acute AR is less common than chronic AR but carries a more ominous prognosis. Common causes of acute AR include trauma, bacterial endocarditis,
and aortic dissection. The pathophysiology of acute AR centers around the fact that it causes an acute increase in the volume coming into the left ventricle. Because the left ventricle has not had time to undergo the process of eccentric hypertrophy, as it does in chronic AR, it is unprepared to accommodate this sudden increase in volume. As shown in the middle loop in Figure 2, this sudden increase in the LVEDP causes a rightward shift in the pressure-volume loop. A sympathetic response is activated — tachycardia and increased contractile state are the chief compensatory mechanisms for maintaining adequate cardiac output. Unless the AR is managed appropriately, these compensatory mechanisms rapidly fail, necessitating emergency cardiac surgery.

Echocardiography is the most important diagnostic tool. Regurgitant volume consisting of < 20% of the total left ventricular stroke volume is considered mild, 20%-39% is considered moderate, 40%-60% is considered moderately severe, and > 60% is considered severe. In reality, the regurgitant volume depends in part upon the diastolic time interval and the diastolic pressure gradient across the valve, as well as the regurgitant orifice area.

ANESTHETIC MANAGEMENT

Maintaining a relatively fast heart rate (approximately 90 beats/min) will minimize the time spent in diastole and leads to a decreased regurgitant fraction. Subendocardial blood flow may actually improve with tachycardia due to a higher diastolic pressure and a lower LVEDP. Sinus rhythm is preferable, but rapid supraventricular tachyarrhythmias are better tolerated in patients with AR than in patients with AS.

Also, due to the increased left ventricular volume, preload should be augmented to maintain filling of the dilated left ventricle and maintain forward flow. Furthermore, reducing afterload (maintaining a relatively low systemic vascular resistance [SVR]) will minimize the pressure gradient back across the aortic valve during diastole, improving forward flow and decreasing LVEDP. Finally, left ventricular contractility should be maintained.

In considering the choice of drugs for general anesthesia in these patients, medications that cause bradycardia should be avoided. Pharmacologic interventions that produce venous dilation may significantly impair cardiac output by reducing preload. Increases in ventricular afterload should be avoided. In some patients with AR, inodilator agents such as phosphodiesterase inhibitors or other inotropic agents such as β-agonists may be needed to improve left ventricular function.

MITRAL STENOSIS

Rheumatic heart disease was once the primary cause of mitral stenosis (MS), although its prevalence in the U.S. is decreasing. In the US and other industrialized nations, mitral valve disease is usually caused by primary degenerative (i.e., age-associated), congenital mitral valvular abnormalities (e.g., mitral valve prolapse), or ischemic heart disease resulting in functional mitral incompetence, rather than by rheumatic heart disease. However, rheumatic heart disease remains a large-scale medical and public health problem for many countries and is still seen in the U.S. due to immigration.

The normal mitral valve orifice area is approximately 4-5 cm². Symptoms of MS, usually dyspnea, can occur with a valve area less than 2.5 cm² and can be precipitated by clinical events associated with increased cardiac output and consequent increased flow across the stenotic valve, e.g., stress, exercise, anemia, pregnancy, or febrile illness. MS is considered to be mild if the valve area is 1.5-2.5 cm², moderate if 1.1-2.5 cm², and severe if ≤ 1.0 cm². Currently, MS is primarily diagnosed and monitored with echocardiography, although MVA can be calculated during cardiac catheterization by using the Gorlin equation. Obstructed flow across the mitral valve is also associated with a pressure differential or “gradient” across the valve. The more severe the MS, the greater the gradient, as long as flow across the valve is held constant. Notably, severe MS may be present with a low measured or calculated gradient across the valve if the patient has low flow due to right heart failure and pulmonary hypertension.

The increased left atrial pressure in patients with MS gradually produces left atrial dilation. Such atrial enlargement can lead to the onset of atrial fibrillation and also to thromboembolic complications if a clot forms in the atrium or appendage due to low velocity blood flow. Treatment may include anticoagulation with IV heparin or oral coumadin, pharmacologic rate control, and pharmacologic or electrical cardioversion for hemodynamically significant or acute onset atrial fibrillation. In patients scheduled for cardioversion, TEE may be performed first to rule out the presence of LA thrombus.

Elevated pressure in the left atrium also leads to passive increases in pulmonary venous and arterial pressures. Many patients with MS have elevated pulmonary pressures secondary to reactive pulmonary vasoconstriction or histologic changes in the medial and intimal layers of pulmonary arteries and arterioles. Chronic elevation in pulmonary pressure caused by MS leads to compensatory right ventricular hypertrophy, similar to the pathophysiology of lesions that obstruct outflow of the left ventricle. However, the response in the right ventricle is less efficient than the left ventricle because of its shape, wall thickness, and smaller muscle mass of the right ventricle. Therefore, chronic pulmonary hypertension can lead to progressive right ventricular dilation and failure.

The effect of MS on the left ventricle is primarily due to obstruction of diastolic inflow. The narrowed mitral valve orifice leads to prolonged early diastolic
mitral inflow and delayed left ventricular filling. Late diastolic filling, occurring during atrial systole, is further compromised in patients who have atrial fibrillation secondary to MS. In cases of MS, pressure-volume loops are shifted to the left, so that LVEDP and LVEDV are lower (Figure 3). Stroke volume is diminished, especially in clinical situations that result in elevated heart rate and shortened diastolic filling intervals. Although left ventricular function or contractility was once thought to be normal in most patients with MS, it has been shown that left ventricular dysfunction is common in patients with MS. Proposed mechanisms include reduced filling of the left ventricle, muscle atrophy, inflammatory myocardial fibrosis leading to wall motion abnormalities, scarring of the subvalvular apparatus, abnormal patterns of left ventricular contraction, reduced left ventricular compliance with diastolic dysfunction, increased afterload leading to left ventricular remodeling, right-to-left ventricular septal shift secondary to the effect of pulmonary hypertension on the right ventricle, and coexistent diseases such as systemic hypertension and coronary artery disease.

**ANESTHETIC MANAGEMENT**

Primary concerns in patients with MS include management of heart rate, ventricular preload, potentially diminished right and left ventricular contractile function, and coexisting pulmonary hypertension. The most important hemodynamic goal is to avoid tachycardia (keep heart rate within its normal range). Tachycardia is poorly tolerated because of the decreased time for diastolic filling. Also, pressure gradients are somewhat flow-dependent in MS. Elevated flow states, such as increased sympathetic activity from any source, can dramatically increase the pressure gradient across the valve. Echocardiographically, the concept of valve gradients is derived through the use of a modified form of Bernoulli’s equation, \( \Delta P = 4v^2 \), where “\( v \)” is the measured velocity of blood flow through the valve. Thus, any increase in transvalvular flow rate caused by an increase in heart rate will have a significant impact on transvalvular flow dynamics and on left atrial pressure.

Also, if possible, sinus rhythm should be preserved. Atrial contributions to stroke volume may be elevated in MS patients who are in the early stages of the disease and who are not in atrial fibrillation. Once atrial fibrillation has occurred, the atrial kick is lost. In this case, however, the most important factor in the deterioration of the patient’s clinical condition is tachycardia itself, rather than loss of the atrial kick. In any event, digoxin should be continued perioperatively. Short-acting \( \beta \)-blockers can then be used for heart rate control.

Flow through a stenotic mitral valve requires a higher-than-normal pressure gradient between the left atrium and the left ventricle. Thus, reduction in preload, from the venodilatory effects of anesthesia or from blood loss, can markedly affect cardiac output. However, patients with MS already have elevated left atrial pressures, so that overly aggressive use of fluids can lead a patient in borderline CHF into florid pulmonary edema. In patients with MS, afterload reduction is usually not helpful in augmenting forward flow, because stroke volume is determined by the mitral valve orifice area and the diastolic filling interval.

**Left ventricular contractility and SVR are usually preserved in MS. If anything, the left ventricle is chronically underloaded. Nevertheless, global systolic dysfunction develops in some MS patients.**

Right ventricular dysfunction probably poses a greater challenge in treating patients with MS than does left ventricular dysfunction. Every effort should be made to avoid increases in pulmonary arterial pressures (e.g., avoid hypoxia, hypercardia, acidosis, lung hyperexpansion, and nitrous oxide).

In patients with MS, oversedation in the preoperative period should be avoided to prevent hypoventilation. Bleeding complications from chronic anticoagulation in patients with atrial fibrillation should be anticipated. Monitoring for these patients includes standard noninvasive modalities and, depending upon the type of surgery, may involve invasive monitoring of blood pressure, central venous pressure, and intraoperative echocardiography. Monitoring pulmonary artery (PA) pressure and monitoring cardiac output with a PA catheter is sometimes employed, but care and judgment must be exercised, given the propensity for PA rupture in patients with long-standing pulmonary hypertension. Management of right ventricular dysfunction includes optimizing acid-base balance and using hypocarbia, hyperoxia, and possibly vasodilators to decrease pulmonary vascular resistance. Inotropic support may be needed for patients with secondary right ventricular dysfunction or failure. Epinephrine and milrinone are good therapeutic options. Newer therapeutic options for treatment of refractory pulmonary hypertension include inhaled prostacyclin or nitric oxide.
MITRAL REGURGITATION

Mitral regurgitation (MR) is a commonly encountered valve lesion. MR can either involve structural abnormalities in the valve or its subvalvar components, or functional abnormalities due to annular or left ventricular dilation causing malcoaptation of the mitral valve leaflets. Examples of structural abnormalities of the mitral valve include mitral valve prolapse, myxomatous degeneration of the mitral valve, rheumatic mitral insufficiency, cleft mitral valve associated with an atrioventricular septal defect, and any infiltrative/fibrotic processes. Functional MR is present in 10%-20% of patients with chronic ischemia due to coronary artery disease. Unlike primary valvular causes of MR, the morphology of the mitral valve is normal in these patients. Nonetheless, the long-term morbidity and mortality associated with this type of MR are significant.

Today, in developed countries, the most common causes of MR are either myxomatous degeneration of the mitral valve (resulting in annular dilation, chordal elongation and rupture, and redundant, prolapsing, or flail mitral valve leaflets) or mitral insufficiency caused by ischemic heart disease.

The incompetent mitral valve allows retrograde passage of blood from the left ventricle into the left atrium during systole. The magnitude of the regurgitant volume is a function of the size of the regurgitant orifice, the pressure differential between the left atrium and the left ventricle, and the duration of the regurgitant cycle. The severity of MR is assessed in the context of whether the MR is acute or chronic. In patients with chronic MR, symptoms range from nonspecific complaints such as easy fatigability and palpitations to severe CHF. Echocardiography is used to serially follow patients with chronic MR. Quantitative estimates of regurgitant fraction (the fraction of regurgitant volume in relation to total stroke volume) are made from the LV angiogram or measured echocardiographically with Doppler. If regurgitant volume is < 30% of total left ventricular stroke volume, the MR is considered mild, 30%-39% is considered moderate, 40%-60% is considered moderately severe, and > 60% is severe. Pulmonary venous systolic flow reversal is another indication that mitral regurgitation is severe.

The left atrium is exposed to both volume and pressure increases. However, in chronic MR, left atrial pressure increases are not dramatic because of compliance changes in the left atrium as a function of gradual chamber dilation. Progressive left atrial enlargement eventually leads to atrial fibrillation, which occurs in about 50% of patients who present for surgical correction of MR. When left atrial compliance thresholds are reached, left atrial pressure and pulmonary arterial pressure become elevated. Eventually, if chronically exposed to elevated PA pressure, the right ventricle progressively enlarges and right ventricular dysfunction develops.

The long-term sequelae of MR are related to chronic pressure and volume effects on the left atrium and left ventricle. The left ventricle is exposed to a chronic, isolated volume-overload state. Eccentric hypertrophy of the left ventricle develops, causing chamber enlargement without significant increases in wall thickness. Forward cardiac output is preserved because of eccentric hypertrophy and the low impedance of the left atrium—a physiologic equivalent of afterload reduction. The larger stroke volume ejected by the left ventricle is composed of normal venous return into the left atrium plus the regurgitant volume from the prior cardiac cycle. With time, however, compensatory eccentric hypertrophy fails to preserve left ventricular systolic function, and gradual systolic failure ensues, as noted on pressure-volume loops (Figure 4). A reduction in left ventricular ejection fraction below 60% or an increase in end-systolic dimension exceeding 40 mmHg indicates the need for surgical repair or replacement of the mitral valve.

With acute onset of MR (e.g., due to myocardial infarction and rupture of papillary muscles), there has been no time for left atrial compensatory changes to occur. Therefore, there is a sudden increase in left atrial pressure and pulmonary capillary wedge pressure. Patients with acute severe MR are usually in cardiogenic shock and do not present for noncardiac surgery. Pharmacologic support of the left ventricle, often accompanied by mechanical support with intra-aortic balloon pump (IABP) counterpulsation, may be necessary to prepare the patient for emergency cardiac surgery.

ANESTHETIC MANAGEMENT

The primary goal in patients with chronic MR is maintaining forward systemic flow. The heart rate should be maintained in the high-normal range, i.e., 80 to 100 beats/minute. Tachycardia decreases the regurgitant volume by shortening systole. Bradycardia has dual detrimental effects on MR: it increases the systolic period duration, thus prolonging regurgitation, and it increases the diastolic filling interval, which can lead to LV distention. A sinus rhythm is preferred, but there is
less dependency on the atrial kick than in stenotic valvular heart disease.

As with most compensated forms of valvular heart disease, patients with hemodynamically significant MR are sensitive to ventricular loading conditions. It must be remembered that anesthetic effects on afterload and preload can drastically alter the severity of MR from its baseline level as seen in preoperative echocardiographic or catheterization assessments. In general, afterload reduction in combination with mild preload augmentation will enhance forward cardiac output and blood pressure. Adequate anesthetic depth, systemic vasodilators, or inodilators may be clinical options, depending on the situation. However, higher systolic driving pressures, as in hypertension, can increase the regurgitant volume, while fluid overload with ventricular distension can lead to expansion of an already dilated mitral annulus and thus worsen MR.

In early compensated MR, left ventricular contractility may be preserved. However, in patients with moderate to severe MR, ejection fraction indices are poorly correlated with left ventricular systolic function so that underlying systolic dysfunction may be underestimated. Hypotension in patients with significant MR can often be managed by manipulating heart rate and volume, but persistent hemodynamic instability may be best treated with inotropic support. Direct-acting α1-agonists increase SVR and blood pressure, lower heart rate, and may worsen MR. Temporary use of small doses of ephedrine may be a better choice. Dobutamine, low-dose epinephrine, and milrinone are all acceptable inotropic support. Direct-acting hemodynamic instability may be best treated with inotropic support. Direct-acting α1-agonists increase SVR and blood pressure, lower heart rate, and may worsen MR. Temporary use of small doses of ephedrine may be a better choice. Dobutamine, low-dose epinephrine, and milrinone are all acceptable inotropic choices for continuous infusion.

Pulmonary artery pressures and pulmonary vascular resistance may be elevated in patients with MR. Factors that may increase pulmonary vascular resistance and unfavorably load an already dysfunctional right ventricle, such as hypoxia, hypercarbia, and acidosis, should be avoided.

REFERENCES


Postoperative Nausea and Vomiting: Past, Present, and Future

Paul F. White, PhD, MD, FANZCA
Department of Anesthesiology & Pain Management, University of Texas Southwestern Medical Center, Dallas, Texas and the Departments of Anesthesia at Policlinico Abano Terme and Parma University in Italy, and Cedars Sinai Medical Center in Los Angeles

Postoperative nausea and vomiting (PONV) is a long-standing, multi-factorial problem for anesthesia practitioners. (1) The incidence of PONV remains high despite the frequent use of prophylactic antiemetics (e.g., 5-HT3 antagonists, glucocorticoids, dopamine antagonists), shorter-acting anesthetics and analgesics (e.g., propofol, desflurane, remifentanil), and less invasive surgical techniques (e.g., laparoscopic procedures). Patient, anesthetic and surgical factors all contribute to the persistently frequent incidence of emetic symptoms in the postoperative period. (1) With the increasingly emphasis on earlier mobilization and discharge (“fast-tracking”) after both minor and major operations, postural hypotension and oral opioid containing analgesics are becoming more important contributors to PONV and post-discharge nausea and vomiting (PDNV). In a recent analysis of factors influencing postanesthesia recovery, Edler et al. (3) reported that the number of episodes of PONV contributes significantly to prolonging the patient’s length of stay in the hospital.

Use of antiemetic prophylaxis has been shown to improve patient satisfaction and speed of recovery compared to simply treating the symptoms when they occur in the postoperative period. (4–6) Therefore, antiemetic drugs are now commonly administered both at the start and/or the end of surgery to patients considered to be at increased risk of developing PONV. (7) In fact, combinations of antiemetic drugs are now routinely administered as part of a multimodal strategy for reducing postoperative emetic symptoms in “at risk” patient populations. (8–10) Apfel et al. (11) have developed a simplified scoring system which has favorable discriminating and calibrating properties for predicting an individual patient’s risk for developing PONV. (12) However, the Apfel risk scoring system appears to be more predictive of (<24 h) versus late (24–72 h) emetic symptoms. (13) A recent publication has also provided preliminary evidence to support the notion that the type of surgical procedure may also play an important role in determining the patient’s overall risk of developing PONV. (14)

It is obvious from reviewing the literature that PONV has been far better studied than PDNV. (15) There is a pressing need for additional clinical studies evaluating the impact of antiemetic therapies on PDNV. Oral opioid-containing analgesics for postoperative pain management are a major factor contributing to the occurrence of nausea and vomiting following discharge from a hospital or ambulatory surgery facility. It is possible that the use of longer-acting antiemetics (e.g., transdermal scopolamine, palonosetron) may offer significant advantages over the commonly used antiemetics in preventing PDNV in the post-discharge recovery period. In a comparative study involving ondansetron and droperidol, transdermal scopolamine was found to be as effective as these popular generic antiemetics for prophylaxis in the early postoperative period even when applied 60-90 min prior to the start of surgery. (16)

We know from an earlier study by Scuder et al. (9) using an aggressive approach involving intravenous anesthesia with propofol and minimal amounts of short-acting opioid analgesics, no nitrous oxide, no neuromuscular blocking or reversal drugs, aggressive IV hydration, triple prophylactic antiemetics (ondansetron, droperidol, and dexamethasone), and ketorolac for preventative analgesia, can effectively prevent emetic symptoms even after high outpatient gynecologic surgery procedures.

Thus, data from the peer-reviewed literature suggest that: (1) the efficacy of prophylactic antiemetic drug therapy is dependent on the patient’s overall risk of PONV; (2) the cost-benefit ratio for using inexpensive antiemetics (e.g., droperidol, dexamethasone, ondansetron) is significantly lower than using an expensive NK-1 antagonist (e.g., aprepitant [Amend]) and 5-HT3 antagonists (e.g., palonosetron [Aloxi]); (3) With the addition of each successive therapeutic intervention, the incremental antiemetic benefit diminishes. Finally, consideration should be given to routinely using equi-efficacious and less costly generic drugs (e.g., droperidol, ondansetron, dexamethasone, transdermal scopolamine) and devices (e.g., acupressure bands) as the first line of prophylaxis in the ongoing battle to effectively eliminate PONV. Other important considerations include the prevention of postoperative pain using non-opioid analgesics an the post-discharge period, and insuring adequate hydration as part of a multimodal approach during the perioperative period. (17)

In conclusion, a combined multimodal approach to preventing PONV will not only improve patient satisfaction with their overall surgical experience, but also lead to a more rapid resumption of their normal activities of daily living in the early postdischarge period. Although there are still additional etiologic factors, as well as prevention and treatment modalities, which need to be further investigated, (18) it is time for all practitioners to begin routinely utilizing existing evidence in the peer-reviewed literature for preventing PONV in their clinical practices.
REFERENCES


News You Can Use: Obstetric Anesthesia in the 21st Century

Cynthia A. Wong, MD
Professor; Northwestern University Feinberg School of Medicine
Medical Director, Obstetric Anesthesiology
Northwestern Memorial Hospital, Chicago, IL

Learner Objectives: By the end of this lecture, participants should be able to

• Understand the relationship between the density of epidural labor analgesia and the outcome of vaginal delivery.
• Explain how the mode of drug delivery into the epidural space (bolus vs. infusion) affects characteristics of neuroblockade.
• Explain the reasoning behind choice of vasopressors (ephedrine and phenylephrine) for the treatment of neuraxial-anesthesia induced hypotension during cesarean delivery.
• Understand the benefits and limits of crystalloid and colloid administration for the prevention of hypotension during spinal anesthesia for cesarean delivery.
• Understand the etiology and risk factors associated with neuraxial anesthesia-associated infections (meningitis and epidural abscess) and the new ASA guidelines for prevention of neuraxial-procedure related infections.
• Understand the current knowledge regarding the association between neuraxial labor analgesia and fetal bradycardia.

LABOR ANALGESIA AND MODE OF VAGINAL DELIVERY

Multiple randomized, controlled studies comparing epidural to systemic opioid analgesia have also assessed the rate of instrumental vaginal delivery (forceps or vacuum) as a secondary outcome variable. Interpretation of these results is clouded by the fact that most studies did not assess that quality of second stage analgesia. Additionally, the “triggers” for instrumental vaginal delivery vary widely among obstetric providers, and may not be well controlled. Many randomized controlled trials and meta-analysis have concluded that epidural analgesia is associated with an increased risk of instrumental vaginal delivery compared to systemic analgesia (Fig. 1). In contrast, impact studies (comparing mode of delivery before and after initiation of widespread availability of neuraxial labor analgesia) how generally not found a change in the rate of instrumental vaginal delivery (Fig. 2). These findings were confirmed in a systematic review of impact studies including 26,443 women: there was no increase in instrumental vaginal delivery rate after the institutional initiation of neuraxial labor analgesia (1.1% change, 95% CI 1.5 to 3.7%).

Several investigators have randomized women with 1st stage epidural analgesia to receive continued epidural analgesia or epidural saline during the 2nd stage of labor. In an editorial review, Chestnut concluded that effective 2nd stage analgesia likely increases the risk of instrumental vaginal delivery. A meta-analysis of available studies concluded that 1) there is insufficient evidence to support the hypothesis that discontinuing epidural analgesia

Figure 1: Neuraxial vs. systemic opioid analgesia and mode of vaginal delivery.©International Anesthesia Research Society. Unauthorized Use Prohibited.
during the 2nd stage of labor reduces the rate of instrumental vaginal delivery rate, but that a larger study was needed, and 2) there is evidence that this practice increases the rate of inadequate pain relief in the 2nd stage of labor.12

The effect of neuraxial analgesia on the outcome of the 2nd stage of labor may be influenced by the density of neuraxial analgesia. High concentrations of epidural local anesthesia may cause maternal motor blockade, causing relaxation of pelvic and pelvic floor musculature, which in turn may interfere with fetal rotation during descent. Abdominal muscle relaxation may decrease the effectiveness of maternal expulsive efforts. A recent multi-center study in over 1000 nulliparas found that the rate of instrumental vaginal delivery was higher in women who received traditional epidural analgesia with bupivacaine 0.25% compared to women who received low-concentration bupivacaine epidural techniques (bupivacaine 0.1% and fentanyl)(37% vs. 29%).13 Similarly, in another study, women randomized to receive CSE analgesia (maintained with bupivacaine 0.0625% plus fentanyl) had a lower rate of instrumental vaginal delivery compared to women who received epidural analgesia (initiated with bupivacaine 0.25% and maintained with bupivacaine 0.125% with fentanyl).14

In summary, the current evidence suggests that effective 2nd stage neuraxial analgesia may cause an increased risk of instrumental vaginal delivery, particularly dense analgesia with motor blockade. Anesthesia providers can minimize this risk by using low-dose epidural techniques, but this may be associated with less effective analgesia.

MAINTENANCE OF EPIDURAL LABOR ANALGESIA

The ideal labor analgesic technique would provide constant pain relief of long duration, minimize undesirable side effects, not interfere with the progress of labor, and minimize physician involvement. Local anesthetic solutions that provide complete analgesia during the whole of labor are often associated with motor blockade and an increased incidence of instrumental vaginal delivery. The method of delivering the anesthetic solution to the epidural space influences the degree of motor block. Given the same concentration of local anesthetic, analgesia maintained by infusion compared to intermittent boluses results in greater drug utilization, a greater degree of motor blockade,15,16 and a higher incidence of instrumental vaginal delivery.17 However, intermittent manual bolus administration by the anesthesiologist results in more breakthrough pain, decreased patient satisfaction, and more work for the anesthesiologist. Hence, in recent years, maintenance of epidural analgesia with continuous infusions has been the norm. This requires a decrease in local anesthetic concentration in order to avoid an increased incidence of motor blockade.

Another method of administering bolus doses while minimizing breakthrough pain and anesthesiologist workload is patient controlled epidural analgesia (PCEA). Studies have compared continuous infusions to PCEA. A meta-analysis of these studies concluded that women who had PCEA had fewer interventions by the anesthesiologist (risk difference 27% (95% CI: 18 to 36%)) (Fig. 3), used less local anesthetic, and had less motor blockade compared to women with continuous infusion epidural analgesia.18 Ropivacaine and levobupivacaine may be associated with less motor blockade compared to equipotent doses of bupivacaine,19-21 although this was not associated with a decreased rate of instrumental vaginal delivery.21

There are conflicting data as to whether PCEA should include a background infusion. Bupivacaine consumption is higher with background infusions compared to a pure PCEA technique without a background infusion.22 In a review of the topic, Halpern and Carvalho concluded that a background infusion of one third to one half the total hourly dose (2 to 10 mL) improves analgesia and may be helpful.
in selected parturients (e.g., nulliparas with long labors).

As discussed above, the bolus administration of epidural anesthetic solution appears to result in improved analgesia with a lower total drug dose. There may be more wide-spread distribution of anesthetic solution within the epidural space when large volumes are injected as a bolus compared to a slow infusion. Investigators have demonstrated that programmed (automated) intermittent boluses (PIEB) administered via a programmable pump results in improved patient satisfaction, less drug use, longer duration of analgesia, and less breakthrough pain compared to a continuous infusion of the same mass of drug per unit time.24-27 The maintenance dose is administered as a bolus at regular intervals, instead of as a continuous infusion (i.e., 5 mL q 30 min instead of 10 mL/h). Commercial pumps that allow easy utilization of this mode of anesthetic solution delivery are not yet currently available.

Ephedrine vs. phenylephrine for treatment of neuraxial anesthesia-induced hypotension

Ephedrine was the drug of choice for the treatment of hypotension during neuraxial anesthesia for cesarean delivery for many years. Studies in pregnant ewes suggested that ephedrine better maintained uterine blood flow compared to direct acting alpha-adrenergic agonists.28 Recent evidence, however, no longer supports this practice. A number of human studies in the last 15 years have demonstrated that phenylephrine is equally effective for treating maternal hypotension. More importantly, in studies of spinal anesthesia for elective cesarean delivery, fetal acid-base status is actually improved with phenylephrine compared to ephedrine.29-32 A meta-analysis found no differences in maternal blood pressure, although bradycardia was more likely after phenylephrine treatment.33 Umbilical artery pH was higher after treatment with phenylephrine (weighted mean difference of 0.03; 95% CI, 0.02-0.04), however there was no difference in the number of neonates with umbilical artery pH < 7.2 (RR 0.78; 95% CI, 0.16-3.92) or Apgar score < 7 at 1 and 5 min.

Cooper et al.34 compared phenylephrine, ephedrine, and phenylephrine combined with ephedrine for the treatment of hypotension after spinal anesthesia. The incidence of fetal acidosis (pH < 7.2) was higher in the ephedrine group (22%) compared to the combined phenylephrine/ephedrine group (2%); the incidence of nausea or vomiting was higher in the two groups that received ephedrine compared to phenylephrine alone.

Traditionally, anesthesiologists have maintained maternal blood pressure within 20% of baseline pressure. However, Ngan Kee and colleagues35 demonstrated that umbilical artery pH is higher, and the incidence of nausea and vomiting is lower, if maternal blood pressure is maintained at 100% baseline compared to 80% baseline. Large amounts of phenylephrine are required to maintain blood pressure at baseline: (median (IQR) infusion dose before delivery 1260 µg (1010-1640 µg)).35

The adverse effect of ephedrine compared to phenylephrine on fetal pH is likely a direct effect of ephedrine on the fetus (increased fetal metabolic activity). Ephedrine crosses the placenta to a greater degree than phenylephrine and undergoes less fetal metabolism.36 It is clear that maintaining maternal blood pressure close to baseline decreases the incidence of fetal acidosis and maternal nausea and vomiting. It is not known whether the minor changes in fetal acid-base status leads to any clinically adverse effects on the healthy fetus. Nor is it known whether there is an adverse effect on fetuses with decreased reserve (e.g., intrauterine growth restriction, non-reassuring fetal status during labor). Clinical outcomes were similar for neonates who mothers were randomized to receive ephedrine or phenylephrine during non-elective cesarean delivery.37 Ephedrine has a longer duration of action than phenylephrine, and a chronotropic effect; whereas the short duration of action of phenylephrine makes it more practical to administer as an infusion. Ngan Kee et al.38 found that combinations of infusions in which phenylephrine and ephedrine are combined in various ratios have no advantage compared to phenylephrine alone for the control of hemodynamic stability in the mother.38 Interesting, despite better fetal acid-base status with phenylephrine, bolus dose phenylephrine compared to ephedrine causes a decrease in maternal cardiac output.39 The decrease in cardiac output correlates with changes in maternal heart rate.39

**CRYSTALLOID AND COLLOID ADMINISTRATION TO PREVENT HYPOTENSION DURING SPINAL ANESTHESIA**

Factors associated with an increased risk for hypotension after spinal anesthesia include dose of local anesthetics (and maximum cephalad extent of blockade), low baseline blood pressure, high interspinous level of dural puncture, lack of labor (e.g., elective procedure), and increased baseline sympathetic tone.40 Traditional preloading with crystalloid prior to the induction of spinal or epidural anesthesia does not significantly decrease the incidence of hypotension. In the presence of euolemia, crystalloid solution is rapidly redistributed from the intravascular to interstitial space.41 This may explain the ineffectiveness of preload (administered prior to the initiation of anesthesia, when the patient is euolemic) in preventing hypotension. Dyer and colleagues42 hypothesized that crystalloid administration may be more effective when administered immediately following the initiation of spinal anesthesia (termed coload), during the development of relative hypovolemia. Indeed, the incidence of hypotension was lower and need for ephedrine less, in a group of parturients randomized to coload (20 mL/kg) compared to a preload 20 min prior to induction.
Several groups of investigators have compared crystalloid preload to colloid (starch) preload and found that the incidence of hypotension after induction of spinal anesthesia is lower after colloid preload.\(^{(43,45)}\) This conclusion is supported by a meta-analysis.\(^{(46)}\) Several randomized controlled trials have compared colloid preload to colloid coload, and found no advantage of colloid preload compared to coload.\(^{(47,48)}\)

Ngan Kee\(^{(49)}\) demonstrated that the combination of crystalloid coload with a prophylactic phenylephrine infusion decreased the incidence of hypotension to 1.9% (95% CI 0.3-9.9%) compared to a group who received minimal fluids with phenylephrine (28.3% (95% CI 18.0 to 41.6%)).

Colloid is expensive, and some patients may have an allergic reaction. Whether routine colloid administration to all healthy women undergoing spinal anesthesia will contribute to improved outcomes is questionable; however, its use may be justified in women at increased risk of hypotension, or in women for whom hypotension or decrease in preload may be associated with clinically adverse outcomes. Taken together, these studies suggest that crystalloid be administered rapidly at the time of induction of spinal anesthesia, and the use of colloid should be considered in women considered at high risk of hypotension. Phenylephrine is no longer contraindicated for the treatment of hypotension and may be the drug of choice.

**NEURAXIAL ANESTHESIA-ASSOCIATED INFECTIONS**

Spinal-epidural abscesses and meningitis are rare complications of neuraxial procedures. In a review of 38 case reports of postpartum meningitis, Reynolds\(^{(50)}\) concluded that all cases were associated with neuraxial procedures (no cases occurred in the absence of a neuraxial procedure). Although there is no denominator, review of the reports suggests that labor and dural puncture are risk factors for meningitis.

In contrast to community acquired meningitis, iatrogenic meningitis is usually caused by streptococcal viridans species;\(^{(51)}\) these organisms are commonly found in the upper airway. Case reports of meningitis following lumbar puncture procedures tend to occur in clusters rather than sporadically, and the offending bacteria have been linked to identical organisms in the airway of the proceduralist.\(^{(51)}\) This suggests that meningitis is due to a break in sterile technique, and is not secondary to hematogenous spread.

Of significant concern is the January 2010 report by the Centers for Disease Control (CDC) of 5 obstetric patients in whom spinal or combined spinal-epidural labor analgesia was complicated by postpartum meningitis.\(^{(52)}\) Three procedures from one hospital were linked to a single anesthesiologist, and 2 from a second hospital were linked to a second anesthesiologist. Streptococcus salivarius was the confirmed cause in 4 of the cases. One patient died. The CDC concluded that S. salivarius was likely transmitted directly from the anesthesiologist to the patients, either by droplet transmission directly from the oropharynx (one anesthesiologist did not wear a mask during the procedure), or contamination of sterile equipment. The CDC\(^{(53)}\) and the American Society of Regional Anesthesia and Pain Medicine (ASRA)\(^{(54)}\) and the American Society of Anesthesiologists (ASA)\(^{(55)}\) all recommend that practitioners wear masks while performing neuraxial procedures.

In contrast to meningitis, epidural abscesses are more likely caused by skin flora (e.g., Staph aureus). Studies have suggested that chlorhexidine\(^{(56)}\) and povidone iodine with alcohol\(^{(57)}\) produce better skin antisepsis than povidone iodine. The ASRA\(^{(54)}\) and the ASA recommend an alcohol based chlorhexidine solution be used for skin asepsis before regional nerve block procedures. Other recommendations include removal of all jewelry (including rings and watches), handwashing with an alcohol-based antiseptic solution, sterile gloves, individual packets of antiseptics for skin preparation (not multidose bottles), sterile draping of the patient, and the use of sterile occlusive dressings.\(^{(54,55)}\)

**NEURAXIAL LABOR ANALGESIA AND FETAL BRADYCARDIA**

Fetal bradycardia not associated with maternal hypotension occurs after the initiation of neuraxial labor analgesia. Although unproved, current information suggests that uterine tachysystole (hypertonus) is responsible. Circulating epinephrine levels are markedly elevated during labor. Levels drop precipitously after the initiation of neuraxial labor analgesia.\(^{(58)}\) Epinephrine is a tocolytic, and an acute decrease may temporarily “unbalance” the equilibrium between tocolytic and uterotonic activity.\(^{(59)}\) Fetal bradycardia seems to occur earlier after initiation of CSE (15 min) than epidural (<30 min) analgesia. There is some disagreement as to whether it occurs more commonly after CSE.\(^{(60-62)}\)

In a randomized controlled trial fetal bradycardia and uterine tachysystole were more common after CSE than epidural analgesia.\(^{(63)}\) However, fetal heart rate was only monitored for 15 min after initiation of analgesia, so that fetal bradycardia after epidural analgesia may have been missed.\(^{(64)}\)

The results of a systemic review suggest that fetal bradycardia is more common after intrathecal opioid analgesia compared to any other neuraxial labor analgesia technique.\(^{(65)}\) Data are inconsistent was to whether there is an intrathecal opioid dose response of fetal bradycardia.\(^{(66-68)}\) Patient selection bias for the CSE technique may play a role in that women in advanced labor more often receive a CSE compared to epidural technique, and these women are at higher risk of fetal heart rate decelerations and bradycardia.\(^{(69)}\) The emergency cesarean delivery rate secondary to fetal bradycardia was not different.
between parturients who received CSE vs. systemic analgesia in a large observational study, and in several large randomized controlled trials. In contrast, another randomized study did find an increased incidence of emergency cesarean delivery in subjects randomized to CSE vs. systemic analgesia (2% vs. 0%). Discontinuing oxytocin administration, administration of terbutaline, IV or sublingual NTG, and a fluid bolus are effective treatments of uterine tachysystole.

REFERENCES

after induction of spinal anaesthesia (coload) for elective caesarean section. Anaesth Intensive Care 2004;32:351-7


45. Siddik SM, Aouad MT, Kai GE, Sfeir MM, Baraka AS. Hypothesized that 10% is superior to Ringer’s solution for preloading before spinal anaesthesia for Cesarean section. Can J Anaesth 2000;47:616-21


50. Reynolds F. Neurological infections after neuraxial anesthesia. Anesthesiology clinics 2008;26:23-52

51. Schneeberger PM, Janssen M, Voss A. Alpha-hemolytic streptococci: a major pathogen of iatrogenic meningitis following lumbar puncture. Case reports and a review of the literature. Infection 1996;24:29-33

52. Bacterial meningitis after intrapartum spinal anesthesia - New York State Health Department. New York, 2002:89-90


Obstructive Sleep Apnea Patients: A Challenge for Anesthesiologists

Frances Chung, MD FRCPC
Professor of Anesthesia, Department of Anesthesia
University Health Network, University of Toronto
Toronto, Ontario, Canada

INTRODUCTION

Upper airway patency is essential for normal respiratory function. The maintenance of a patent airway is dependent primarily on the pharyngeal structures. In some individuals, there is a loss of this airway patency from collapse of pharyngeal soft tissue, and interruption of airflow occurs during sleep. Obstructive sleep apnea (OSA) is caused by repetitive partial or complete obstruction of the upper airway, characterised by episodes of breathing cessation during sleep, which lasts 10 or more seconds.

From the anesthesiologists’ standpoint, OSA patients pose significant problems in the perioperative period – ranging from difficult airways, sensitivity to anesthetic agents, and postoperative adverse events. OSA has been associated with an increase in postoperative complications, and is an independent risk factor for increased morbidity and mortality.

A recent retrospective matched cohort study in elective surgical patients with OSA showed that OSA patients had an increased incidence of postoperative oxygen desaturation with a hazard ratio of 2. In addition, there is a growing body of literature showing that OSA patients undergoing upper airway surgery, joint replacement surgery, and cardiac surgery have an increased risk of postoperative complications.

Optimal patient care begins with a tailored preoperative assessment, to facilitate patient risk stratification and optimization, followed by formulation of an individualized perioperative management plan.

PREVALENCE

OSA is the most prevalent breathing disturbance during sleep, with an incidence in the general population estimated in the range of 1 in 4 males and 1 in 10 females. Moderately severe OSA was present in twice as many more men (11.4%) than women (4.7%). A significant proportion of OSA patients are undiagnosed prior to surgery. It is therefore increasingly being recognized as a significant perioperative problem.

DIAGNOSIS OF OSA

The diagnosis of OSA is established by an overnight sleep study or polysomnography. The apnea hypopnea index (AHI) is the number of abnormal respiratory events per hour of sleep.

AHI cutoffs have been frequently used to describe the severity of OSA. The American Academy of Sleep Medicine defines mild OSA as AHI > 5 - 15, moderate OSA as AHI >15 – 30, and severe OSA as AHI > 30. Clinicians should be cognizant that different published standards of hypopnea definitions might lead to differences in AHI.

Some other factors used in the evaluation of OSA severity include duration of oxygen desaturation, rate of desaturation, adequacy of ventilation recovery, and level/stability of arousal threshold.

PRACTICAL SCREENING OF SUSPECTED OSA PATIENTS IN THE PREOPERATIVE CLINIC

A large number of surgical patients with OSA are undiagnosed when they present for surgery and anesthesia. Polysomnographic diagnosis of OSA is prohibitive as it is costly and resource-intensive. Therefore, anesthesiologists are in need of a practical preoperative screening tool to identify patients more likely to have true OSA. For safety reasons, the screening tool should have a high degree of sensitivity, at the expense of lower specificity.

In a preoperative survey of elective surgeries, 24% of patients were identified as having a high risk of OSA using the Berlin questionnaire. In another study screening over 2000 patient, 27.5% of them were classified as being at high risk of OSA when the STOP questionnaire was utilised. In the preoperative anesthesia assessment, a high index of suspicion for OSA is important.

Snoring is the premier symptom of OSA, and is 100% sensitive. However, it is not specific and its positive predictive value is low. Several questionnaire-based screening tools have been successfully developed. The Berlin Questionnaire is a 10-item self-report instrument validated initially in the primary care setting. It consists of 5 questions on snoring, 3 questions on excessive daytime sleepiness, 1 question on sleepiness while driving, and 1 question inquiring about a history of hypertension. Details pertaining to age, gender, weight, height, and neck circumference are also recorded. A study screening preoperative patients using the Berlin questionnaire determined that it had a sensitivity of 69% and a specificity of 56% in surgical patients. The drawback of the Berlin Questionnaire is the complicated scoring system and the large number of questions.

In 2006, the American Society of Anesthesiologists (ASA) taskforce on OSA developed a tool to assist anesthesiologist in identifying patients with OSA. It comprises a 14-item checklist categorised into physical characteristics, history of apparent airway obstruction during sleep, and complaints of
somnolence (20). The sensitivity of the ASA checklist was 79% and 87% at AHI cutoff level of >15 and >30.

Subsequently, a more concise and easy-to-use clinical screening tool for anesthesiologists was developed (Table 1) – the STOP questionnaire

STOP Questionnaire
1. Snoring: Do you snore loudly (loud enough to be heard through closed doors)?
   Yes  No
2. Tired: Do you often feel tired, fatigued, or sleepy during daytime?
   Yes  No
3. Observed: Has anyone observed you stop breathing during your sleep?
   Yes  No
4. Blood pressure: Do you have or are you being treated for high blood pressure?
   Yes  No

High risk of OSA: answering yes to 2 or more questions
Low risk of OSA: answering yes to less than 2 questions

STOP-Bang Scoring Model
1. Snoring: Do you snore loudly (loud enough to be heard through closed doors)?
   Yes  No
2. Tired: Do you often feel tired, fatigued, or sleepy during daytime?
   Yes  No
3. Observed: Has anyone observed you stop breathing during your sleep?
   Yes  No
4. Blood pressure: Do you have or are you being treated for high blood pressure?
   Yes  No
5. BMI: BMI more than 35 kg/m2?
   Yes  No
6. Age: Age over 50 years old?
   Yes  No
7. Neck circumference: Neck circumference greater than 40 cm?
   Yes  No
8. Gender: Male?
   Yes  No

High risk of OSA: answering yes to 3 or more items
Low risk of OSA: answering yes to less than 3 items


Table 1: Obstructive Sleep Apnea Screening Tools

Table 2: Screening Questionnaires for Obstructive Sleep Apnea

Cut-offs of >15 and >30 respectively. The specificity of the STOP-Bang was 43% and 37% respectively.

There was no significant difference in the predictive parameters of the Berlin questionnaire, the ASA check-list, and the STOP questionnaire. All the questionnaires demonstrated a moderately high level of sensitivity for OSA screening (Table 2). The sensivities of the Berlin questionnaire, the ASA checklist, and STOP questionnaire were similar, 69-87%, 72-87%, and 66-80% at different AHI cutoffs.

A recent meta-analysis of clinical screening tests for OSA identified 26 different clinical prediction tests with 8 in the form of questionnaires, and 18 algorithms, regression models or neural networks. As a preoperative screening test, the summary recommendation based on ease of use, false negative rate, and test accuracy stated that the STOP-Bang questionnaire was as a user-friendly and excellent method to predict severe OSA (AHI >30) with a diagnostic odds ratio of 142. The linear scale and the simple acronym make the STOP-Bang practical and easy-to-use in the preoperative setting.

Several other simple screening modalities have been described and may add value to predicting the OSA patient in the preoperative period. The modified Mallampati score assesses the relative tongue size in the oral cavity. A class 3 or 4 modified Mallampati score suggests possible anatomical obstruction and the presence of OSA. Waist circumference of 102
Physician; taking into account the patient-specific correlation between oxygen desaturation index (ODI) from nocturnal oximetry and the AHI from polysomnography, ODI > 5, ODI > 15, and ODI > 30 were sensitive and specific predictors for surgical patients with AHI > 5, AHI > 15, or AHI > 30 respectively. The sensitivity was found to be 75–95% and the specificity 67-97%. Multichannel home sleep testing is another modality which is easy-to-use and may be accurately performed. It improves access and may be an excellent diagnostic tool for OSA.

EVALUATION OF SUSPECTED OSA PATIENTS IN THE PREOPERATIVE CLINIC (FIGURE 1)

A patient is at high risk of OSA if ≥ 2 items score positive on the STOP questionnaire, or ≥ 3 items score positive on the STOP-Bang questionnaire (Table 1). Urgent or emergent surgery should not be delayed for the detailed evaluation of suspected OSA. Based on recent research, expert opinion and the collation of various departmental protocols on OSA, a flow diagram for the suggested preoperative evaluation of a suspected OSA patient is outlined in Figure 1. If the high risk patient is presenting for major elective surgery and has comorbidities suggestive of long-standing severe OSA, the anesthesiologist could consider a preoperative referral to the sleep physician. Subsequently, a formal polysomnography or a multichannel home sleep test may be performed if resources permit. These comorbidities include uncontrolled hypertension, heart failure, arrhythmias, cerebro-vascular disease, morbid obesity and metabolic syndrome. A timely and early consult would be helpful so that the sleep physician may have adequate time to prepare a perioperative management plan, which may include positive airway pressure (PAP) treatment. Major elective surgery may have to be deferred in patients with a suspected OSA patient is outlined in Figure 1.

It has to be noted that the specificity of these screening tests are in the range of 37-53% for severe OSA. Therefore a fairly high false positive rate exists. Ultimately, the decision for further preoperative testing (e.g. polysomnography) should depend on the clinical judgement and expertise of the attending physician; taking into account the patient-specific and logistical considerations in its totality.

On the other hand, there may be patients who are at high risk on the OSA screening questionnaires, but who are otherwise without significant comorbidities. These patients may be scheduled to undergo minor surgery. In addition, some of them may have had uneventful general anesthesia in the past. These at risk patients may represent false positives on screening, or represent patients with mild OSA with AHI < 15. Screening positive on the OSA questionnaires would raise the awareness of the anesthesia healthcare team so that perioperative precautions for possible OSA may be undertaken (Table 3). These patients

<table>
<thead>
<tr>
<th>Phase</th>
<th>Anesthetic Concern</th>
<th>Principles of Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREOPERATIVE PERIOD</td>
<td>Cardiac arrhythmias and unstable hemodynamic profile</td>
<td>Indirect evidence advocating the usefulness of PAP to reduce cardiac arrhythmias, stabilize variable blood pressure, and decrease myocardial oxygen consumption.</td>
</tr>
<tr>
<td></td>
<td>Multisystemic comorbidities</td>
<td>Preoperative risk stratification and patient optimization. Individualized intraoperative anesthetic management tailored to comorbidities.</td>
</tr>
<tr>
<td></td>
<td>Sedative premedication</td>
<td>Alpha-2 adrenergic agonist (clonidine, dexmedetomidine) premedication may reduce intraoperative anesthetic requirements and have an opioid-sparing effect.</td>
</tr>
<tr>
<td></td>
<td>OSA risk stratification, evaluation and optimization</td>
<td>Preoperative anesthesia consults for symptom evaluation, airway assessment, polysomnography if indicated, and formulation of anesthesia management.</td>
</tr>
<tr>
<td>INTRAOPERATIVE PERIOD</td>
<td>Difficult intubation (8X more prevalent)</td>
<td>“Sniffing” position. Ramp from scapula to head. Adequate preoxygenation. ASA Difficult Airway Algorithm.</td>
</tr>
<tr>
<td></td>
<td>Opioid-related respiratory depression</td>
<td>Opioid avoidance or minimization. Use of short-acting agents. Regional and multimodal analgesia (NSAIDs, acetaminophen, tramadol, ketamine, gabapentin, pregabalin, dexamethasone).</td>
</tr>
<tr>
<td></td>
<td>Carry-over sedation effects from longer-acting intravenous sedatives and inhaled anesthetic agents</td>
<td>Use of propofol for maintenance of anesthesia. Use of insoluble potent anesthetic agents (desflurane).</td>
</tr>
<tr>
<td></td>
<td>Excessive sedation in monitored anesthetic care</td>
<td>Use of capnography for intraoperative monitoring.</td>
</tr>
<tr>
<td>REVERSAL OF ANESTHESIA</td>
<td>Post-extubation airway obstruction and desaturations</td>
<td>Verification of full reversal of neuromuscular blockade. Ensure patient fully conscious and cooperative prior to extubation. Semi-upright posture for recovery.</td>
</tr>
<tr>
<td>IMMEDIATE POSTERATIVE PERIOD</td>
<td>Suitability for day-case surgery</td>
<td>Lithotripsy, superficial or minor orthopedic surgeries using local or regional techniques may be considered for day surgery. No requirement for high dose postoperative opioids. Transfer arrangement to inpatient facility should be available.</td>
</tr>
<tr>
<td></td>
<td>Postoperative respiratory event in known and suspected high risk OSA patients</td>
<td>Longer monitoring in the PACU. Continuous oximetry monitoring and PAP therapy may be necessary if recurrent PACU respiratory events occur (desaturation, apnea, bradypnea, pain-sedation mismatch).</td>
</tr>
</tbody>
</table>

Table 3: Perioperative Anesthetic Management of the Patient with Obstructive Sleep Apnea

©International Anesthesia Research Society. Unauthorized Use Prohibited.
can be assumed as possibly having mild / moderate OSA. If subsequent intraoperative (difficult airway) or postoperative events (postanesthesia care unit recurrent respiratory events) suggest a higher probability of OSA, a polysomnography and a sleep physician referral after surgery may be indicated. More research needs to be done to define the optimal clinical pathways for these surgical patients with increased OSA risk.

Because of the high sensitivity and negative predictive value of the OSA screening tools, the incidence of false negatives would be low. Therefore patients who are at low risk of OSA (<2 on STOP or <3 on STOP-Bang) would not likely have OSA. These patients may be managed with routine perioperative care (Figure 1).

**EVALUATION OF KNOWN OSA PATIENTS IN THE PREOPERATIVE CLINIC (FIGURE 1)**

In patients who are known to have OSA, the severity of the sleep disorder may be assessed from the patient history or from previous polysomnography.

---

**Figure 1: Flow Chart on Preoperative Evaluation of Known or Suspected Obstructive Sleep Apnea Patient in the Anesthesia Clinic**

- **Suspected OSA patient**
  - Screening using STOP or STOP-Bang questionnaire (30)
  - High risk of OSA (≥2 on STOP, ≥3 STOP-Bang)
  - Comorbidities and Major Elective Surgery
    - Heart failure
    - Arrhythmias
    - Uncontrolled hypertension
    - Cerebrovascular disease,
    - Metabolic syndrome
  - Yes
    - Consider preoperative Sleep Medicine referral.
  - No
    - Assume possibility of moderate OSA. Perioperative OSA precautions.

- **Known OSA patient**
  - Severity Assessment from History or Polysomnography
  - Low risk of OSA (π < 2 on STOP, <3 on STOP-Bang)
  - Routine perioperative management. No preoperative PAP therapy required
  - Mild OSA
    - AHI 5 – 15
    - Oximetry ≥ 94% on room air
  - Moderate or Severe OSA
    - AHI > 15
    - Oximetry < 94% on room air
  - Preoperative PAP therapy¹.
  - Perioperative OSA precautions.

---

# Recurrent PACU Respiratory Event - any event occurring more than once in each 30-min evaluation period (not necessary to be the same event) (68).

† Monitored bed - environment with continuous oximetry and the possibility of early nursing intervention (e.g. step-down unit, general surgical ward near nursing station, or remote pulse oximetry with telemetry in surgical ward).

¹ Perioperative OSA precautions include - anticipating possible difficult airway, use of short-acting anesthetic agents, opioid avoidance, verify full neuromuscular block reversal, and extubation in a non-supine position.

¹ PAP therapy – continuous PAP, bilevel PAP, or auto-titrating PAP.
results. Long-standing OSA may have systemic complications, which should be ascertained. These include hypoxemia, hypercarbia, polycythemia, and cor pulmonale. A simple screening tool in the preoperative clinic may be the pulse oximetry. In our opinion, an oxygen saturation value of < 94% on room air in the absence of other causes should be a red flag for severe long-standing OSA. The presence of comorbidities such as uncontrolled hypertension, arrhythmias, cerebro-vascular disease, heart failure, metabolic syndrome, and obesity should be determined. The use of continuous positive airway pressure or other PAP devices and the compliance to PAP therapy should be assessed for the subgroup of patients who have been prescribed with PAP therapy.

Patients with a known diagnosis of OSA, who have been lost to sleep medicine follow up, have had recent exacerbation of OSA symptoms, have undergone OSA-related airway surgery, or have been non-compliant with PAP treatment, may have to be referred to the sleep physician for reassessment preoperatively. Due consideration should be given for the re-initiation of preoperative PAP in the non-compliant patient, although evidence is lacking in this preoperative context.

Patients with moderate and severe OSA who have been on PAP therapy should continue PAP therapy in the preoperative period. Perioperative OSA precautions should be taken (Table 3). Some of these measures would include anticipating possible difficult airways, the use of short-acting anesthetic agents, opioid-avoidance or minimization if possible, full reversal prior to endotracheal extubation, and extubation in a non-supine position. It is unclear from the current literature if mild OSA (AHI > 5 – 15) is a significant disease entity. In our opinion, patients with mild OSA would not require preoperative PAP therapy. Mild OSA patients, without respiratory events in the postanesthesia care unit (PACU), may be managed with routine perioperative care.

For all patients with known OSA, there should also be a focus on airway assessment, Mallampati scoring, and formulation of a perioperative management plan. Patient-specific comorbidities should be assessed and optimized. The anesthesiologist should engage the patient to explore the various anesthetics options and discuss patient-specific risks pertaining to OSA. Sedative premedication should be avoided.

PREOPERATIVE POSITIVE AIRWAY PRESSURE THERAPY

Conventional PAP therapy acts as an airway stent and is the primary treatment for patients with OSA. There are several kinds of PAP devices: continuous positive airway pressure, auto-titrating positive airway pressure, and bi-level positive airway pressure. PAP therapy has been shown to alleviate undesirable symptoms of OSA. PAP has the potential of reducing cardiac rhythm abnormalities, stabilizing variability of blood pressure, and improving the hemodynamic profile. One week of PAP treatment has been shown to improve pharyngeal collapsibility and increase pharyngeal cross-sectional area. In an 18-year follow-up cohort study, PAP was found to be protective against cardiovascular death and improved survival.

However, high level of evidence is lacking in the perioperative context. It is still unclear if the use of PAP therapy will reduce adverse events attributed to OSA in rigorous randomized controlled trials. Only one study of 53 severe OSA patients undergoing uvulopalatopharyngoplasty with preoperative PAP therapy showed reduction in the surgical risk and perioperative complications.

Taking into account the low level of invasiveness of PAP therapy, its short-term use immediately preoperatively may be considered, particularly in patients with severe OSA. Based on consensus opinion, patients already on treatment with PAP should be advised to continue the treatment perioperatively, and to bring the PAP device to the hospital on admission. Further research in this area is warranted.

Anesthesiologists should be aware that asymptomatic patients might not easily accept PAP therapy. Appropriate timing for surgery should be a joint decision made by the anesthesiologist, the surgeon, and the patient, weighing the risks of delaying the surgery and the benefits of preoperative OSA investigation and PAP treatment.

OSA AND DIFFICULT AIRWAYS

Upper airway abnormalities, which predispose to OSA, share a similar etiological pathway with difficult airways - mask ventilation and tracheal intubation. Snoring and OSA were found to be independent risk factors for difficult or impossible mask ventilation. In a retrospective matched case-control study of 253 patients, difficult intubations was found to occur 8 times as often in the OSA patient versus the control group (21.9% versus 2.6%, p < 0.05). OSA therefore is a risk factor for difficult endotracheal intubation. In another study of more than 1500 patients, OSA, but not the magnitude of the body mass index, was associated with a higher incidence of difficult laryngoscopy. In patients undergoing uvulopalatopharyngoplasty, an AHI greater than 40 was a predictor for difficult intubation.

In support of the strong association between OSA and a difficult airway, the corollary is also true that patients with difficult intubations have a higher risk of being diagnosed with OSA. In a prospective study looking at the correlation between OSA and difficult intubations, we found that 66% of patients with unexpected difficult intubation were later diagnosed with OSA by polysomnography. Patients with difficult intubation are at high risk for OSA and should be screened for signs and symptoms of sleep apnea and may have to be referred for sleep studies.
There are several clinical features that the anesthesiologist associates with difficult intubations, which are likewise linked with the propensity for obstruction in the unsupported upper airway during sleep and anesthesia. These include obesity, increased neck circumference, limited neck extension, nasal obstruction, a crowded oropharynx (including decreased pharyngeal width, a high Mallampati score, decreased retrolingual airway size, an enlarged tongue or tonsils), dental abnormalities, limited mouth opening, hypoplasia of the maxilla or mandible, decreased thyromental distance, and increased mandibular angle. A detailed airway assessment should be performed in the preoperative clinic in anticipation of possible difficult airways.

A variety of airway adjuncts and skilled anesthesia assistance should be made available in advance for dealing with the possible difficult airway. ASA practice guidelines for the management of the difficult airway may be used as a roadmap to assist the anesthesiologist.

**PLANNING FOR LOCAL, REGIONAL OR GENERAL ANESTHESIA**

The use of local and regional blocks (neuroaxial or peripheral nerve blocks) as a sole anesthetic without sedation may potentially be beneficial to the OSA patient as it circumvents the issue of upper airway patency in the perioperative period. Based on expert opinion and consensus by consultants, ASA guidelines recommend regional anesthesia rather than general anesthesia for peripheral surgery. The ASA guidelines however remain equivocal on regarding whether combined regional and general anesthetics techniques are useful.

**PLANNING FOR POSTOPERATIVE ANALGESIA**

Optimal intraoperative management encompasses knowledge of the problems associated with OSA, and taking measures to minimize the aggravating effects of anesthesia. OSA patients are sensitive to the respiratory depressant effects of anesthetic drugs, in particular opioid analgesic agents. This is largely due to the propensity of airway collapse, sleep deprivation, and blunting of the physiological response to hypercarbia and hypoxia. Therefore avoidance or minimization of the use of longer acting anesthetic drugs should be recommended.

The dangers of opioid use in patients with evidence of a compromised upper airway have been highlighted in several case reports. The use of morphine in OSA patients has been associated with severe respiratory depression and even death. Postoperative oxygen desaturations were 12-14 times more likely to occur in OSA patients receiving oral or parenteral opioids after surgery versus non-opioid analgesic agents.

A multimodal approach for analgesia is therefore advocated, where a combination of analgesics from different classes is used. Medications such as nonsteroidal anti-inflammatory drugs, acetaminophen, tramadol, ketamine, gabapentin, pregabalin, clonidine, and dexamethasone are used to alleviate the opioid-related adverse effects of respiratory depression in susceptible OSA patients. Dexmedetomidine, has been purported in several case reports as having beneficial effects in patients with OSA because of the lack of respiratory depression and opioid-sparing effects in the perioperative period.

The postoperative use of nerve block catheters or epidural catheters with local anesthetics obviates the need for systemic opioid analgesics. This potentially reduces the risk of sedation and upper airway obstruction. However, this is not the case if neuroaxial opioids are administered. The occurrence of sudden postoperative respiratory arrests from epidural opioids has been reported in a case series of three OSA patients. Likewise, if postoperative systemic strong opioid analgesics are administered after a regional anesthetic, the OSA patient will be at increased risk for respiratory complications.

**PLANNING FOR AMBULATORY SURGERY**

Controversy exists as to whether OSA patients should be done on an ambulatory basis. ASA guidelines highlighted that superficial surgeries or minor orthopedic surgery using local or regional techniques, and lithotripsy may be done on an ambulatory basis. Considerations would include the types of surgeries, the comorbidities, patient age, status (treat versus untreated) and severity of OSA, use of postoperative opioids, type of anesthesia, and the level of home care.

Based on expert opinion, in the absence of moderate to severe OSA, recurrent postanesthesia care unit respiratory events (apnea, bradypnea, desaturation), and the need for strong postoperative opioids for analgesia, patients may be discharged home at the discretion of the attending anesthesiologist (Figure 2). Ambulatory surgical facilities managing OSA patients should have transfer arrangements to an inpatient facility, and be equipped to handle the problems (e.g. difficult airway, postoperative respiratory depression) associated with the OSA patient.

**PLANNING FOR IN-PATIENT SURGERY (FIGURE 2)**

Depending on the severity of the OSA, the extent of the surgery, and the type of anesthetics administered, and postoperative analgesics required, the patient may shift to the higher end of the risk continuum, increasing the need for step-down care. The anesthesiologist should ensure that a postoperative monitored bed is available for a patient with a high AHI, undergoing major surgery or airway surgery. A monitored bed refers to an environment with continuous oximetry with the possibility of
early nursing intervention (e.g. step-down unit, or general surgical ward near the nursing station, or remote continuous oximetry with telemetry).

After general anesthesia, we recommend that all known OSA patients or suspected OSA patients (positive on screening with STOP or STOP-Bang) should be observed in postanesthesia care unit with continuous pulse oximetry for a longer period than a patient without OSA.

Very often, the decision of whether the patient requires postoperative in-patient monitoring is dependent on the judgement and discretion of the attending anesthesiologist. Based on expert opinion and a collation of various departmental protocols on OSA, we suggest a simple algorithm in Figure 2 to guide the anesthesiologist in making the decision regarding the postoperative disposition of the OSA patient. For all known OSA patients or suspected OSA

* Perioperative OSA precautions include - anticipating possible difficult airway, use of short-acting anesthetic agents, opioid avoidance, verify full neuromuscular block reversal, and extubation in a non-supine position.
† PAP therapy = continuous PAP, bilevel PAP, or auto-titrating PAP.
patients (≥2 criteria on STOP, or ≥3 criteria on STOP-Bang) who have undergone general anesthesia, we propose an extended PACU observation of at least a 30-60 minute period of time in an unstimulated environment after the patients has met the modified Aldrete criteria for discharge.

To determine whether the known OSA patient or suspected OSA patient requires continuous postoperative monitoring, observation of recurrent PACU respiratory events can be used as a second phase approach to guide further management. A single PACU respiratory event occurs when a patient has apnea for ≥ 10 s (1 episode needed for yes), bradypnoea of < 8 breaths per minute (3 episodes needed for yes), pain-sedation mismatch, or desaturation to < 90% with nasal cannula (3 episodes needed for yes). Recurrent PACU respiratory events occur when any one of the PACU respiratory events occurs in two separate 30 minute time blocks (not necessary to be the same event).51

Patients who are at high risk of OSA on the screening questionnaires, and have recurrent PACU respiratory events are associated with higher postoperative respiratory complication.51 It may be prudent to place these patients in a monitored bed postoperatively. Depending on the degree of desaturation, these patients may also require postoperative PAP therapy (Figure 2).

Known OSA patients who have been non-compliant with PAP therapy or have severe OSA (AHI > 30) may have to be fitted with postoperative PAP therapy and cared for in a monitored environment with oximetry, especially if there has been a recurrent PACU respiratory event (Figure 2). Moderate OSA patients (AHI 16-30) requiring postoperative parenteral opioids or higher dose oral opioids (> codeine 60 mg every 4 hourly or equivalent), and without recurrent PACU respiratory events can be managed postoperatively on the surgical ward with continued periodical monitoring (Figure 2). It may also be expedient to place patients requiring postoperative parenteral opioids on supplemental oxygen.52 Mild OSA patients who have undergone minor surgery, without recurrent PACU respiratory events, and without the need for higher dose of oral opioids, may be discharged home (Figure 2).

Newer remote pulse oximetry monitoring devices enable data from a bedside monitor to be continuously streamed wirelessly to a central observation station (e.g. Oxinet® III telemetry, Nellcor, Colorado, USA) or paging system. This technology may be useful in the context of postoperative monitoring of OSA patients. Studies are however lacking in this area. This technology potentially allows OSA patients to be cared for postoperatively in the surgical ward instead of the step-down unit, thus lessening care-giver burden.

Recently our research found that OSA patients have more profound increases in AHI after surgery, with a peak on night 3 and returned to preoperative level only on night 7.51 Therefore monitoring the OSA patient overnight may not safeguard against all respiratory event in the first postoperative week. Further research on the postoperative management of OSA patients is essential.

CONCLUSION

The OSA patient poses special challenges to the anesthesiologist in the perioperative period. Preoperative evaluation through vigilant screening and formulation of an anesthesia management plan may ameliorate the perioperative morbidity associated with OSA patients.

REFERENCES:


41. Lofsky A. Sleep apnea and narcotic postoperative pain medication: a morbidity and mortality risk. APSF Newsletter 2002;17:24-5.


Does fluid restriction improve outcomes of surgical patients?

Tong J Gan, MD, FRCA, MHS
Department of Anesthesiology,
Duke University Medical Center,
North Carolina, USA

INTRODUCTION
Perioperative fluid management has been a topic of much debate over the years and has intensified especially over the past several years. The controversies include the type of fluid, the timing of administration and the volume administered. Following much discussions and ongoing controversy on colloids versus crystalloids (1-4) and the ideal composition of the various intravenous solutions (5-7), the main focus more recently has been on the volume of fluids. Over a decade of clinical studies demonstrating the benefits of goal directed fluid therapy (GDT), more recent studies have shown improved postoperative outcomes with a restricted fluid administration in the perioperative period.

FLUID COMPARTMENT PHYSIOLOGY
Total body water for a 75 kg individual is around 45 liters. Two-thirds of this (30 liters) is intracellular water. The remaining third (15 liters) in the extracellular compartment is divided between the intravascular (3 liters) and extravascular (12 liters) compartments. The total intravascular volume (or blood volume) is around 5 liters and has intracellular (red and white cells, platelets make up 40% or 2 liters) and extracellular (plasma makes up 60% or 3 liters) components. Plasma is a solution in water of inorganic ions (predominantly sodium chloride), simple molecules such as urea and larger organic molecules such as albumin and the globulins (Figure 1).

It is important to note that the extracellular deficit after usual fasting is low.(9) The basal fluid loss via insensible perspiration is approximately 0.5 to 1 mL/kg/h during major abdominal surgery.(10) It has been demonstrated that a primarily fluid-consuming third space does not exist. (11) Plasma losses out of the circulation have to be replaced with iso-oncotic colloids, assuming the vascular barrier to be primarily intact and acknowledging that colloidal volume effects are context sensitive. There also should be a timely replacement of visible blood losses, and supplemented by additional fluid guided by hemodynamic variables.

“RESTRICTED” VERSUS “LIBERAL” FLUID ADMINISTRATION STRATEGY
More recently, clinical trials in the surgical literature have advocated a “restricted” fluid administration strategy in the perioperative period and demonstrated its advantages in improvement in postoperative outcomes over a more “liberal” strategy.

Nisenavich et al. (12) prospectively evaluated in 152 patients undergoing elective intraabdominal surgery. Patients were randomized to receive intraoperatively either with a bolus of 10 mL/kg followed by 12 mL/kg/h of lactated Ringer’s solution (liberal protocol group) or a continuous 4 mL/kg/h of the same solution with no bolus (restrictive protocol group). The primary endpoint was the number of patients who died or experienced complications. The secondary endpoints included time to initial passage of flatus and feces, duration of hospital stay, and changes in body weight, hematocrit, and albumin serum concentration in the first 3 postoperative days. The amount of fluid the patients received were 3,670 mL (1,880–8,800) and 1,230 mL (490–7,810) (mean [range]) in the liberal and restrictive groups, respectively.

The authors found a lower complication rate in patients in the restrictive protocol group (RGP). The liberal group (LPG) passed flatus and feces significantly later (flatus, median [range]: 4 [3–7] days in the LPG vs. 3 [2–7] days in the RPG; P < 0.001; feces: 6 [4 –9] days in the LPG vs. 4 [3–9] days in the RPG; P < 0.001), and their postoperative hospital stay was significantly longer (9 [7–24] days in the LPG vs. 8 [6 –21] days in the RPG; P < 0.01). Significantly larger increases in body weight were observed in the LPG compared with the RPG (P < 0.01). They concluded that patients undergoing elective intraabdominal surgery, intraoperative use of restrictive fluid management was associated with a reduction in postoperative morbidity and shortens hospital stay.

Bandstrup et al (13) investigated restricted fluid regimen versus standard regimen in patients undergoing colorectal surgery. All patients received an epidural for postoperative analgesia in addition to a general anesthetic. As for fluid management regimen, the restricted group did not receive fluid preloading prior to epidural placement or replacement of “third space” loss. Blood loss was replaced with equal volume of 6% hydroxyethyl starch with replacement of red blood cell based on hematocrit. In the standard regimen, fluid administration was similar to the restricted group. In addition, 500 mL of 6% hetastarch was administered before placement of the epidural and normal saline in a range of 3-7 mL/kg/h was delivered during the intraoperative period.

The restricted group had a significantly reduced postoperative complications (33% versus 51%, P<0.05). The numbers of both cardiopulmonary (7% versus 24%, P < 0.007) and tissue-healing...
complications (16% versus 31%, P < 0.04) were also significantly reduced. No patients died in the restricted group compared with 4 deaths in the standard group (0% versus 4.7%, P < 0.12).

Interestingly, there was significant weight gain in patients in the standard fluid regimen group. Patients in this group received more than 3 L of normal saline on the day of surgery compared to the restricted regimen group. It is unclear if the increased in complication rate was attributed to the larger volume of crystalloid (predominantly saline) or due to the unbalanced nature of the fluid.

In contrast, other studies have shown better outcomes when a liberal fluid administration regimen were adopted. In a double-blind study, Holte et al (14) investigated 48 relatively healthy patients undergoing laparoscopic cholecystectomy. They were randomized to 15 mL/kg (restricted group) or 40 mL/kg (liberal group) intraoperative administration of lactated Ringer's solution.

Intraoperative administration of 40 mL/kg compared with 15 mL/kg LR led to significant improvements in postoperative pulmonary function and exercise capacity and a reduced stress response as measure by a lower aldosterone, anti-diuretic hormone, and angiotensin II.

Nausea, general well-being, thirst, dizziness, drowsiness, fatigue, and balance function were also significantly improved, as well as significantly more patients fulfilled discharge criteria and were discharged on the day of surgery with the high-volume fluid substitution. The volume administered in the 15 mL/kg group vs. 40 mL/kg group were 997.5 (721.5–1455.0) and 2928 (1950–3920) (mean[range]), respectively. The authors concluded that a more liberal intraoperative fluid administration compared with a restricted one improves postoperative organ functions and recovery and shortens hospital stay after laparoscopic cholecystectomy.

In a follow up study, the same group of investigators randomized 32 patients undergoing elective colonic surgery to restrictive or liberal perioperative fluid administration. (15) Fluid algorithms were based on fixed rates of crystalloid infusions and a standardized volume of colloid. Pulmonary function measured by spirometry was the primary outcome measure, with secondary outcomes of exercise capacity (submaximal exercise test), orthostatic tolerance, cardiovascular hormonal responses, postoperative ileus (transit of radio-opaque markers), postoperative nocturnal hypoxemia, and overall recovery within a well-defined multimodal, fast-track recovery program. Hospital stay and complications were also noted.

The volumes of fluid administered were (median 1640 mL, range 935–2250 mL) and (median 5050 mL, range 3563–8050 mL) in the restrictive and liberal groups, respectively. The liberal group was associated with a significant improvement in pulmonary function and postoperative hypoxemia, with lower concentrations of cardiovascularly active hormones such as renin, aldosterone, and angiotensin II. Although the average length of hospital stay was not significantly different between the groups, total hospital stay including readmission was significantly longer in the restrictive group compared with the liberal group [4 (2–39) vs. 2.5 (2–9) days], median (range); P<0.03. Six patients developed a total of 18 complications in restrictive group compared with one patient in the liberal group. The authors advocated that goal-directed fluid therapy strategies should be individualized rather than a fixed fluid amounts.

MECHANISMS UNDERLYING OPTIMAL FLUID ADMINISTRATION

Both ‘dry’ and ‘wet’ strategies can both lead to postoperative complications and morbidity. A fluid replacement regimen that is conservative has the potential for a decrease in cardiac output and in perfusion to the splanchnic bed. This can lead to intestinal acidosis, postoperative ileus, and the translocation of bacteria and endotoxin into the vascular system, potentially causing sepsis or multiple system organ failure.

Conversely, the use of a liberal or ‘wet’ approach to fluid replacement especially when crystalloid is used can increase bowel edema, weight gain, decrease the tolerance for enteral feeding and increase the incidence of postoperative ileus. The liberal administration of fluid is also known to increase the venous pressure in the intestines (secondary to the edema) and therefore cause a decrease in splanchnic oxygenation by reducing the perfusion pressure. This can also lead to the transmigration of bacteria and endotoxin into the circulation.

It appears that more mechanistic studies in animal models are warranted to explain the observed discrepancies in the fluid administration strategies and clinical outcomes. Kimberger et al(16), in a recent study compares the effects of goal-directed colloid fluid therapy with goal-directed crystalloid and restricted crystalloid fluid therapy on healthy perianastomotic colon tissue in a pig model of colon anastomosis surgery. The animals were randomized to one of the following treatments: GDT-colloid group, GDT-crystalloid group and a restrictive group. Boluses consisting of 250 mL of hydroxyethyl starch were administered to target a mixed venous oxygen saturation at or above 60%. Intestinal tissue oxygen tension and microcirculatory blood flow were measured continuously. The tissue oxygen tension in healthy colon increased to 150 ± 31% from baseline in the GDT-Colloid group versus 123 ± 40% in the GDT-crystalloid group versus 94 ± 23% in Restrictive group, mean ± SD; P < 0.01). Similarly perianastomotic tissue oxygen tension and microcirculatory blood flow increased in a similar manner.
There are many perioperative goal directed fluid therapy trials that demonstrated an improvement in outcomes from recovery of gastrointestinal functions to a reduction in hospital length of stay.(17-25) Giglio et al(26) recently performed a systematic analysis of 16 randomized controlled trials (>3000 subjects) with a focus on gastrointestinal outcome. They noted a significant reduction in major GI complications in the GDT group when compared with a control group (OR, 0.42; 95% CI, 0.27–0.65). Minor GI complications were also significantly decreased in the GDT group (OR, 0.29; 95% CI, 0.17–0.50).

CONCLUSIONS
Replacing fluid loss in the operating room should not follow a cookbook approach, but rather should be targeted to specific endpoints. Using heart rate, blood pressure and urine output might not be adequate monitor of end organ perfusion. Continuous monitoring of flow-based hemodynamics e.g. stroke volume and cardiac output may help in more optimal perioperative fluid management. The use of the terms liberal/wet or restrictive/dry fluid administration strategies do not precisely define the optimal volume of fluid needed, and it can add to confusion. The use of individualized goal directed therapy in surgical patients allows the clinician to target specific hemodynamic and tissue perfusion endpoints that will more likely improve patient outcome.

REFERENCES
What’s New in Critical Care Medicine?

Robert N. Sladen, MD
Professor and Executive Vice-Chair, and Chief, Division of Critical Care
Department of Anesthesiology
College of Physicians & Surgeons of Columbia University
New York, NY

Learner Objectives:
• Update on management of vasodilatory shock, including vasopressin, selective vasopressin analogs, methylene blue;
• Update on management of acute lung injury, including new approaches to mechanical ventilation, HFO and ECMO;
• Update on renal protection, including new biomarkers and the evidence basis for pharmacologic interventions;
• Update on palliative care, and its role in the intensive care unit.

VASODILATORY SHOCK AND VASOPRESSOR THERAPY
Vasopressin and its Analogues
Arginine vasopressin (AVP) is a nonapeptide produced in the paraventricular and supraoptic nuclei of hypothalamus as a prohormone, cleaved to AVP and stored in secretory vesicles in the posterior pituitary. AVP has a plasma half-life of 6-20 min and is rapidly metabolized by vasopressinases in the liver and kidney. Vasopressin receptors, sites of action and actions are summarized in Table 1.

Increased serum osmolality (> 1%), generates plasma AVP levels of 1-5 pg/mL that act on V2 receptors, inducing an antidiuresis. Severe hypotension generates plasma AVP levels of 10-100 pg/mL that act on V1 (formerly called V1a) receptors, inducing peripheral vasoconstriction as a component of the baroreflex response. Activation of V3 (V1b) receptors induces ACTH and insulin release and may reflect the relationship between AVP and glucocorticoid metabolism (see below). At high levels, AVP may activate purinergic (P2) receptors in the cardiac endothelium, inducing coronary vasoconstriction. Oxytocin is a nonapeptide that differs from AVP by only two amino acids, yet its actions are very different (uterine contraction, milk let-down) and there is little cross-reactivity.

Pathogenesis of vasodilatory shock:
Vasodilatory shock has multiple pathways for induction. Contact activation with any foreign surface, e.g. cardiopulmonary bypass (CPB), ECMO, ventricular assist device (VAD) triggers Hagemann (Factor XII) activation and simultaneously activates the intrinsic pathway of coagulation, fibrinolysis and the complement system. Severe sepsis or systemic inflammatory response syndrome (SIRS) cause massive activation of inducible nitric oxide synthase (iNOS) and release of endogenous nitric oxide (NO). Protracted intracellular acidosis opens potassium-dependent ATP (KATP) channels in cell membranes, which allows potassium egress and hyperpolarization of the cell membrane, inactivating calcium channels and inhibiting the vasoconstrictor response to catecholamines such as norepinephrine (NE) or epinephrine, a syndrome known as vasoplegia. There is considerable evidence that in protracted shock, there is depletion of endogenous AVP from posterior pituitary, so that plasma AVP declines to < 3 pg/mL.

Actions, benefits and limitations of AVP infusion in vasodilatory shock:
Low dose AVP infusion (1-4 u/hr, or 0.015-0.067 u/min) has a number of potentially beneficial effects in vasodilatory shock. AVP appears to inhibit activation of inducible nitric oxide. It binds to and closes KATP channels, restores membrane polarity and the vasoconstrictor response to catecholamines. Depleted endogenous AVP levels are restored: infusion of 1-4 u/hr achieves plasma AVP levels of 20-30 pg/mL.

These actions consistently result in increased blood pressure and decreased catecholamine requirement. Diminution of high-dose NE decreases pulmonary vascular resistance (PVR) and cardiac arrhythmias. Compared to NE, AVP preferentially induces efferent arteriolar constriction and thereby may enhance glomerular filtration rate (GFR) and renal function.

The 2008 Surviving Sepsis Campaign recommends that AVP infusion (0.03 u/min) may be added to NE (still recommended for initial therapy) if the mean arterial pressure (MAP) cannot be maintained above 65 mmHg. Infusion of AVP must always be via a central line because extravasation may cause intense cutaneous vasoconstriction and injury. At excessive doses (> 6 u/hr) especially in low flow states, AVP infusion may cause acral cyanosis and cutaneous necrosis, and at higher doses still it promotes mesenteric vasoconstriction (thus its erstwhile use in variceal bleeding), hepatic dysfunction and even coronary vasoconstriction.

Table 1: Receptors, Sites of Action and Actions of Endogenous Vasopressin (AVP)1

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Site of Action</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1 (V1a)</td>
<td>vascular smooth muscle</td>
<td>vasoconstriction</td>
</tr>
<tr>
<td>V2</td>
<td>collecting duct of nephron</td>
<td>antidiuresis</td>
</tr>
<tr>
<td>V3 (V1b)</td>
<td>anterior pituitary, pancreas</td>
<td>ACTH, insulin release</td>
</tr>
</tbody>
</table>

1 Oxytocin is a nonapeptide that differs from AVP by only two amino acids, yet its actions are very different (uterine contraction, milk let-down) and there is little cross-reactivity.
Evidence basis for use of AVP and its analogues in vasodilatory shock

The most definitive randomized controlled study (RCT) performed on AVP thus far is the Vasopressin and Septic Shock Trial (VASST). It was designed to test the hypothesis that low-dose AVP infusion (0.01-0.03 u/min or 0.6-1.8 u/hr) would decrease 28-day mortality among patients with septic shock who were being treated with NE 5-15mcg/min. In the 778 patients studied, there was no significant difference in mortality between the AVP and NE (35.4% vs. 39.3%). However, in patients with less severe septic shock (prospectively defined as requiring NE 5-14 mcg/min), there was a significant improvement in mortality with AVP over NE (26.5% vs. 35.7%, p < 0.05). It is possible that the lack of benefit in more severe septic shock (NE > 14 mcg/min) was due to an inadequate dose of AVP or late intervention.

Role of corticosteroids in vasodilatory shock

An retrospective analysis of the VASST study by its authors demonstrated that the concomitant administration of corticosteroids with AVP significantly decreased mortality (35.9% vs. 44.7%, p = 0.03), and increased plasma AVP levels by one to two thirds. This further implicates the relationship between AVP and steroid metabolism, considering that V3 receptor activation increases ACTH release and cortisol levels. It also warrants future prospective studies.

Indeed, the role of steroids in septic shock remains in flux. The use of ACTH-stimulation tests to evoke adrenal hyporesponsiveness as an indication for hydrocortisone therapy has been discredited by subsequent equivocal outcomes, intra-study use of etomidate (which impairs cortisol synthesis), and the observation that these studies were based upon total rather than free cortisol levels. The 2008 Surviving Sepsis Campaign recommends the administration of hydrocortisone (≤ 300 mg/day) when hypotension responds poorly to adequate fluid resuscitation and vasopressors, and that it should be weaned once vasopressors are no longer required.

Terlipressin

Terlipressin (tricyl-lysine vasopressin) is an AVP analogue used in Europe but not currently available in the US or Canada. It is twice as potent at the V1 receptor than AVP, but has a much more prolonged half-life (4-6 hr), which makes it more difficult to titrate. A small European RCT (TERLIVAP) compared continuous infusion of AVP (0.03 u/min) and terlipressin (1.3 mcg/kg/hr) with NE (15 mcg/min) as first-line therapy in septic shock in 45 patients. Terlipressin appeared superior to AVP in decreasing NE requirements, with lower bilirubin levels and less rebound hypotension, but had a greater effect in lowering platelet count.

METHYLENE BLUE

Actions of methylene blue

Methylene blue appears to inhibit guanylate cyclase, the enzyme that catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), which mediates the vasodilator effect of NO. It may also cause selective inhibition of iNOS.

Evidence basis for use of methylene blue in vasodilatory shock

Anecdotal observations of the benefits of methylene blue (MB) in severe vasodilatory shock have been made for many years. Dosing has ranged between 1-4 mg/kg given as a single dose infused over 30 min to 4 hrs. MB increases MAP and cardiac index (CI). The latter may be due to increase preload secondary to venoconstriction, or a decrease in the impact of high levels of NO, which is a myocardial depressant that impedes the inotropic effect of catecholamines. Arterial lactate decreases, but this may be in part from its effect as a reducing agent. However, PVR also increases and arterial oxygenation may decrease. Although decreases in endogenous production of NO, interleukins and tumor necrosis factor (TNF) have not been noted, urinary excretion of NO metabolites is substantially lower. Attenuation of the urinary excretion of renal tubular injury markers has also been noted.

Most recently a small dose-ranging RCT on 15 patients evaluated MB at 1mg/kg, 3mg/kg or 7mg/kg over 20 min. The authors noted a dose-dependent enhancement of hemodynamic function even at the lowest dose, but cautioned that high doses of MB may compromise splanchnic perfusion. We have observed occasionally dramatic responses to MB 2 mg/kg administered over 30 min in severe vasoplegia. However, because of its potential to increase PVR, in our practice we restrict its use to patients who are already receiving inhaled NO.

MANAGEMENT OF ACUTE LUNG INJURY

Protective Lung Ventilation

During mechanical ventilation, progressive lung parenchymal injury (ventilator-induced lung injury or VILI) is induced by excessive alveolar distension (large tidal volumes) alternating with collapse (low or inadequate PEEP). The primary mechanism for VILI appears to be surfactant depletion with loss of its barrier function, and a subsequent cytokine-induced inflammatory response.

The compliance, or pressure–volume (PV) curve of the lung is sigmoid-shaped, with a lower and upper inflection point. Between the inflection points, alveoli have the best compliance and a small pressure increase results in large volume increase. Below the lower inflection point, the alveoli are collapsed, and above the upper inflection point, excessively distended. In both regions the alveoli are “stiff”, i.e. a large pressure increase results in minimal volume
increase. Protective lung ventilation implies alveolar ventilation between the lower and upper inflection points, i.e., relatively small tidal volumes with moderate PEEP.  

This concept was supported by evidence from the first ARDSNet trial that demonstrated a significant mortality benefit (31.0% vs. 39.8%, p < 0.007) with the use of low tidal volume (6 mL/kg) plateau pressure (<30 cmH2O) versus high tidal volume (12 mL/kg) and plateau pressure <50 cm H2O). This approach has since become the paradigm for protective lung strategy.

**THE OPEN LUNG CONCEPT**

**Physiologic basis**

However, low tidal volumes are not very effective in recruiting collapsed alveoli. The open lung concept is based on achieving an ideally inflated lung, by opening up collapsed alveoli with an initial sustained recruitment maneuver that overcomes a critical opening pressure, then followed by high levels of PEEP with low tidal volumes. Of note, studies comparing lower vs. higher levels of PEEP alone have not demonstrated an outcome difference. The goal is to sustain ventilation between the lower and upper inflection points of the lung pressure–volume curve, minimize airway pressures during inflation and avoid alveolar collapse during deflation. When all alveoli are equally expanded, oxygenation is maximized and shear force (and potential for VILI) is minimized.

**Evidence basis**

There are only limited data available on open lung ventilation in patients. The most widely quoted study is that reported in 1998 by Amato et al., who performed an RCT on 53 patients with early ARDS comparing protective and conventional lung ventilation. Their strategy included a recruitment maneuver (35–40 cmH2O for 40 sec), PEEP above the lower inflection point of static PV curve, a tidal volume of < 6 ml/kg, peak pressures <20 cmH2O above PEEP and permissive hypercapnia. 28-day mortality was 38% vs. 71%, ventilatory weaning more successful (66% vs. 29%), and barotrauma much less common (7% vs. 42%).

Using computed tomography (CT) studies,Gattinoni found that peak airway pressures of 45 cm H2O recruited anything from 0% to 50% of atelectatic lung, and that about 25% was not recruitable. The “potentially recruitable lung” was inversely proportional to the severity of ARDS. However, it has been suggested that total alveolar recruitment might have required higher airway pressures. Subsequently, the Amato group demonstrated that recruitment pressures of up to 60 cmH2O could permanently reverse hypoxia and collapse in the majority of patients with early ARDS.

Peter Papadakos in Rochester, NY, has been a strong advocate of the use of pressure controlled inverse ratio ventilation (PC-IRV) to achieve open lung strategy. He advocates an initial recruitment maneuver with peak airway pressures 40–60 cm H2O on PC for 10–30 ventilator cycles, using IRV with in inspiration:expiration (I:E) ratio of 1:1 or 2:1 and PEEP of 10–20 cm H2O. Success in recruitment is largely determined by an improvement in oxygenation. The PC is then adjusted to decrease the peak airway to the lowest that will sustain a stable tidal volume or oxygenation, usually 15–30 cm H2O below the recruitment maneuver.

**HIGH FREQUENCY OSCILLATORY VENTILATION (HFOV)**

**Mechanisms and delivery**

High frequency oscillatory ventilation (HFOV) potentially provides lung protection in ARDS by avoiding alveolar distension and collapse. Oscillation is provided at rates of 180–900 cycles per minute, or 3–15 Hz (1 Hz = 60 cycles per minute or 1 cycle per second), with sub-dead space tidal volumes (0.1–0.3 mL/kg), high gas flow, and an active expiratory phase.

During HFOV there are multiple potential mechanisms of gas exchange other than direct ventilation, including convective transport, “pendeluft” (inter-regional to-and-fro gas flow), longitudinal dispersion, and diffusion. High mean airway pressures (25–30 cmH2O) are necessary to support and maintain alveolar recruitment and an open lung. The HFOV device has an adjustable power control that determines the amplitude of piston displacement and peak and trough pressure excursions (delta P) above and below the mean airway pressure. The piston sets up a body “wiggle” that typically extends to the thighs. The oscillation frequency (Hz) determines the time for piston displacement, thus a lower Hz will lead to larger bulk tidal volumes. The FiO2 and mean airway pressure determines oxygenation, whereas delta P and Hz determined ventilation and CO2 elimination. Occasionally it may be necessary to create a small endotracheal tube cuff leak to facilitate CO2 washout. HFOV provides a number of management challenges, including the necessity for a firm bed surface with increased risk of pressure injury, and difficulty in adequate hydration of inspired gas.

HFOV has established itself as a ventilatory mode in pediatric ICUs and trauma units, where it facilitates ventilation in the presence of abdominal compartment syndrome and constrained lung volume.

**Evidence basis**

In adults, HFOV has been reported primarily as a rescue mode that enhances oxygenation in ARDS in patients failing to improve with conventional ventilation. Thus far, only one large RCT has compared HFOV with conventional ventilation. After 2–4 days of conventional ventilation, 148 patients were
injury, embolism, and limb ischemia.

Circulatory assist (analogous to CPB) and more ECMO). This provides partial or near complete lung support is provided most often via a veno-arterial circuit (VA-ECMO, or the patient is hemodynamically unstable, rapid (< 72 h) lung function improvement.

Types of ECMO

Extracorporeal membrane oxygenation (ECMO)

for pulmonary support is provided most often via a veno-venous circuit (VV-ECMO) that creates an oxygenated circuit in parallel to the venous system. From an internal jugular cannula, venous blood is pumped through an extracorporeal membrane oxygenator and thence returned to the femoral vein. More recently, an adult double-lumen bicaval internal jugular cannula has facilitated single cannula placement for VV-ECMO; it simultaneously withdraws blood from the superior and inferior vena cava and returns it to the right atrium. Circulatory support is not provided by VV-ECMO, so the patient needs to be relatively hemodynamically stable, or supported by a right ventricular assist device (RVAD), into which the VV circuit can be inserted. The goal is to oxygenate venous blood returning to the heart, which in turn enhances arterial oxygenation sufficiently to sustain tissue metabolism.

In our hands, we have found VV-ECMO to be a life-saving intervention in selected patients with ARDS, especially ischemic-perfusion injury after double lung transplantation. A salutary outcome is predicated on good cardiovascular function, the absence of multisystem organ failure, and relatively rapid (< 72 h) lung function improvement.

If oxygenation is not sufficiently supported by VV-ECMO, or the patient is hemodynamically unstable, ECMO is provided via a veno-arterial circuit (VA-ECMO). This provides partial or near complete circulatory assist (analogous to CPB) and more complete oxygenation of arterial blood. However it requires cannulation of a major artery (most often, the femoral artery) with increased risk of vascular injury, embolism, and limb ischemia.

ECMO is an expensive, complex, resource intensive modality that requires considerable expertise. It requires systemic anticoagulation to prevent contact activation-induced thrombosis, and there is high risk of major bleeding and coagulopathy, thromboembolism, stroke, sepsis, and multisystem failure.

More recently, a poly-methylpentene (PMP) membrane oxygenator (Quadrox D) has become available that is very small and portable, driven by a centrifugal pump. This system avoids the plasma leakage associated with conventional standard hollow-fiber oxygenators. Studies are underway at our institution to use this form of VV-ECMO as a bridge to lung transplantation in decompensated patients.

Evidence basis

Initial studies, such as the U.S. ECMO trial (1974–1977) used ECMO with complete lung collapse, and dismal survival (9%). Over the next 10 yr,Gattinoni demonstrated the effectiveness of maintenance of low frequency positive pressure ventilation (LFPVV, pressure limit 35 cm H2O, rate 3–5/min), utilizing low flow VV-ECMO for CO2 removal (ECCO2R). This approach was associated with a 49% survival in very severe ARDS; in survivors, lung function improved within 48 h. In a subsequent randomized study in the U.S., Morris compared LFPVV-ECCO2R with PC-IRV, using computerized protocols in 40 patients. There was no statistical significance in 30-day survival (33% vs 42%).

The most recent large scale RCT is the CESAR trial (Conventional ventilatory support versus ECMO for Severe Adult Respiratory failure) performed on 180 adults in the UK. An independent central randomization service randomly assigned patients to either treatment modality within 7 days of the onset of severe ARDS (Murray score > 3.0, pH < 7.20). Patients who were referred to a specialty center for consideration of ECMO had significantly improved 6-month survival (63% vs. 47%). However, 20% of the referred patients did not undergo ECMO and had an 80% survival, thus some of the benefit was likely due to the provision of protective lung ventilation in a highly specialized center.

RENNAL PROTECTION: BIOMARKERS AND PHARMACOLOGIC INTERVENTIONS

Biomarkers

Ischemic acute kidney injury (AKI) progresses through several phases (prerenal, initiation, extension, maintenance and recovery). The success of any intervention to restore GFR thus depends on its timing – the earlier, the better. However, traditional renal function tests do not allow early recognition of AKI. Development of robust, easily detectable and prompt biomarkers of renal injury might allow us to assess the site, duration, etiology, prognosis and course of renal injury, and the effect of prophylactic or therapeutic interventions.
Serum Creatinine

Serum creatinine (SCr) is not a marker of renal injury, but of renal function, and reflects the balance between muscle creatinine production and renal excretion.\textsuperscript{30} SCr is a useful marker of glomerular filtration rate (GFR) in a steady state, but it is important to appreciate that the relationship between SCr and GFR is inverse and exponential. A doubling of the serum creatinine implies a halving of the GFR. There are numerous limitations to SCr as a reflection of steady state GFR as well as of acute changes in GFR.

Many physiologic molecules (e.g. glucose, protein, ketones) or drugs (e.g. cephalosporins) interfere with the chromogenic assay for creatinine. N-acetylcysteine (NAC), an antioxidant renoprotective agent in radiocontrast nephropathy (RCN) actually decreases SCr levels.

SCr does not increase above the normal range until GFR is <50 mL/min, so any decrease in GFR above this level will still be associated with a “normal” SCr. This is pertinent in the elderly (whose normal GFR is 50-80 mL/min) and cachectic patients (who have very low creatinine generation). Creatinine is freely soluble and distributes throughout the total body water (TBW), so perioperative increases in TBW are reflected by artifactualy low SCr immediately after surgery.

Importantly, it may take 2 to 7 days before the SCr reaches a new steady state that reflects acute changes in GFR. This explains why intraoperative AKI is so often reflected by a postoperative SCr that does not peak until 5-7 days after surgery. Indeed, after a transient renal insult (e.g. suprarenal aortic cross-clamping) SCr may increase for a few days while GFR is actually recovering.\textsuperscript{51}

Cystatin C

Cystatin C is a cysteine-protease inhibitor that is released into the circulation by all nucleated cells. It is completely filtered by the glomerulus, reabsorbed and not secreted by the tubules; thus, increased serum cystatin C levels reflect decreased GFR, and increased urinary levels reflect tubular injury.\textsuperscript{42} Elevation of urinary cystatin C within 6 hr of cardiac surgery has been shown to have a strong correlation with AKI defined by subsequent elevation of SCr.\textsuperscript{43} Unlike creatinine, cystatin C levels are not affected by muscle mass, age or gender, and there is evidence that it more accurately tracks GFR and responds more quickly.\textsuperscript{44,45} However, certain factors such as cigarette smoking, inflammation and immunosuppressive therapy do independently elevate cystatin C.\textsuperscript{46}

New biomarkers of tubular injury

Neutrophil gelatinase-associated lipocalin (NGAL) is a small 25 kDa polypeptide expressed in proximal tubular cells. Within minutes after ischemic tubular injury NGAL expression is dramatically up-regulated - 3-4 fold within 2-3 hrs, and up to 10,000 fold by 24 hrs.\textsuperscript{49} NGAL is readily detected by ELISA in tiny (micromilliliter) amounts of urine almost immediately after renal injury, preceding the appearance of NAG and beta2-microglobulin.

Urinary NGAL increases significantly within two hr of CPB in pediatric or adult patients who subsequently go on to develop a 50% increase in postoperative SCr, whose peak is delayed until 2-5 days after surgery.\textsuperscript{50} However, the sensitivity and specificity in individual patients is much greater in pediatric (AUC 0.98) than adult cardiac surgery (0.74).\textsuperscript{51} This may be explained by pediatric patients having a single insult imposed upon previously normal renal function, whereas, adults have varying preoperative GFR and co-morbidity, with multiple disparate renal insults. Thus although urinary NGAL may represent an early, sensitive, noninvasive urinary biomarker for ischemic and nephrotoxic AKI, it is not yet useful for management decisions in an individual patient.

Interleukin-18 (IL-18) is a pro-inflammatory cytokine that is involved in ischemic AKI. After CPB, urinary IL-18 is elevated within 4-6 hrs (i.e. later than NGAL), and levels may reflect the severity and duration of ischemic AKI.\textsuperscript{52}

Kidney injury molecule-1 (KIM-1) is an immunoglobulin that normally resides in proximal renal tubular cells. After ischemic or nephrotoxic AKI, KIM-1 levels become dramatically elevated, perhaps because the protein plays a role in scavenging apoptotic and necrotic tubular cells.\textsuperscript{53} However, compared with NGAL and IL-18, the levels of KIM-1 peak considerably later; at about 12-24 hrs.

Conclusions

Despite their promise, individual biomarkers of AKI have not yet replaced traditional markers in clinical and investigational studies. There is considerable interest in the development of a panel of early markers of acute tubular injury (NGAL, IL-18, KIM-1) together with a more reliable marker of GFR (cystatin C).\textsuperscript{38} The hope is that these panels will be...
more useful for timing the initial insult and duration of AKI, and in predicting outcome (requirement for dialysis, mortality). Much work remains to be done to validate their sensitivity and specificity in large, diverse patient populations.

PHARMACOLOGIC PROTECTION

Osmotic and Loop Diuretics

Mannitol (25-50 g) is routinely added to the pump prime, although there are few clinical data that define its true role in renal protection during CPB. It does not prevent subclinical renal injury (microalbuminuria, tubular enzymburia), but AKI after uncomplicated CPB in patients with previously normal renal function is rare. Mannitol increases urine flow during infra-renal cross-clamping but does not prevent intraoperative decreases in GFR. Postoperative osmotic diuresis can exacerbate hypovolemia and hypokalemia; persistent isostenuria actually is predictive of CPB-induced tubular injury.

Loop diuretics (furosemide, bumetanide, torsemide, ethacrynic acid) have long been used to “convert” oliguric to nonoliguric AKI. However, it is most likely that oliguric patients who respond to diuretics have a lesser renal injury than those who do not, with an intrinsically more favorable outcome. Once dialysis is required, high dose furosemide does not alter the natural history of AKI.

Dopaminergic Agonists

Dopaminergic agents (dopamine, fenoldopam) potentially confer renal protection by increasing renal blood flow (RBF), diuresis and saliuresis. By activating cyclic AMP they “turn off” the energy-dependent tubular sodium pump and thereby decrease tubular oxygen consumption; increased intratubular urine flow protects against tubular obstruction.

Low dose (1-3 µg/kg/min) dopamine, added to high dose furosemide and mannitol, can also convert oliguric to nonoliguric states if given within a few hours of injury. However there is little evidence that “prophylactic” low dose dopamine has any role in cardiac surgery. In part this may be because there is very wide variability in dopamine pharmacokinetics, i.e., some patients given low dose dopamine may achieve high plasma levels, i.e. in the beta- or alpha-adrenergic range.54 When oliguria is associated with slow heart rate and low blood pressure in a volume repleted patient, initiation of dopamine as an inotropic agent can be very helpful. However, its usefulness is limited by its propensity to induce supraventricular arrhythmias especially postoperative atrial fibrillation.55

Fenoldopam is a phenol derivative of dopamine that is selective for the DA-1 receptor and lacks any beta- or alpha-adrenergic effects. There is increasing evidence that prophylactic perioperative administration at low doses (0.5-1.0 mcg/kg/min) can preserve GFR during and after CPB and decrease the requirement for postoperative dialysis.56,57

Natriuretic Peptides

The natriuretic peptides are formed by the endogenous synthesis of chains of 22-32 amino acids. They specifically oppose the sympathoadrenal, renin-angiotensin, aldosterone, and arginine vasopressin (AVP) systems, and induce vasodilation and natriuresis via activation of cyclic GMP. A-type (atrial) natriuretic peptide (ANP) is released by atrial stretch; B-type (brain) natriuretic peptide (BNP) is released by ventricular dilation. Assay of BNP (and its precursor, N-terminal-pro-BNP) is an established diagnostic tool for acute cardiac failure.58 C-type natriuretic peptide (CNP, great vessels) and urodilatin (kidney) are endogenous analogs.

Human recombinant ANP (anaritide) infusion during CPB significantly decreases renin-angiotensin and aldosterone responses, and preserves GFR. Preliminary data suggested that administration in patients with severe AKI it could decrease dialysis requirement and mortality.59 However, mortality was increased in nonoliguric patients, perhaps because the surviving nephrons are more sensitive to hypotension induced by ANP. A subsequent trial in oliguric patients showed no difference in outcome.60

Human Recombinant BNP (nesiritide) is FDA-approved for the parenteral treatment of patients with advanced decompensated CHF (ADCHF). Infusion decreases cardiac preload and afterload, promotes diuresis and relieves pulmonary edema and anasarca. Considerable controversy has been elicited by implications that nesiritide may adversely affect renal function in ADCHF.61 However, in a prospective, controlled study in patients undergoing coronary revascularization of mitral valve surgery with CPB, a perioperative infusion of nesiritide (0.01 mcg/kg/min) was associated with lower SCR and 6-month mortality.62

N-Acetylcysteine

N-acetylcysteine (NAC) is naturally occurring glutathione precursor and free radical scavenger. It is well established in the treatment of acetaminophen toxicity, and there is considerable experimental evidence of its effectiveness in ameliorating nephrotoxic AKI. When combined with hydration, prophylactic oral NAC (600 mg PO bid x 2 days) provides significant renal protection in radiocontrast nephropathy (RCN).63,64 However, NAC may decrease creatinine production and thereby give a false impression of the extent of its benefit.65

No renal benefit has been demonstrated by the perioperative infusion of NAC during cardiac surgery.66 NAC must pass through the liver to be converted to glutathione, so in part this may be due to inadequate knowledge regarding the appropriate parenteral dose of NAC to protect against clinical IRI.67
Sodium Bicarbonate

It is well established that urinary alkalization (pH > 6.5) protects against tubular injury in myoglobinuria (rhabdomyolysis) as well as RCN. There is now preliminary clinical evidence that urinary alkalization can ameliorate AKI during cardiac surgery. 68

PALLIATIVE CARE
Benefits of a Palliative Care Service in the ICU

Intensive care and palliative care might appear to be contradictions: the former focuses on restoration of health or at least prolongation of life; the latter focuses on control of symptoms and relief of suffering. 69 However, these are not opposite ends of a spectrum – there is considerable overlap. There is considerable evidence that integration of palliative care experts into the ICU is of benefit to patients, families and caregivers. It has been estimated that nearly 50% of Americans who die in hospitals spend time in the ICU in their last 3 days of life, and about 15% of patients admitted to an ICU (half a million patients a year in the US) will die in the ICU. 70

Palliative care in the ICU may be associated with improved quality of life, higher rates of formalization of advanced directives and utilization of hospices, and lower use of certain non-beneficial life-prolonging treatments for critically ill patients who are at the end of life.

For example, at Montefiore Medical Center in the Bronx, New York a palliative care team integrated into the operations of an ICU included an advance practice nurse (APN) – who attended rounds - and social worker. 71 The team provided recommendations on pain management; education on the death process; guidance for formalized advance directives (especially non-English speaking patients of low socio-economic status); helped with withdrawal of support such as mechanical ventilation, inotropic support, artificial nutrition, or dialysis; and referred patients to hospice with access to formal bereavement services. Charges for opioid medications increased but use of laboratory and radiology tests decreased.

An important emphasis of palliative care is to enhance communication between the ICU team and families. Palliative care staff can facilitate more in-depth meetings to allow families to express concerns and emotions, which may reduce posttraumatic stress reactions and to allay misconceptions regarding the ICU team’s recommendations to limit or withdraw care. The “ABCDE” approach has been advocated to enhance communication with families of diverse cultural origin. The team should explore attitudes to death and dying (ethnically based); beliefs (religious); context (historical and political origins and experiences); decision-making style (individual or family-centered); and environmental resources. 70

The Palliative Care Consult

Common symptoms triggering a palliative care consult include delirium, dyspnea, pain, fatigue and anxiety. In addition to counseling, interventions offered include opioid management, steroids, antipsychotic drugs, do not resuscitate conversion, withdrawal of invasive and non-invasive ventilatory support. 72

Attempts have been made to systematize the criteria for a palliative care consult. This is an area where disagreement persists. For example, a group of surgical intensivists offered criteria primarily on family request, or evidence of medical futility such as poor Glasgow coma scores, death expected during same SICU stay, median expected survival <6 months, SICU stay >1 month, and so on. 73 The editorial accompanying the report expressed concern at the lack of any reference to management of treatable pain, delirium or depression by the palliative care team and wondered whether intensivists and surgeons fear sending patients or families “the wrong prognostic message.” 74

At the other end of the spectrum are practitioners of palliative care who believe that “all ICU patients experience... suffering regardless of prognosis or goals, thus palliative therapy is a requisite approach for every patient, of which pain management is a principal component.” 70

End-of-Life Care

Palliative care can help with the three aspects of “good dying” advocated by the Institute of Medicine in 1997: avoidance of distress and suffering; accord- ance with the patient’s preferences and wishes; and consistent with clinical and cultural standards. 70 It can help in the shift to comfort-oriented care for dying patients; it can enhance communication and cultural sensitivity with the patient and family; it can help resolve misconceptions about opiate escalation to alleviate pain and suffering. It can also address family and caregiver stress. It may facilitate the use of standardized instruments to gauge pain and discomfort.

Palliative care teams can help to educate caregivers and families that aggressive palliation of pain, even though it might shorten survival, is ethically justifiable as long as the primary goal is the relief of suffering. This is the so-called doctrine of the “double effect”. In fact, relief of uncontrolled pain and its severe systemic effects may delay demise. However, a European survey suggested that there is no clear-cut distinction between treatments administered to relieve pain and suffering and those intended to shorten the dying process, which many intensivists feel directly leads to patient demise. 75 Specific guidelines or orders for analgesia and sedation may be helpful during withdrawal of life-support; these may include protocols for palliative (total, terminal or controlled) sedation for patients in extreme distress.
REFERENCES


How does an injury cause pain?

Tony L. Yaksh, PhD
Department of Anesthesiology,
University of California, San Diego

Learning Objectives:
1) Understand mechanisms by which injury/inflammation activates the terminals of subpopulations of primary afferents. 2) Define the dorsal horn connections by which afferent traffic leads to supraspinal activation. 3) Review systems by which injury can lead to aberrant and persistent (chronic) pain states.

Acute application of a stimulus of such intensity as to potentially produce tissue injury will evoke an escape and an autonomic response (e.g. hypertension and tachycardia). The magnitude of these responses varies directly and their latency inversely with stimulus intensity. Removal of the acute stimulus results in a rapid attenuation of the sensation and attendant behaviors. In the face of local tissue injury and inflammation, a distinct pattern of aversive sensations are reported. This behavioral phenotype after injury or with inflammation is typically composed of signs of ongoing pain and an enhanced response to somatic stimulation or hyperalgesia.

A. THE EFFECTS OF AN ACUTE STIMULUS.
To understand the mechanisms associated with pain after injury, it is worthwhile to contrast that augmented state with the events which transpire with acute high intensity stimulation. Under normal conditions, activity in sensory afferents is absent. However, peripheral mechanical and thermal stimuli will evoke intensity-dependent increases in firing rates of lightly myelinated (Aβ) or unmyelinated (C) afferents. This in turn leads to the activation of populations of marginal cell and wide dynamic range spinal neurons, which then project via the ventrolateral tracts to higher centers and thence to

Figure 1. Summary of ascending pathway activated by an acute stimulus. High intensity stimuli activate subpopulations of high threshold afferents that project to the superficial spinal dorsal horn. (B) The afferent activation occurs through terminal channels that depolarize the terminal of small (Aβ/C fiber) primary afferents and generate action potentials, the frequency of which is proportional to the intensity of the stimulus. (A) This input leads to the release of several excitatory transmitters. (C) This pathway projects to the classical somatosensory thalamus (Ventralbasal) (E-Left). Neurons in this region then project to the somatosensory cortex. This pathway is characterized by retention of a precise somatotopic mapping of the body surface at each link. A second system projects into the medial aspects of the thalamus and Ventromedial, thalamus and these neurons project to the anterior cingulate and the inferior insula, respectively, areas of the old limbic forebrain (E-Right). This pathway is characterized by a poor somatotopic map. Jointly, one notes that the classical somatosensory pathway (left) appears to encode precise localization and intensity, while the right system appears to encode information for regions that are classically associated with emotionality and affect.
cortical levels. In these cases, the nervous system maintains a specific intensity - spatial - and modality-linked encoding of the somatic stimulus as summarized in Figure 1. This pathway possesses the characteristics that relate to the psychophysical report of pain sensation in humans and the vigor of the escape response in animals. In the absence of tissue injury, removal of the stimulus leads to a rapid abatement of the afferent input and disappearance of the pain sensation.

B. THE EFFECTS OF A TISSUE INJURY STIMULUS

1. Psychophysics of tissue injury.

Following tissue injury, there is an ongoing sensory experience that is described as dull, throbbing aching. Psychophysical examination reveals that in addition moderate stimuli applied to the injury site is reported as extremely noxious (primary hyperalgesia), while mechanical stimuli applied adjacent to the injury site is considered very unpleasant (secondary tactile allodynia).

2. Tissue Injury evoked afferent activity.

In the event that such a stimulus leads to local injury as in a tissue crush (trauma) or an incision, such stimuli may lead to the subsequent elaboration of active products that directly activate the local terminals of afferents (that are otherwise essentially silent), innervating the injury region and facilitating their discharge in response to otherwise sub-maximal stimuli. This then leads to an ongoing afferent barrage (see Figure 2).

In addition to the appearance of spontaneous afferent traffic, single unit recording show that after local injury, afferent terminals show increased response for any given stimulus (Figure 3).

C. PERIPHERAL AFFERENT TERMINAL PHARMACOLOGY AND TISSUE INJURY

As noted above, mild damage to cutaneous receptive fields produces significant increases in the excitability of polymodal nociceptors (C-fibers) and high threshold mechanoreceptors. This altered response results from changes in the milieu of the peripheral terminal that occur secondary to tissue damage and the accompanying extravasation of plasma due to an increased permeability of the capillary wall (Figure 4). These injury events are mechanistically responsible for the “triple response of Lewis” noted after tissue injury: a red flush around the site of the stimulus (local arterial dilation), a local edema (capillary permeability) and a regional reduction in the magnitude of the stimulus required to elicit a pain response, i.e., a hyperalgesia.

These effects result from the release of algogenic agents from damaged tissue, inflammatory cells

---

**Figure 2.** Figure presents firing rate of a single small afferent in response to tissue pinch and crush (resulting in tissue injury). In the absence of stimulation, there is no spontaneous activity. With a brief pinch, there is a stimulus-linked discharge. The induction of local injury by a crush leads to a prolonged ongoing discharge that continues long after the crushing stimulus has been removed.

**Figure 3.** Firing of small afferent in the skin (left) at increasing temperatures. Following carrageenan injection into skin, afferent shows increasing spontaneous activity, a left shift, and an increase in slope of stimulus-response curve, indicating a facilitated response to the thermal stimulus. (Right) Firing of articular afferent under normal state and in presence of nonnoxious and then noxious rotation of knee. After injection of PGI2 into the joint, there is spontaneous activity mild rotation results in significant discharge.
migrating into the injury site from blood vessel (by diapedesis through the vascular wall), mast cell degranulation and products released from the peripheral terminals of sensory afferents activated by local antidromic C-fiber axon reflexes. Organizationally, it is interesting to note that free nerve endings in the tissue often terminate in close proximity to the local arteriole/venule and there is an increased incidence of mast cells in the vicinity (see inset in Figure 4).

Though complex, it has become increasingly appreciated that these chemical intermediaries may have two distinct effects: i) direct excitation of C-fibers leading to ongoing activation of C-fiber terminals and small afferent traffic and a pain sensation; and, ii) facilitation of C-fiber activation, resulting in a left shift and increasing slope of the frequency response curve of the C-fiber axon leading to an increase in the reported magnitude of the pain response evoked by a given stimulus (hyperalgesia (see Figure 3). The peripheral pharmacology of the systems that process information is exceedingly complex. After injury a variety of products are released from i) damaged tissue (e.g., K+, H+), ii) local inflammatory cells (mast cells: histamine. Peptidase; macrophages: Prostaglandins; TNF), iii) blood products (platelets: 5HT; endothelial cells: bradykinin) and transmitters released from local C fiber primary afferents (e.g., substance p, calcitonin gene related peptide).

There is not enough space here to review all aspects of the peripheral sensitization process, but it is evident that a primary motif is that many of the terminal receptors can activate a variety of protein kinases such as protein kinase (PKC A and C as well as so called mitogen activated protein kinases (MAPK). These kinases can phosphorylate transducer proteins (e.g. the TRPV1) and ion channels such as the voltage sensitive sodium channels (NaV) leading to their enhanced activation by a degree of depolarization or activation. (Figure 5).

---

**Figure 4.** Primary afferent terminal innervating an injury site. Local damaging stimulus leads to firing of the fine afferents leading to orthodromic potentials back to the spinal cord. In addition, there is local activation of inflammatory and mast cells. As the inset shows, fine afferent terminals frequently are found coursing with arterioles and venules and there is a high frequency of mast cells present in the vicinity of the terminal. Afferent fiber terminal activation leads not only to orthodromic potentials to the cord, but the action potentials also proceed antidromically to release of neuropeptides (sP/CGRP). These peptides can further degranulate mast cells and activated inflammatory cells. Hormones, such as bradykinin, prostaglandins and cytokines, or K+/H+ released from inflammatory/ mast cells and plasma extravasation products result in stimulation and sensitization of free nerve ending, which serve to depolarize and sensitize the terminal causing an enhanced response to any given stimulus.

**Figure 5.** Schema showing an afferent terminal activated by bradykinin (BK) through a BK2 receptor and prostaglandins acting through an EP receptor. These receptors activated protein kinases such as A and C, which in turn can phosphorylate voltage sensitive sodium channels (NaV) or TRPV1 receptors. The phosphorylation of the NaV and lowers the activation temperature for the TRPV1. In this manner the BK and PG agonists activate the terminal and through the activation of these kinases lead to its sensitization.
TABLE 1: Summary of Classes of Agents Released by Tissue Injury and Alter Activity and Sensitivity of Primary Afferent Fibers

| i. Amines: | Histamine (granules of mast cells, basophils and platelets) and serotonin (mast cells and platelets) are released by a variety of stimuli, including mechanical trauma, heat, radiation, certain byproducts of tissue damage, thrombin, collagen, and epinephrine as well as members of the arachidonic acid cascade, leukotrienes and prostanoids. |
| ii. Kinin: | A variety of kinins, notably bradykinin, are released by physical trauma. Peptide is synthesized by a cascade that is triggered by the activation of factor XII by agents such as kallikrein and trypsin. Bradykinin acts by specific bradykinin receptors (B1/B2) to activate free nerve endings. |
| iii. Lipidic acids: | Agents are synthesized by lipoxygenase or cyclooxygenase (prostanoids) upon the release of cell membrane-derived arachidonic acid secondary to the activation of phospholipids A2. A number of prostanoids, including PGE2, can directly activate C-fibers. Others, such as PGI2 and TXA2, and several leukotrienes, can markedly facilitate the excitability of C-fibers. These effects are also mediated by specific membrane receptors. |
| iv. Cytokines: | Cytokines such as TNF and IL1β are formed as part of the inflammatory reaction involving macrophages and have been shown to exert powerful sensitizing effects on C-fibers. Interleukin such as IL-1 may sensitize C-fibers via a prostaglandin intermediary. TNF can interact with several TNF receptors (typically TNF2) that excites axons and terminals. |
| v. Primary afferent peptides: | CGRP and sP are found in and released from the peripheral terminals of C-fibers and will produce local cutaneous vasodilation, plasma extravasation, and sensitization in the region of skin innervated by the stimulated sensory nerve. |
| vi. [H ] / [K ]: | Elevated H+ (low pH) and high K+ are found in injured tissue. Protons can directly stimulate C-fibers through TRPV1 receptors and specific acid sensing channels (ASICs) and facilitate the discharge produced by a given stimulus, e.g., hyperalgesia. This in turn can activate the local axon reflex and results in the local release of calcitonin gene-related peptide, a potent vasodilator and modulator of plasma extravasation. A population of C-nociceptors sensitive to noxious intensities of mechanical and thermal stimuli also responded in a stimulus-related fashion to solutions of increasing proton concentration injected into their receptive fields. These receptors develop a lower threshold and enhanced response to mechanical stimuli. Similar injections in humans induce a sustained graded pain and hyperalgesia. Increasing evidence suggests that agents such as capsaicin may interact directly with peripheral terminal membranes to increase proton conductance. |
| vii. Proteinases, | such as thrombin or trypsin, are released from inflammatory cells and can cleave tethered peptide ligands that exist on the surface of small primary afferents. These tethered peptides after cleavage act upon adjacent receptors (PARs: proteinase-activated receptors) that can activate the terminal. |
| viii. Growth factors. | Nerve growth factor (NGF) for example is released from inflammatory cells and Schwann cells. This factor and others can act through GGF receptors on the terminals and activate them, leading to activity and sensitization. Growth factors may also be transported back to the DRG where they can initiate protein synthesis that can increase the expression of a variety of proteins such as receptors, and channels (e.g. sodium) that can promote long-term changes insensitivity. |

D. SPINAL ACTIVITY EVOKED BY ACUTE STIMULATION

Acute activation of small afferents by high intensity mechanical or thermal stimuli will result in a clearly defined pain behavior in humans and animals. This event is believed to be mediated by the release of the excitatory afferent transmitters outlined above and consequently the depolarization of projection neurons. The magnitude of the response of a dorsal horn neuron, either wide dynamic range or nociceptive-specific, is related to the frequency (and identity) of the afferent input. The frequency of the afferent input is proportional to the magnitude of the acutely applied stimulus. The organization of this system’s response to an acute stimulus is thus typically modeled in terms of a monotonic (linear) relationship between activity in the peripheral afferent and the activity of neurons that project out of the spinal cord to the brain. As noted above, in the face of tissue injury the afferent input is characterized by a persistent afferent barrage. As will be discussed below, such input reveals the initiation of a variety of processes that lead to a nonlinear increase in the spinal input-output function.

E. PLASTICITY OF THE SPINAL RESPONSE TO PERSISTENT AFFERENT INPUT

1. Wind-up and central facilitation

In animal studies, wide-dynamic-range (WDR) neurons in the dorsal horn display a stimulus dependent response to discrete activation of afferent C-fibers. Repetitive stimulation of C (but not A) fibers at a moderately faster rate results in a progressively facilitated discharge.

The exaggerated discharge of WDR (Lamina V) neurons evoked by repetitive small afferent stimulation was dubbed “wind up” by Mendell and Wall (see Figure 6). Intracellular recording in the WDR neuron has indicated that the facilitated state
is represented by a progressive and long sustained partial depolarization of the cell, rendering the membrane increasingly susceptible to afferent input.

Given the likelihood that WDR discharge frequency contributes to the encoding of a high threshold stimulus as aversive, and that many of these WDR neurons project through the ventrolateral quadrant of the spinal cord (i.e., spinothalamic or spinobulbar projections), this augmented response to a given stimulus is believed to be an important component of the encoding of the pain message.

In addition, to the augmented response of the WDR neuron, the conditioning of the afferent input as described has the added effect of increasing the receptive field size of the neurons, such that afferent input from dermatomal areas that previously did not activate the given WDR neuron now evokes a prominent response. Moreover, low threshold tactile stimulation also becomes increasingly effective in driving these neurons.

This facilitation by repetitive C-fiber input, therefore, increases the subsequent neuronal response to low threshold afferent input, and enhances the response generated by a given noxious afferent input. Given the likelihood that WDR discharge frequency is part of the encoding of the intensity of a high threshold stimulus, and that many of these WDR neurons project in the ventrolateral quadrant of the spinal cord (i.e., spinobulbar projections), this augmented response is believed to be an important component of the pain message.

2. Changes in receptive field size

As noted, with tissue injury or repeated small afferent input (as in Figure 6), there is a tactile allodynia in which light touch applied to an adjacent non-injured region will yield discomfort. The mechanism for this is believed to be the presence of subliminal excitatory input between adjacent segments. As indicated in Figure 7, the sensitization of the segmental neurons receiving input from afferent innervating an injured tissue leads to the enhanced excitability of these cells (as seen in Wind up) and this leads this neuron to be activated by the otherwise subliminal input coming from an adjacent non-injured receptive field.

**F. FUNCTIONAL CORRELATES OF INJURY-EVOKED CENTRAL FACILITATION**

Protracted pain states, such as those that may occur with inflamed or injured tissue (leading to the peripheral release of active factors), would routinely result in such an augmented afferent drive of the WDR
neuron and thence to the ongoing facilitation. Such observations are consistent with the speculation that the afferent C-fiber burst may initiate long lasting events resulting in changes in spinal processing that will alter the response to subsequent input. The above observations regarding this dorsal horn system have been shown to have behavioral consequences. This phenomenon has clear functional correlates.

Studies in animals have shown that the acute injection of an irritant will induce an acute afferent barrage followed by a prolonged, low level, of activity. However, examination of behavior has shown that the animal displays an exaggerated response to the second, low intensity phase of the afferent activity, e.g. a central facilitation. This disproportionate level of late behavioral activity following formalin injection is also displayed by WDR dorsal horn neurons. During this period, single cell recordings indicate an enhanced response to both high and low intensity stimulation as the post-injury pain state cannot be minimized. After tissue injury, in animals and in humans, inflammation and cellular/vascular injury lead to the local peripheral release of active factors. Such active factors will produce a prolonged activation of C-fibers that evoke a facilitated state of processing in WDR neurons, and thence, to an ongoing facilitation of nociceptive perception. Such observations are consistent with the speculation that the afferent C-fiber burst may initiate long lasting events, resulting in changes in spinal processing that will alter the response to subsequent input. The relevance of this C-fiber-evoked facilitation to humans has been emphasized by psychophysical studies. In observers, the activation of C-fibers by the intradermal injection of capsaicin will lead to an initial pain state followed by an extended period of time by a large region of profoundly enhanced mechanical and thermal sensitivity. This phenomena is referred to as secondary hyperesthesia. Thus, in humans, following local injury where C-fibers are similarly activated, there is every reason to believe that similar processes apply and that important components of the post-injury pain state are the events consequent to the afferent barrage and not, strictly speaking, the input present in the post-injury phase.

G. PHARMACOLOGY OF CENTRAL FACILITATION

Based on the above commentary, a reduction in C-fiber-evoked excitation in the dorsal horn by blocking axon transmission, release of small afferent transmitter or the post synaptic receptor (e.g. NK1 for sP or AMPA for glutamate) will diminish the magnitude of the afferent drive and, accordingly, diminish the facilitated processing evoked by protracted small afferent input. However, early work indicated that the wind-up state reflects more than the repetitive activation of a simple excitatory system.

1. Glutamate receptors and spinal facilitation.

The pharmacology of this central facilitation suggests that the windup state reflects more than simply the repetitive activation of a simple excitatory system. The first real demonstration of this unique pharmacology was presented by showing that the phenomenon of spinal wind-up was prevented by the spinal delivery of antagonists for the n-methyl-d-aspartate (NMDA) receptor. (see Figure 8). Importantly, this agent had no effect upon acute evoked activity, but reduced the wind-up. Subsequent behavioral work demonstrated that such drugs had no effect upon acute pain behavior, but reduced the facilitated states induced after tissue injury.

As noted, the NMDA receptor does not appear to mediate acute excitation. This reflects upon an important property of this receptor. Under normal resting membrane potentials, the NMDA receptor is in a state referred to as a magnesium block. In this condition, occupancy by glutamate will not activate the ionophore. If there is a modest depolarization of the membrane (as produced during repetitive stimulation secondary to the activation of AMPA (glutamate) and neurokinin1 (NK1) (substance P) receptors, the Mg block is removed, permitting glutamate to now activate the NMDA receptor. When this happens, the NMDA channel permits the passage of Ca (Figure 9). This increase in intracellular calcium then serves to initiate the downstream components of the excitatory and facilitatory cascade. It is also appreciated that some subtypes of AMPA receptors are also able to gate calcium and these receptors have been shown to play a role in spinal facilitatory processes.
As noted, with ongoing afferent drive, a progressive increase in excitation is noted. Aside from activation of the NMDA receptors other components to this facilitatory process can be noted. These can be broadly considered in terms of those systems that are local to the neuronal networks in the dorsal horn, extraspinal networks and non-neuronal networks. Several examples of each will be reviewed below.

### a. Facilitatory dorsal horn neuronal components

#### Multiple excitatory neurons.

Primary afferent glutamate or sP can activate local interneurons which often contain and release glutamate. This poly neuronal chain can enhance the excitatory drive from a given afferent.

**Activation of Kinases.** Excitatory input arising from a persistent afferent barrage induce additional excitation via the release of several products including glutamate, peptides (substance P). This leads to a marked increase in intracellular Ca\(^{2+}\) and the activation of a variety of phosphorylating enzymes. including protein kinases A and C; Mitogen activated kinases (MAPKs) including p38 MAP kinase and ERK. Several examples will be noted.

i) PKC activated by increased intracellular Ca phosphorlates a variety of proteins. One such protein is the NMDA receptor. Such phosphorylation serves to reduce its threshold for activation leading to an enhanced response of the NMDA ionophore to further depolarization.

ii) P38 MAPK is activated by increased intracellular Ca. This activation leads to several events. The first is to phosphorylate prostaglandin synthesis cascade through PLA2 and constitutively expressed COX1 and COX2. Prostaglandins (PG) act preterminally to increase opening of voltage sensitive calcium channels and post terminally decrease the activation of inhibitory glycine receptors.
phospholipase A2 (PLA2), which initiates the release of arachidonic acid and provides the substrate for cyclooxygenase (COX) to synthesize prostaglandins. The second is that this MAPK activates a variety of transcription factors (such as NFKB), which activates synthesis of a variety of protein, including COX2. The spinal delivery of P38 MAPK inhibitors will thus reduce acutely initiated hyperalgesia and reduce the upregulation of COX2 otherwise produced by injury.

**Lipid cascades.** Cyclooxygenase (COX) products (prostaglandins: PGs) are formed from arachidonic acid and released. These agents diffuse extracellularly and facilitate transmitter release (retrograde transmission) from primary and nonprimary afferent terminals though interaction with a variety of eponymous receptors.

Prostaglandins released act presynaptically to enhance the opening of voltage sensitive Calcium channels. This augments transmitter release. In addition prostaglandins can act post synaptically to block glycineric inhibition. Such a reduction in the activation of inhibitory glycine or GABA interneuron regulation can lead to a potent facilitation of dorsal horn excitability. The spinal delivery of PGE will increase while PLA2 or COX2 inhibitors will reduce spinal PGE2 release and reduce injury-induced hyperalgesia.

**Reorganization of inhibitory phenotype of interneurons.** As implied above, second-order dorsal horn neurons (WDR neurons) also receive excitatory input from large afferents. This input is likely mediated by glutamate and may be mediated by input into excitatory interneurons, which also release glutamate. Based on the effects of various inhibitory amino acid antagonists, it appears that the excitatory effect of large afferents is also under a presynaptic GABA-A/glycine modulatory control, removal of which results in a behaviorally defined allodynia. (Figure 11) . The intrathecal delivery of low doses of GABA A or glycine site inhibitors will yield a potent allodynia.

In the spinal dorsal horn there are a large number of small interneurons that contain and release GABA and glycine. GABA / glycineric terminals are frequently presynaptic to the large central afferent terminal complexes and form reciprocal synapses, while GABAergic axosomatic connections on spinothalamic cells have also been identified (Figure 12). According these amino acids normally exert an important tonic or evoked inhibitory control over the activity of Aß primary afferent terminals and second order neurons in the spinal dorsal horn. The relevance of this intrinsic inhibition to pain processing is provided by the observation that the simple intrathecal delivery of GABA A receptor or glycine receptor antagonists will lead to a powerful behaviorally defined tactile allodynia. Similarly, lacking glycine-binding sites often display a high level of spinal hyper-excitability. These observations led to consideration that following nerve injury there may be a loss of GABAergic neurons. While there are data that do support a loss of such GABAergic neurons, the loss appears to be minimal. GABA acts at two receptors (GABA A and B). The pharmacology of the modulatory site suggests the importance of
the GABA A receptor (blocked by bicuculline and pitocin). Glycine is an ionophore activated by glycine and blocked by strychnine. (See Fig 12).

Recent observations now suggest that after nerve injury or chronic inflammation, spinal neurons may regress to a neonatal phenotype in which GABA-A activation becomes excitatory. This excitatory effect is secondary to reduced activity of the membrane Cl- transporter that changes the reversal current for the Cl- conductance (Figure 13). Here increasing membrane Cl conductance as occurs with GABA-A receptor activation results in membrane depolarization. Under normal conditions transmembrane [Cl-] are at equilibrium at or just below resting membrane potentials. Increasing Cl permeability by GABA-A or glycine-r (Cl- channels) yields hyperpolarization and inhibition. “Cation-Cl” co-transporters regulate Cl- gradient by exporting [Cl-] The loss of dorsal horn DHN-KCC2 after nerve injury leads to a failure of GABA-A / glycine inhibition or in fact turning the GABA/glycine effect into excitation of the 2° neuron.

Nitric oxide synthase (NOS). NOS forms diffusible nitric oxide (NO) from arginine. There are three principal NOS isoforms: endothelial, neuronal inducible. The neuronal and inducible forms have been found to play facilitatory role in the CNS though the formation of NO, acting presynaptically through cGMP can enhance transmitter release. NOS inhibitors can reduce post tissue injury hyperalgesia.

b. Extraspinal neuronal networks

Bulbospinal pathways are descending pathways, typically originating in nuclei in the medullary brainstem. activated by increases in ascending activity in nociceptive transmission pathways. While a large component of this descending inhibition mediates a local inhibition , there is considerable evidence that at least one element (the serotonergic pathway) which is facilitatory in character contributing to spinal facilitation (see Fig 14,15). Spinal projections originating in the brainstem and projecting into the spin al cord are characterized by being largely serotonergic (originating in the midline raphe) or noradrenergic and originating in several brain nuclei including the locus coruleus. The noradrenergic systems have been shown to act though dorsal horn alpha 2 receptors to inhibit dorsal horn neurons (serving to down regulate excitability). The serotonergic systems act through a variety of dorsal horn receptors that may be either inhibitory (5HT1a/b) or directly excitatory (5HT2/3). As reviewed in Figure 13, the situation is rendered more complex by virtue of the fact that the excitation may be on projection neurons in which the case the effects are predominantly excitatory or on inhibitory interneurons in which case the net effects are inhibitory. Of interest these bulbospinal

---

**Figure 14.** Inhibitory role of bulbospinal NE/5HT pathways. Bulbospinal NE (left) arise from locus coreus/Lateral medulla and project to dorsal horn to act upon a2 receptors which are pre and post synaptic to the primary afferent. These are inhibitory links. 5HT (right) projects from caudal raphe to the dorsal horn. S- HT may be inhibitory (5HT1-r) or excitatory (5HT3) on inhibitory interneurons (GABA?).

**Figure 15.** Excitatory effects of bulbospinal projections. Bulbospinal 5HT arising from caudal Raphe projects to the dorsal horn. To synapse 5HT3 cells and enhance excitability. This pathway may be activated by projections from Lam I neurons projecting to the Raphe, the periaqueductal gray and the parabirachial region.
projection can be driven by high intensity afferent input (Figure 14).

2. Non-neuronal cells.

In the CNS, there are a variety of non-neuronal cells. Among these are astrocytes and microglia. Microglia are resident macrophages that appear in brain from the circulation during development. These astrocytes, microglia and neurons form a complex net work in which each can influence the excitability of the other (see Figure 17):

i) Transmitters from primary afferents and intrinsic neurons (glutamate, ATP, sP) can over flow from the synaptic cleft to these adjacent non-neuronal cells and lead to their activation.

ii) Astrocytes may communicate over a distance by the spread of excitation through local nonsynaptic contacts referred to as “gap” junctions.

iii) Astrocytes may communicate with microglia by the release of a number of products including glutamate/cytokines and the “S100 protein.

iv) Neurons may activate microglia by the specific release of a membrane chemokine (fractalkine), which can upon specific receptors found on microglia. This process is part of a complex cascade referred to broadly as “neuroinflammation” (Fig. 16).

v) Non-neuronal cells can influence synaptic transmission by their release of a variety of active products (such as ATP, cytokines, See Figure 16). These glial cells regulate extracellular their glutamate transporters. This can serve to increase extracellular, activating neuronal glutamate receptors.

vi) Finally, after tissue injury and inflammation, circulating cytokines (such as IL1ß/TNF) can activate perivascular astrocytes/ microglia.

vii) As noted, microglia are in fact brain resident macrophages. Importantly, current evidence emphasizes that these cells are constitutively active. However, it is also clear that the activity of these cells can be upregulated after peripheral injury and inflammation.

I. OPIATE MEDIATED HYPERALGESIA.

The preceding section have dealt in some detail with facilitation that arise from tissue injury and inflammation. It should be stressed that these systems may also play a role in pain processing generated by surprising manipulations. One example will be considered here. Such pathways as described in the preceding section are regulated by the action of opioid receptors in the brain stem and spinal dorsal horn. It is appreciated opiates delivered chronically will result in a loss of effect, tolerance. During this process, it appears likely that opiates have the ability to initiate a paradoxical increase in nociceptive processing, leading to a state of hyperalgesia. Some have argued that the phenomena of tolerance may in fact result from a countering enhanced sensory processing that results in higher doses of opiate required to block the small afferent traffic, leading to a left shift in the opiate dose response curve. The mechanisms for these effects are not clear, but several systems may be involved that interact with the above facilitatory cascades.

i) Gs coupling. µ receptors are believed to be coupled though Gi protein that blocks the opening of calcium channels and increase K conductance leading to inhibition. It has been argued that at very low concentrations, there may be a Gs (stimulatory coupling) that becomes evident as the Gi coupling becomes tolerant and inactive.

ii) Opiate have been shown to activate protein kinase C (among others). PKC activation can lead to phosphorylation of various receptor subunits such as the for the NMDA receptor (see above). Such phosphorylation would thus lead to a paradoxical sensitization of the NMDA receptor, the role of which in spinal facilitation is well known.

iii) Bulbo-spinal facilitatory loop. As reviewed above, descending serotonergic pathways have been implicated in a pro excitatory component of the dorsal horn. Earlier work indicated that opiates with an action in the brainstem can indeed lead to the activation of such descending pathways for noradrenaline (considered to be largely inhibitory) and serotonin which may be mixed in its effects. Such excitation has been offered as a mechanisms for increasing dorsal horn excitability.

iv) Inhibit inhibition. Opiates are considered to be largely inhibitory. Opiate receptors have been identified on inhibitory interneurons such as for GABA and Glycine. The earliest work on spinal opiate actions was to shown that the glycine inhibition of the Renshaw cell in the motor horn was blocked and this was considered to the because of the increased motor tone observed with high dose opiates. A similar arrangement likely exists in the dorsal horn and would serve to exacerbate afferent input, particularly that arising from µ afferents.

v) Excitatory metabolite. Opiates with –OH can be glucuronyl conjugated. Considerable work has shown that such conjugates are highly excitatory and can lead to hyperalgesic states. This conjugation is considered to occur in the periphery, but central conjugation may also occur: (GABA).
J. TRANSITION FROM ACUTE – INFLAMMATORY TO CHRONIC PAIN.

In the preceding sections, we have reviewed the mechanisms underlying the encoding of acute high intensity stimuli to a pain response and then the systems which are activated by virtue of a peripheral injury to tissue. It is now appreciated that following certain surgical interventions, that persistent (>3-6 months) may occur pain lasting for more than 3 to 6 months after a surgical intervention. The mechanisms for these persistent changes are not clear. Direct injury to peripheral nerves as induced by stretching or compression are an important possibility. The risk for neuropathic pain after tumor resection may increase when a tumor has infiltrated or compressed peripheral nerves, or when surgery is combined with radiation or neurotoxic chemotherapy. More recently, it has become evident that in the face of chronic local inflammation there may be substantive changes in the biology of the afferent systems. Thus, after chronic inflammation in animals models of 18-20 days or greater, there are notable changes including the appearance of markers for nerve injury such as activation transcription factor 3 (ATF3) in the dorsal root ganglia. Current work thus leads to the speculation that chronic inflammation may indeed lead to changes in afferent biology that initiates persistent changes in function and pharmacology. Thus in such chronic arthritis model. In the early phase antiinflammatories and certain anticonvulsants are known to be effective. In the later stages, when ATF3 is observed, the anti-inflammatories were found to be considerably less effective while the anticonvulsant remained active.

K. SUMMARY

In summary, as indicated in Figure 17:
- Post tissue reflects sensitization of the peripheral terminal in response to the local release of a variety of factors that initiate spontaneous activity and a sensitization of the peripheral terminal
- There is also a potent central (spinal) sensitization that leads to an enhanced responsiveness of dorsal horn neurons that receive ongoing small afferent traffic.
- This condition leads to an enhanced response to input from the injured receptive field and an enlargement of the peripheral fields that can now activate those neurons though originally ineffective subliminal input.
- Over longer interval of inflammation there may be a transition to the biology that reflects nerve injury.

Figure 17. Summary of mechanisms of peripheral injury evoked pain processing. See Text for details.
READINGS


L. HISTORICAL NOTES

Patrick Wall (left) and Ronald Melzack (right) proposed in 1966 a formalization of the idea that encoding of high intensity afferent input was subject to modulation. A variety of interventions could lead to alterations in the stimulus-response relationship: increase / decrease in the pain response to a given stimulus. This was referred to as the “Gate Control Theory”. Although the details of the concept are not precisely correct, it led to the model shown below in which facilitatory and inhibitory input led to the augmentation or decrementation of output of a spinal transmission neuron. These mechanisms were believed to account for the newly discovered “wind-up and the effects of various manipulations on altering pain perceptions e.g. absence of pain in men wounded in battle, etc.

Robert Galambos in the early 60’s argued for the role of non neuronal cells in modulating neuron to neuron transmission.
Malignant Hyperthermia (MH) is an inherited muscle disorder characterized by hypermetabolism and triggered by potent volatile anesthetics and the depolarizing muscle relaxant succinylcholine. Clinical signs include hypercarbia, tachycardia, hyperthermia and metabolic acidosis due to abnormal calcium homeostasis resulting in runaway hypermetabolism in the skeletal muscle. Rhabdomyolysis can occur along with disseminated intravascular coagulopathy (DIC) and multi-system organ failure. Early reports of mortality in excess of 70% have been reduced to less than 10% by improved monitoring resulting in early detection and treatment with dantrolene.

HISTORY
One of the earliest references to an MH-like problem was 1929 when the French pathologist Ombredanne\(^1\) reported postoperative pallor and hyperthermia associated with high mortality in children, however this condition was not identified as a genetic trait. In 1960 Australian physicians Denborough and Lovell\(^2\) reported the first case of a familial history of anesthetic deaths during ether administration. The reported patient barely survived a halothane-induced MH episode. In 1969 Canadian physicians Kalow and Britt\(^3\) described a metabolic error of muscle metabolism noted in patients recovered from MH episodes, forming the basis for diagnostic contracture testing. In 1975 Harrison\(^4\), a South African, described the efficacy of dantrolene in treating porcine MH. This became the foundation for successfully managing a condition that had been termed “the anesthesiologist’s nightmare” due to its unexpected nature and high mortality.

INCIDENCE
The incidence of MH is reported to range from 1:4500 to 1:60,000 general anesthetics (geographic variation is related to the gene prevalence). Approximately 50% of MH-susceptible individuals have had a previous triggering anesthetic without developing MH\(^5\). MH is rare in infants and the incidence decreases after 50 years of age with males more commonly reported than females.\(^6\) The reasons for these variations are not understood.

MH has been clearly associated with Central Core Disease, multiminicore disease, and King or King-Denborough Syndrome. Association with other disorders such as Duchenne Muscular Dystrophy, myotonia, mitochondrial myopathies, sudden infant death syndrome (SIDS), and neuroleptic malignant syndrome (NMS) is controversial. Exercise-induced MH-related death in adults, especially during exposure to hot environments, has been reported.\(^7\),\(^8\)

MECHANISM
Exposure to triggering anesthetics (all potent volatile anesthetics and succinylcholine) causes decreased control of intracellular calcium resulting in a release of free unbound ionized Ca\(^{++}\) from storage sites in the skeletal muscle. The calcium pumps attempt to restore homeostasis which results in ATP utilization, increased aerobic and anaerobic metabolism, and a runaway metabolic state. Rigidity occurs when unbound myofibrillar Ca\(^{++}\) approaches the contractile threshold.

CLINICAL PRESENTATION
Onset of clinical signs can be acute and fulminant or delayed. MH can occur at any time during the anesthetic, and has been reported to occur as late as 24 hours postoperatively. Trismus or masseter muscle spasm following inhalation induction and succinylcholine is associated with an approximately 50% incidence of MH diagnosed by contracture testing. Trismus is often not associated with signs of a fulminant MH episode, however patients must be closely observed for evidence of hypermetabolism as well as rhabdomyolysis. The presence of whole body rigidity or signs of hypermetabolism following trismus increase the risk of MH susceptibility as an etiology. Elevation of CK postoperatively to greater than 20,000 has a strong association with a subsequent MH diagnosis.

Clinical signs and symptoms reflect a state of increasing hypermetabolism. The onset of hyperthermia can be delayed. The earliest signs of MH include tachypnea (in the nonparalyzed patient) and increased end-tidal CO2 levels. Rigidity, masseter or whole body, occurs in about 75% of cases. Signs of increased sympathetic activity include tachycardia, dysrhythmias, sweating and hypertension.

Supportive laboratory tests for confirmation of MH diagnosis include elevated end-tidal CO2, blood gas analysis showing a mixed respiratory-metabolic acidosis, elevated serum creatine phosphokinase (CK) postoperatively, elevated serum and urine myoglobin and increased serum K\(^+\), Ca\(^{++}\), and lactate (these findings can be very transient).

TREATMENT
Discontinue triggers immediately and hyperventilate with 100% oxygen. IV Dantrolene should be given early and rapidly when MH is suspected.
The initial dosage is 2 mg/kg IV, repeated every five minutes to effect or to a maximum of 10 mg/kg (this limit may be exceeded if necessary). After successful treatment, dantrolene is continued at 1 mg/kg IV q 6 hr for 24 to 48 hours to prevent recrudescence of symptoms. Calcium channel blockers should not be given in the presence of dantrolene as myocardial depression has been demonstrated in swine. Symptomatic treatment during an MH episode may include cooling (stop cooling interventions at 38-39 degrees C to avoid post-treatment hypothermia), antiarrhythmics, management of hyperkalemia, mannitol and/or furosemide to induce diuresis (note that mannitol is present in dantrolene) and sodium bicarbonate. Interventions should be guided by blood gas analysis and clinical signs; administration of dantrolene will usually reverse symptoms rapidly. It is critical that all sites where general anesthesia is administered, including ambulatory and oral surgery centers, have adequate dantrolene supplies to treat an adult patient with MH. Several tragic injuries and deaths have occurred due to delay in treatment in these settings.

**ANESTHESIA FOR MH SUSCEPTIBLE (MHS) PATIENTS**

Pretreatment with Dantrolene 1.5-2 mg/kg IV prior to induction is no longer recommended. Choose non-triggering anesthetic agents. Safe anesthetic agents include nitrous oxide, etomidate, ketamine, propofol, all narcotics, all local anesthetics, all barbiturates, all benzodiazepines and all non-depolarizing muscle relaxants. Agents used for reversal of muscle relaxants are also safe. Prepare the machine by removing vaporizers (if possible) or taping over the dials and replacing rubber hoses and soda lime. Flush with high flow oxygen (5 L/m) for 10 minutes.

Standard monitors are used with an emphasis on end-tidal CO2, oxygen saturation, and core temperature (skin monitors may not reflect core changes). Arterial and central venous pressures need be monitored only if indicated by the surgical procedure or the patient’s medical condition. Avoidance of perioperative exposures to potential trace-gas contamination (e.g. the recovery room) is not necessary.

**EVALUATION OF SUSCEPTIBILITY**

Patients are referred for evaluation for a number of reasons including unexplained intraoperative death in family members, history of adverse anesthetic event (e.g. trismus), perioperative fever, persistently elevated serum creatine phosphokinase (CK) levels, history of rhabdomyolysis, and associated myopathies (e.g. central core disease). A resting level serum CK level is often obtained in patients suspected of being MHS and may be elevated in approximately 70% of affected individuals.

A clinical grading scale has been devised, and while imperfect, it can help determine whether an individual case fits the diagnosis of MH.

**TABLE 2 – CRITERIA USED IN THE CLINICAL GRADING SCALE FOR MALIGNANT HYPERTHERMIA (MH)**

<table>
<thead>
<tr>
<th>PROCESS</th>
<th>CLINICAL CRITERIA</th>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle rigidity</td>
<td>Generalized rigidity</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Master muscle rigidity</td>
<td>15</td>
</tr>
<tr>
<td>Muscle breakdown</td>
<td>Creatine kinase &gt; 10,000 units/l</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Cola-colored urine</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Excess myoglobin in urine or serum</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory acidosis</td>
<td>End-tidal CO2 &gt; 55 mmHg; PaCO2 &gt; 60 mmHg</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Inappropriate tachypnea</td>
<td>10</td>
</tr>
<tr>
<td>Temperature increase</td>
<td>Rapidly increasing temperature</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Inappropriate temperature &gt; 38.8°C</td>
<td>10</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>Unexplained sinus tachycardia, ventricular tachycardia, or ventricular fibrillation</td>
<td>3</td>
</tr>
<tr>
<td>Family History</td>
<td>MH history in first-degree relative</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>MH history in family, not first-degree relative</td>
<td>5</td>
</tr>
</tbody>
</table>

Only the highest score in any one process should be used when more than one event or sign occurs in a process. The more criteria that a patient fulfills, the more likely that an MH episode has occurred. If only one criterion is fulfilled, then malignant hyperthermia is not likely, whereas malignant hyperthermia is almost certain if all criterial are fulfilled. Other criteria to consider include base excess > -8 mEq/L (10 points), pH < 7.25 (10 points), and rapid reversal of malignant hyperthermia signs with dantrolene therapy (5 points). The likelihood according to point score: 0, almost never; 3-9, unlikely; 10-19, somewhat less than likely; 20-34, somewhat greater than likely; 35-49, very likely; ≥ 50, almost certain. Adapted from Larach et al., with permission.

The muscle biopsy contracture testing known as either the caffeine/halothane contracture test (CHCT) or the in vitro contracture test (IVCT) has always been considered the “gold standard” diagnostic test for MH. Freshly excised muscle, usually from the vastus lateralis or gracilis, is dissected into strips which are mounted in baths and tested with caffeine and halothane alone or in combination; contracture
responses are measured and interpreted according to standardized values. Testing centers in North America have been reduced to five due to several factors including reluctance of insurance companies to pay for the expense of surgery and testing and increased availability of genetic testing. Contracture testing cannot be done on children under 5 years or under 20 Kg weight.

**MOLECULAR GENETICS**

MH is an autosomal dominant trait; therefore, patients with this condition will have inherited it from at least one parent. However, it is quite common for neither parent to have shown signs of MH either because they have not been exposed to triggering anesthesia or because they did not react.

Two MHS-causative genes have been identified: **RYR1** (MHS1 locus) and **CACNA1S** (MHS5 locus).  
**RYR1** encodes the type 1 ryanodine receptor of skeletal muscle and mutations of this gene are identified in up to 70-80% of individuals with confirmed MH and in patients with Central Core Disease (CCD). More than 180 mutations in **RYR1** have been associated with MH or CCD, with over half appearing in only one or a few families. **CACNA1S** encodes the 1-subunit of the skeletal muscle dihydropyridine receptor L-type calcium channel. Mutations in this gene account for about 1% of all MHS (2 gene mutations identified). Three additional loci have been mapped, but the genes have not been identified: MHS2, MHS4 and MHS6.

Patients must be carefully selected for genetic testing in order to maximize sensitivity. Usually this means either a positive muscle contracture test or strongly suggestive family or clinical histories for MH. In these cases, complete sequence analysis of the entire **RYR1** coding region increases the detection rate to 70-80%. Linkage analysis for all MHS loci is considered in families with multi-generational (at least two) unequivocal MH diagnosis in 10 family members or more. Discordance between contracture testing and molecular genetic testing is observed in up to 10% of individuals.

**MHAUS**

The Malignant Hyperthermia Association of the United States (MHAUS) is an active organization which provides support for patients and physicians. Their website found at www.MHAUS.org provides resources for patients, families, and medical providers. MHAUS also sponsors a 24-hour hotline for providing assistance to physicians who are managing MH susceptible patients or treating acute MH episodes.

Also associated with MHAUS is the North American MH Registry, situated in Pittsburgh, PA. Information about MH episodes (via the American Medical Record Association AMRA report) and testing is stored in the Registry where it is available for approved research and reporting.

**REFERENCES**