

# IARS



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# Anaesthesia for Secreting Endocrine Tumours

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Secreting endocrine tumours represent an uncommon group of clinical problems, but provide substantial anaesthetic challengers that require knowledge of the underlying pathology, high levels of clinical skill and a well structured management plan.

The consequences of endocrine tumours will depend on the anatomical site and on the nature of the secretions that are produced. A number of malignant conditions giving rise to the paraneoplastic syndrome may liberate hormonal substances closely resembling normal endocrine secretions (notably TSH and PTH). The range of endocrine disease is vast, with pituitary disease potentially affecting every other endocrine system in addition to exerting anatomical neurological problems. It is not possible to cover all of the endocrine conditions in a single topic and therefore the focus of this lecture will be on hyperthyroid states, hyperparathyroidism, carcinoid syndrome and pheochromocytoma.

## **HYPERTHYROIDISM**

Thyrotoxicosis affects approximately 2% of women and 0.2% of men in the general population. The commonest cause of hyperthyroidism is Graves' disease, but other causes include toxic nodular goitre, thyroiditis, follicular carcinoma, pregnancy (especially molar pregnancy), TSH-secreting pituitary adenoma and drug induced hyperthyroidism, for example during amiodarone therapy.

The metabolic consequences of hyperthyroidism include weight loss, increased appetite and diarrhoea. The often dramatic eye signs are limited to patients suffering from Graves' disease, but all patients may have hyperactivity, anxiety, nervousness and tremor. Muscular weakness may also occur, particularly in the proximal muscle groups.

The cardiovascular consequences include sleeping heart rates greater than 90 beats per minute and an exaggerated increase with exercise. Atrial fibrillation occurs in 5-15% of hyperthyroid patients. Cardiac output is generally elevated, but some degree of exercise impairment may be seen. Increased flow during left ventricular ejection may lead to an aortic flow murmur. Systolic arterial pressure may be elevated, but systemic vascular resistance is reduced and pulse pressure is wide. Thyroid hormone has a direct inotropic effect on cardiac muscle in addition to catecholamine stimulation. Cardiac failure may occur for a variety of reasons, including rate-related heart failure, cardiomyopathy or ischaemic disease. Generally, the increased cardiac output is sufficient

to meet the needs of the tissues and therefore the term "high output cardiac failure" is not strictly accurate. Treatment with beta blockade improves the range of cardiovascular disturbances and it is not contraindicated in thyrotoxic cardiac failure<sup>1</sup>.

The diagnosis of suspected hyperthyroidism is based on the measurement of TSH and free T4. If these are both normal, then hyperthyroidism is excluded, whereas a low TSH and a high T4 confirms the diagnosis. A low TSH with a normal T4 requires the measurement of T32.

Hyperthyroid states should be corrected preoperatively with the thionamides, carbimazole (or its pre-drug methimazole) or propylthiouracil. Carbimazole requires only once daily dosage of 20-30mg, whereas propylthiouracil needs a much larger dose of 1-200 mg three times daily. Propylthiouracil inhibits conversion of T4 to T3 but this is of little practical value in preoperative preparation, although it may be useful in managing hyperthyroid states. Both of these agents take 2-4 weeks to achieve adequate control in over 90% of patients.<sup>2</sup> In the absence of beta-blockade, clinical euthyroid states are sufficient to allow surgery to proceed; it is not necessary to establish completely normal T4 and TSH levels prior to surgery. Preoperative iodine therapy used to be advocated as iodine loading switches the thyroid gland into an uptake mode and inhibits hormone release. It may also decrease the vascularity of the gland. However, the value of this technique is debated and, if surgery is delayed for any reason, it poses the risk of an exacerbation of the thyrotoxicosis. While beta-blockade will control most of the symptoms of hyperthyroidism, it is not recommended as a sole preoperative preparation as it does not adequately protect the patient against the risk of thyroid storm.

There is no evidence that any one anaesthetic technique is superior to any other for thyroid surgery. Regional anaesthesia has been recommended for ill patients requiring thyroidectomy, but there is no evidence of that it is superior and bilateral deep cervical plexus block carries the risk of bilateral phrenic nerve paralysis. Although many anaesthetic texts recommend that enlarged thyroids should be regarded as difficult intubations, there is no evidence of a higher incidence of failed intubation in patients with large goitres in the absence of malignancy or gross and obvious anatomical distortion.<sup>3</sup>

The greatest risk is the development of thyroid storm, which carries significant morbidity and mortality.<sup>4</sup> As thyroid hormone acts by nuclear

transcription, the consequences of increased hormone release do not manifest for several hours after the event, and so thyroid storm generally only presents 4-6 hours postoperatively. The classic symptoms include a sudden increase in temperature with tachycardia, moderate hypertension, agitation and confusion. The presentation may be confused with malignant hyperthermia and, if there is doubt, dantrolene should be given as it will decrease the temperature but not affect the other aspects of thyrotoxicosis. Beta-blockade is the mainstay of haemodynamic control. Propranolol has the advantage of inhibiting the conversion of T4 to T3, but esmolol has the benefit of its short action and more specific  $\beta_1$ -adrenergic blockade. In the presence of hypertension and arrhythmias, the anti-catecholamine effect of magnesium may be of benefit. Verapamil may assist in the control of acute onset atrial fibrillation. If sedation is necessary, chlorpromazine 5 mg is probably the drug of choice as it has central antipyretic effects in addition to its excellent sedative properties. There is no point in administering thionamides following thyroidectomy, as the source of hormone has been removed.

## HYPERPARATHYROIDISM

Primary hyperparathyroidism occurs with an incidence of about 25 per 100,000 of the population. Over 90% have a single parathyroid adenoma, and the remainder have multiple lesions, and are usually part of the MEN disorders. Less than 1% of all parathyroid tumours are malignant.

The presentation of primary hyperparathyroidism may be subtle, and may remain clinically undetected for many years. All patients with primary hyperparathyroidism have elevated plasma calcium concentrations and the principle features of hypercalcaemia due to hyperparathyroidism are summarised in table 1. Untreated, these patients have a significantly higher mortality than the general population, and even after tumour excision, the risk of death is higher than the normal population.<sup>5</sup>

Organ System	Symptoms and Signs
Renal	Polyuria*, polydypsia* and diabetes insipidus*; nephrocalcinosis and renal stones; diminished bicarbonate absorption and renal tubular acidosis; phosphate and magnesium loss; glycosuria*
Cardiovascular	Hypertension, diminished circulating blood volume*, ECG changes: short QT interval, prolonged PR interval
Gastrointestinal	Abdominal pain, weight loss, vomiting*; peptic ulceration; pancreatitis
Skeletal	Osteitis fibrosa cystica; bone pain; demineralization; pathological fractures; joints: chondrocalcinosis, pseudogout, ligamentous calcification
Central Nervous System	Depression; personality changes; memory loss; psychosis*; fatigue
Metabolic	Electrolyte abnormalities; muscle weakness

Table 1: Features of hyperparathyroidism. (\*denotes features usually found in acute dysequilibrium states.)

Mild hypercalcaemia is seldom symptomatic. Dysequilibrium hypercalcaemia, refers to a progressive and rapid rise in total plasma calcium levels (usually above 3mmol/L), with the clinical features of listed above. This is a medical emergency, and may necessitate ICU admission. The most crucial factor is the re-establishment of cardiovascular homeostasis and adequate renal function, rather than the reduction of the plasma  $\text{Ca}^{2+}$  to any predetermined value. Hypercalcaemia induces a diuresis, due to the stimulation of the renal  $\text{Ca}^{2+}$  receptor and, consequently, patients with dysequilibrium hypercalcaemia are usually severely fluid depleted. Fluid replacement should be with saline solutions, using central venous access. Hypokalaemia and hypomagnesaemia may occur with increased risk of cardiac dysrhythmias; potassium and magnesium supplementation should be considered. There is no literature to support any specific plasma  $\text{Ca}^{2+}$  concentration as a cut-off value above which anaesthesia becomes unacceptably hazardous. Once the plasma volume is re-expanded, the patient stabilised and the disease confirmed by PTH measurement, an emergency parathyroidectomy should be performed. The operation leads to an almost immediate correction of the condition.

Various other approaches have been used, but are of questionable value. Diuretics such as furosemide can reduce serum calcium levels, but are controversial. Phosphate to lower calcium concentrations can no longer be recommended due to the risk of calcium phosphate deposition in the tissues. Other agents that lower the plasma  $\text{Ca}^{2+}$  include plicamycin (mithramycin), calcitonin and glucocorticoids. Plicamycin, a cytotoxic, impedes osteoclastic bone resorption, but may have toxic effects. The diphosphonates (pamidronate, etidronate, clodronate) also inhibit osteoplastic activity but take several days to be effective, and their use to lower  $\text{Ca}^{2+}$  prior to parathyroidectomy is seldom necessary and are reserved for the hypercalcaemia found in metastatic bone cancer.

Preoperative preparation for conventional parathyroidectomy should include a full cardiovascular workup, as these patients have an increased risk of hypertension and may have non-specific ECG abnormalities, thrombo-embolic disease and stroke. The main anaesthetic considerations for a patient undergoing parathyroidectomy are fluid balance management, neuromuscular blockade and the possibility of cardiac dysrhythmias. Intraoperative invasive pressure (venous or arterial) monitoring should not be necessary. The response to muscle relaxants may be unpredictable, and neuromuscular transmission monitoring is essential if muscle relaxants are used.<sup>6</sup> Apart from the slight distortion of the neck, there is no reason to avoid using a laryngeal mask airway, and this would obviate the need for muscle relaxation. Increasingly, there is a trend towards regional anaesthesia, particularly where improved tumour location techniques permit

unilateral neck exploration. Superficial cervical plexus blockade with local anaesthetic supplementation is a simple, safe technique for either unilateral or bilateral parathyroid exploration, and may be performed on an outpatient basis on suitable patients.<sup>7,8</sup> However, bilateral deep cervical plexus blockade should not be necessary<sup>9</sup> and carries the risk of bilateral phrenic nerve paralysis.

In the immediate post operative period, airway problems may occur due to recurrent laryngeal nerve injury. The "hungry bone syndrome" of rapid reuptake of calcium, phosphate and magnesium into bone following the removal of a parathyroid tumour, and the consequent hypocalcaemia, may precipitate cardiac arrhythmias, and very occasionally, life-threatening laryngeal spasm. It usually occurs in patients who have had a dysequilibrium syndrome or when severe osteopaenia is present and may occur within hours of surgery. Treatment consists of intravenous calcium chloride, and oral calcium gluconate or carbonate.

### CARCINOID SYNDROME

These tumours are derived from enterochromaffin cells and occur mainly in the gut, but may also arise from the lungs and bronchi. Carcinoid tumours contain and secrete a large number of amine and peptide hormones including serotonin, corticotrophin, histamine, dopamine, substance P, neurotensin, prostaglandins and kallikrein (which stimulates the production of bradykinin and tachykinins). Despite this only a minority (15-18%) of patients with carcinoid tumours progress to develop carcinoid syndrome.

The management of carcinoid tumours is essentially surgical, and complete removal of the tumour will often result in a cure, unless there are widespread metastases. Liver transplantation has occasionally been performed in an attempt to remove multiple hepatic metastases.

The carcinoid syndrome occurs when the various hormones are released into the systemic circulation and usually follows metastatic disease, as the liver normally metabolises the active peptides and amines before they reach the systemic circulation. Rarely, tumours not drained by the portal system (such as the lungs or ovaries) may produce carcinoid syndrome without hepatic metastases.

Diarrhoea and flushing are the commonest symptoms of the carcinoid syndrome. The diarrhoea is characterised by watery stools, colicky abdominal pain and urgency of defecation and may respond to ondansetron.<sup>10</sup> It may be associated with significant fluid and electrolyte abnormalities that should be corrected prior to anaesthesia. Bronchoconstriction and hypotension may be severe and resistant to conventional therapy, particularly in the perioperative period.

Carcinoid heart disease, with abnormal echocardiographic findings, occurs in up to 70% of

patients with carcinoid syndrome. The characteristic lesions are plaque formation and thickening of the pulmonary and tricuspid valves leading to valvular insufficiency and occasionally stenosis. Left-sided valvular lesions are uncommon, probably because the lung reduces the high concentrations of serotonin and the tachykinins, to which the right heart is subject.

Diagnosis is based initially on symptomatology supported by biochemical tests. Urinary 5HIAA is the standard initial confirmatory test although false positives may occur in patients taking chlorpromazine or who have recently ingested bananas, avocado, pineapple, walnuts, chocolate or coffee. Plasma chromagrannin A is almost invariably elevated in metastatic carcinoid and is a useful marker of the success of treatment. The cardiac status of patients with carcinoid syndrome should be evaluated by echocardiography preoperatively, given the high incidence of cardiac involvement. Carcinoid-associated cardiac disease and right heart failure are significant predictors of post-operative morbidity and mortality<sup>11</sup>[Connolly]. Careful fluid and electrolyte assessment and correction are essential.

The major intraoperative concern is the occurrence of carcinoid crisis with severe hyper/hypotension and bronchospasm. Prior to the advent of somatostatin, the generally recommended approach to patients with carcinoid syndrome was preoperative preparation with a variety of serotonin antagonists including ketanserin, methysergide and cyproheptadine. However, introduction of the long-acting somatostatin analogue, octreotide proved so immediately and obviously efficacious<sup>12-14</sup> as to reduce previous forms of perioperative management to the status of secondary level therapy. There is no absolute guideline for the perioperative use of octreotide but recommendations include the administration of 100 µg subcutaneously prior to surgery. It is generally recommended that 50-100 µg octreotide be given intravenously at induction. An intravenous infusion at a rate of 50-100 µg/hour can be used intraoperatively, with further bolus doses given intraoperatively as required for the control of symptoms. As intraoperative blood loss may be considerable, the presence of hypovolaemia must always be considered should hypotension prove unresponsive to octreotide.

Most of the currently available anaesthetic agents have been used in conjunction with carcinoid syndrome, with shorter acting agents preferred.<sup>15</sup> Agents that release catecholamines or histamine should be avoided. Regional anaesthesia is controversial, since the high quality post-operative pain relief available from regional techniques is likely to be advantageous, but intraoperative management of hypotension associated with neuraxial blockade may be problematic. Although most texts recommend the avoidance of catecholamines, there are reports of good responses to epinephrine and phenylephrine in patients with otherwise unresponsive hypotension<sup>16</sup>

and catecholamines have been successfully used in cardiac surgery for carcinoid heart disease.<sup>17</sup> There have been no reports of triggering of carcinoid crisis by catecholamines since the introduction of octreotide. Both phenylephrine and ephedrine have been extensively used during carcinoid resections.<sup>11</sup> Bronchospasm should be managed in the first instance with deepening levels of volatile anaesthesia, and non-catecholamine bronchodilators such as ipratropium bromide. Antihistamines may be useful, but inhaled  $\beta$ -agonists should not be withheld if bronchospasm fails to respond to other measures. There are no restrictions on post-operative pain management.

## PHAECHROMOCYTOMA

Phaeochromocytomas are catecholamine-secreting tumours derived from neural crest tissues and may arise from either the adrenal medulla or from other neural crest derivatives, mainly the sympathetic chain. The clinical features of phaeochromocytoma are frequently pathognomonic, but it may also present with a bewildering variety of symptoms. One or other of a triad of excessive sweating, headache and palpitations occurs in over 90% of patients on careful inquiry, but all three are present in less than 50%. Patients may present with anxiety, tremor, nausea, vomiting and weight loss, chest and abdominal pain, peripheral vascular disease, cardiac failure and cerebral vascular accident. Hypertension is classically episodic, but may be sustained in up to 50% of patients. Heart rate is unpredictable and arrhythmias may occur. Left ventricular failure and pulmonary oedema may be present, particularly if the patient has developed a catecholamine-induced cardiomyopathy. Abdominal pain, presumably due to bowel ischaemia, together with chronic constipation and pseudo-obstruction may lead to an erroneous diagnosis of an acute abdomen. Phaeochromocytoma crisis may present with severe pounding headache, sweating, pallor, palpitations and a feeling of impending doom but only a minority of patients with phaeochromocytoma will have experienced such a crisis. Metabolic problems, including weight loss and frank diabetes mellitus may be presenting signs, and occasionally patients may present in diabetic keto-acidosis.<sup>18</sup>

Measurement of urine plasma free metanephrines are now the standard diagnostic screening tests.<sup>19</sup> CT scanning of both adrenals should be performed.<sup>20</sup> If this is negative, or if malignancy or multiple tumours are suspected, radionuclide scanning with <sup>123</sup>I-MIBG should follow. Occasionally, octreotide scintigraphy has revealed small tumours not detected with MIBG.<sup>21</sup> PET scanning offers a highly effective method for tumour localization.<sup>22</sup>

Patient evaluation should include a detailed cardiovascular assessment, looking particularly for evidence of catecholamine-induced cardiomyopathy. A chest x-ray and 12-lead ECG should be performed

and evidence of myocardial dysfunction evaluated. Left ventricular hypertrophy is frequently seen, as are ST and T-wave abnormalities, but there appears to be little point in attempting to correct these by medical management. These changes generally resolve once the tumour is removed. Target organ damage from hypertension should be sought.

Medical management, predominantly with alpha-adrenergic blockade, prior to surgery is advised.<sup>23</sup> Phenoxybenzamine is generally favoured as it is non-competitive and offers control during surges of release of catecholamines, but it produces significant, unpleasant postural hypotension, lethargy and nasal congestion and can result in post-operative hypotension. Selective alpha1-blocking drugs, including prazosin, and the longer acting agent doxazosin<sup>24</sup> have also been suggested. Beta-adrenergic blockade is controversial, and it is the author's personal practice to avoid using these drugs if at all possible. Calcium channel blocking have been used successfully.<sup>25</sup>

There are no absolute guidelines as to the adequacy of preparation of a patient prior to surgery. Suggested guidelines have included the following:

- Supine arterial pressure not greater than 160/90 mm Hg
- Orthostatic hypotension, with the arterial pressure not falling below 90/50 mm Hg
- ECG free of ST segment and T-wave changes for at least two weeks
- Not more than 1 premature ventricular contraction every five minutes<sup>26</sup>

There is little evidence that patients with relatively stable disease are hypovolaemic, but patients who have recently suffered a hypertensive crisis may have significantly diminished blood volume. In these circumstances, regular monitoring of haematocrit may be helpful. Adequate preoperative preparation, may be achieved in as little as 5-7 days. The most practical guide is to increase alpha blockade on a daily basis until adequate haemodynamic control is achieved and then to proceed to surgery.

Various approaches to the management of anaesthesia have been recommended. Most anaesthetic agents have been used with relative safety, although agents releasing histamine should be avoided, as should agents that might induce tachycardia such as atropinics. Droperidol inhibits the reuptake of catecholamines, and is best avoided. Where phenoxybenzamine has been used, it should be omitted on the morning of surgery as it has a very long half-life. Beta-blockade, where utilised, should also be withdrawn timeously, so that the patient is not under beta-blockade at the time of tumour excision. Whether or not epidural anaesthesia is performed as part of the anaesthetic technique is largely a matter of choice, although it will not enhance haemodynamic control due to catecholamines release and may make management

of hypotension after tumour extirpation more difficult.

Before induction, good intravenous access should be obtained and direct arterial pressure monitoring established. Induction of anaesthesia may be followed by either hypotension or hypertension, and a range of pharmacological agents to handle either of these eventualities should be immediately to hand. Indirect-acting vasopressors, such as ephedrine, should be avoided. Once the patient is stabilised, central venous access should be established for both monitoring and drug administration purposes. There is little evidence to support the use of pulmonary artery catheters in these patients, even where cardiomyopathy has been shown to be present preoperatively. However, transoesophageal echocardiography can be valuable, particularly in terms of assessing adequate ventricular filling and myocardial performance.

Intraoperative haemodynamic control has been performed with a variety of  $\alpha$ -adrenergic blocking agents,  $\beta$ -adrenergic blocking agents and direct acting vasodilators. Sodium nitroprusside has been the most widely used vasodilator although it may be difficult to titrate the infusion with sufficient accuracy to control the very rapid changes in blood pressure. Phentolamine has been used, but has also proved difficult to control adequately. On the basis that calcium antagonism will oppose both the release of catecholamines and their peripheral effects, calcium channel blocking drugs have recently been used for intraoperative control with some success,<sup>25</sup> particularly with nicardipine<sup>27</sup> at a rate of 2-6 micrograms/kg/min, often with accompanying beta adrenergic blockade. However, nicardipine has a long half-life of 4-6 hours and shorter-acting drugs may be preferable. A similar rationale applies to the use of magnesium sulphate, given as an initial bolus of 2-4 gm with an infusion of 2 gm/hour and intermittent 2 gm boluses to a maximum of 26 gm. Good results have been achieved with this technique, often as a sole agent or in emergency situations.<sup>28-32</sup> Magnesium has the additional advantages that it is rapidly excreted through the kidneys and an immediate antagonist is available in the form of calcium chloride. It has been successful in circumstances where sodium nitroprusside has failed.<sup>33</sup> Once the tumour is removed, vasodilator therapy should be withdrawn and aggressive volume expansion undertaken. Care should be taken to ensure an adequate haematocrit, as this is a vital component of peripheral resistance in a maximally vasodilated patient. Brief periods of adrenergic support, particularly with phenylephrine, may be necessary immediately after tumour excision, but it should be possible to withdraw or adrenergic support by the end of the procedure. Blood sugar monitoring should be performed at hourly intervals throughout the procedure.

A range of surgical approaches is available, and the surgical technique should be determined by the size and location of the tumour, the possi-

bility of multiple tumour sites and the skill of the operator. Laparoscopic excision has received considerable recent support<sup>34,35</sup> but the creation of a capnoperitoneum has been associated with increased haemodynamic instability,<sup>36</sup> leading to the abandonment of the procedure in one report.<sup>37</sup>

Postoperatively, high care for continuing monitoring is appropriate. Ventilatory support should not be necessary, unless dictated by the nature of surgery and the site and size of the tumour. Provided that adequate haemodynamic control was established intraoperatively, post-operative haemodynamic instability should not occur, and if hypotension is problematic, the possibility of bleeding should be considered. Elevated blood pressures, together with persistently elevated plasma catecholamines may be seen for several days following surgery, presumably because of uptake and storage of catecholamines in sympathetic nerve terminals, and does not necessarily imply incomplete tumour excision. Withdrawal of catecholamines may produce marked alterations in insulin sensitivity, and blood sugar monitoring should be performed on an hourly basis for 24 hours.

The long-term prognosis is generally good, with 75% of patients returning to normal haemodynamic states. Catecholamine-induced cardiomyopathy has a surprisingly good prognosis and normal myocardial performance architecture can be re-established following complete tumour removal. Some patients will remain persistently hypertensive, but the hypertension is not paroxysmal and can be regarded as "essential" hypertension. Patients with paragangliomas, multiple tumours or with multiple endocrine neoplasias have an increased risk of tumour recurrence and should be monitored on an annual basis for at least five years following tumour excision. However recurrence of tumours as late as 15 years after original excision has been reported.

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# New Adjuvants and Agents in Pediatric Anesthesia

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## **ALPHA-2 AGONISTS**

### **PHARMACOLOGY**

Adrenergic receptors can be divided into 2 groups alpha and beta. Both of these receptors have subgroups with the alpha receptors being divided into alpha-1 (postsynaptic) and alpha-2 (presynaptic) types. However, alpha-2 adenoreceptors were subsequently discovered both postsynaptically and extrasynaptically. Currently three alpha-2 isoreceptors alpha-2a, alpha-2b and alpha-2c have been defined. The three alpha-2 subtypes bind alpha-2 agonists and antagonists with similar affinities. Alpha-2 adenoreceptors inhibition of neurotransmitter release is mediated through a decrease in calcium ion conductance that involves direct regulation of calcium entry of voltage gated calcium channel ions.<sup>1</sup>

Alpha-2 receptors are located throughout the central nervous system (as previously stated) both pre and post synaptically. The afferent terminals are found in the brain stem nuclei and spinal cord. They are located (although to a lesser extent) in the peripheral nervous system in the afferent terminals of peripheral nerves. These alpha-2 agonists presynaptically suppress the release of norepinephrine and other neurotransmitters. This suppression accounts for the circulatory effects and the effects on MAC, pain and sedation.

The locus coeruleus is a small neuronal nucleus located bilaterally in the upper brainstem and is the largest noradrenergic cell group in the brain. It is an important modulator of wakefulness and may be the major site for the hypnotic action of alpha-2 receptor agonists.<sup>2</sup> The dorsal horn of the spinal cord contains alpha-2a subtype adenoreceptors, whereas the primary sensory neurons contain both alpha-2a and alpha-2c subtypes.

Alpha-2 adenoreceptors are not found in mammalian heart and the bradycardia due to these drugs is a vagomimetic action. Two alpha-2 agonists are available for clinical use clonidine and dexmedetomidine.

### **CLONIDINE**

Clonidine is a partial agonist with an alpha-2 to alpha-1 selecting ratio of 39. It is available as 100, 250 and 300 ug tablets for oral administration, an injectable solution containing 150 ug/ml for intravenous, intramuscular local and regional use and as a transdermal patch releasing 100, 200 or 300 ug over 24 hours.

### **CENTRAL NERVOUS SYSTEM**

Oral clonidine has both sedative and anxiolytic properties. Clonidine also confers sedation and anesthetic sparing when given by the neuraxial route.

### **CARDIOVASCULAR SYSTEM**

These drugs decrease blood pressure by decreasing sympathetic outflow from the brainstem, block preganglionic sympathetic neurons in the spinal cord and reset the baroreflex. Clonidine lowers the set point around which arterial blood pressure is modulated. Heart rate decreases by decreasing sympathetic outflow and tone and resetting the baroreflex response, thus decreasing heart rate for a given increase in blood pressure. It also broadens the responses to changes in blood pressure.<sup>3</sup> Alpha-2 agonists inhibit SA node firing (via vagal effects) and prolong PR, AV and QT interval. A decrease in cardiac output is the result of activation of postjunctional vascular alpha-2 adenoreceptors.

### **RESPIRATORY EFFECTS**

In dose up to 300 ug clonidine decreases minute ventilation slightly and increases expired carbon dioxide.<sup>4</sup> It confers no significant effect on hypercapnic or hypoxic ventilatory drive. Children who receive clonidine via the caudal route do not experience depressed respiration.<sup>5,6</sup>

### **RENAL SYSTEM**

Stimulation of alpha-2 adenoreceptors decreases the secretion of vasopressin and antagonists action on renal tubules.<sup>7</sup>

### **ANALGESIA**

Alpha-2 agonists may decrease pain by blocking afferent fibers in the peripheral or central nervous system. They also may modulate efferent pain responses from the brainstem. The major effect may be due to the release of substance P in the dorsal horn cells of the spinal cord.

### **USE IN THE PEDIATRIC PATIENT**

#### **PREMEDICATION**

Clonidine is slowly but completely absorbed orally reaching peak concentrations in 60-90 minutes. It can be administered by dissolving the parenteral formulation in apple juice. The elimination half life is 9-12 hours. Half the drug is metabolized in the liver while the remainder is excreted unchanged by the kidneys or feces.

Clonidine given 1.5-2 hs prior to surgery at a dose of 4  $\mu\text{g}/\text{kg}$  mixed in apple juice gives adequate sedation children when compared with 0.4 mg/kg of diazepam. Atropine .03 mg/kg was given 60 min prior to the induction of anesthesia to avoid side effects such as bradycardia. It also attenuated the cardiovascular response to intubation in pediatric patients.<sup>8</sup> This may be especially useful in children at risk for cerebral vascular accidents and cardiac dysrhythmias. Such children would include those with hypertension from renovascular disease or renal failure, those with cerebral arteriovenous malformations or aneurysm and those with myocardial disease or aortic insufficiency. No other serious side effects were observed in this study but the long onset time to sedation was noted. Clonidine 4  $\mu\text{g}/\text{kg}$  decreased the halothane requirement needed to attenuate fluctuations in blood pressure and heart rate from 1.1% to 0.6% in children (45% reduction).<sup>9</sup>

In 90 children age 5-12 undergoing ophthalmic, urologic or otologic surgery, oral clonidine 4  $\mu\text{g}/\text{kg}$  given 105 min before induction followed by atropine 0.03 mg/kg 60 min prior to induction showed reduced pain scores and only 33% required rescue medications as compared to 90% of the placebo group in the first 12 hours postoperatively.<sup>10</sup> This may particularly be useful in longer more invasive surgeries to decrease the amount of opioid use and allow patients to be extubated earlier with adequate pain control.

In tonsillectomy patients, oral clonidine 4  $\mu\text{g}/\text{kg}$  was compared with midazolam 0.5 mg/kg. The clonidine group exhibited more intense anxiety on separation and during induction. However, the clonidine group had lower mean intraoperative blood pressure, shorter surgery, anesthesia and emergence times and decreased need for supplemental oxygen during recovery. A major problem was that the clonidine group had larger postoperative opioid requirements, pain scores and maximum excitement. Even though discharge readiness, postoperative emesis, and 24 hour analgesic requirements were the same in both groups, midazolam was judged to be better for premedication in tonsillectomy patients. Another disadvantage clonidine must be given 60 minutes prior to induction of anesthesia as compared to 30 minutes for midazolam.<sup>11</sup>

However, a recent study compared oral midazolam 0.5 mg/kg or oral clonidine 4  $\mu\text{g}/\text{kg}$  and found the onset of the two similar (30-40) with a better level of sedation, parental satisfaction and less emergence agitation in the clonidine group.<sup>12</sup> Nasal clonidine 4  $\mu\text{g}/\text{kg}$  compared with oral clonidine 4  $\mu\text{g}/\text{kg}$  allowed a steal induction in children but the onset of nasal clonidine was longer 47.5 minutes versus 38.3 minutes.<sup>13</sup>

Clonidine has been shown to decrease the anesthetic requirement for inhalational agents.<sup>14</sup> MAC reducing effects may be due to the effect on central noradrenergic neurotransmission or alpha-2 agonists may themselves be anesthetics. A recent

study evaluated the effect of premedication with clonidine 4  $\mu\text{g}/\text{kg}$  and the effect on the reduction of MAC of sevoflurane for tracheal intubation in children (MACTI). The MACTI was 3.2 in children unpremedicated without the use of N<sub>2</sub>O. Adding 60% N<sub>2</sub>O but no premedication the MACTI was 2.4. After clonidine premedication (4  $\mu\text{g}/\text{kg}$  orally) the MACTI without N<sub>2</sub>O was 1.9 and with 60% N<sub>2</sub>O, 1.4. Therefore premedication with clonidine 4  $\mu\text{g}/\text{kg}$  decreased MACTI by 56% in the presence of 60% N<sub>2</sub>O. It must be noted at least 107 minutes after premedication with oral clonidine had elapsed before the induction of anesthesia.<sup>15</sup>

Oral clonidine for premedication may have other side effects. An oral dose of 4  $\mu\text{g}/\text{kg}$  has been shown to attenuate the hyperglycemic response to infusion of glucose and surgical stress in children undergoing minor surgery possibly by inhibiting the surgical stress release of catecholamines and cortisol. It failed to suppress the increase in plasma insulin concentration, in response to glucose infusion. However it did not completely prevent hyperglycemia associated with 5% glucose administration. In addition those who received placebo and 0% dextrose infusions responded to surgery with an increase in plasma glucose concentrations but the oral clonidine group did not increase glucose. Patients who were involved in surgeries that lasted 1.7 hours had no problem with hypoglycemia. But if no intraoperative glucose is administered there is a potential risk for hypoglycemia during long operations.<sup>16</sup> Therefore glucose levels must be monitored in longer surgeries.

### NAUSEA AND VOMITING

Clonidine 4  $\mu\text{g}/\text{kg}$  orally has been shown to have a lower incidence of nausea and vomiting in patients undergoing strabismus surgery, an incidence of only 11%. However in this study all patients were hospitalized for 2 days after surgery so whether the decrease in nausea and vomiting was due to postoperative restfulness due to the sedation from the clonidine has yet to be determined.<sup>17</sup>

### SHIVERING AND DELIRIUM

Alpha-2 agonists have been shown to decrease shivering after general anesthesia without decreasing blood pressure or prolonged sedation.<sup>18</sup> Post anesthetic shivering occurs in 5-65% of patients and in addition to discomfort may be associated with hypoxemia, hypercapnia and acidosis. Caudal or intravenous clonidine 3  $\mu\text{g}/\text{kg}$  may prevent postop delirium after sevoflurane anesthesia.<sup>19</sup> Even a lower dose of intravenous clonidine 2  $\mu\text{g}/\text{kg}$  decreased emergence agitation in children after sevoflurane anesthesia.<sup>20</sup>

### CONTROLLED HYPOTENSION

Oral clonidine 5  $\mu\text{g}/\text{kg}$  the night before surgery and again 90 minutes before surgery was effective for controlled hypotension during maxillofacial surgery.

The heart rate and blood pressure during induction and intubation was decreased in the clonidine group. Children who took clonidine required significantly less isoflurane to maintain a mean arterial blood pressure of 60 mm Hg, and less fentanyl and labetalol. They also had a faster recovery and shorter recovery room stay.<sup>21</sup>

### EPIDURAL USE

Epidural clonidine has been shown to increase the duration of action of caudal analgesia in pediatric patients. Lee found that clonidine 2 µg/kg added to 0.25% bupivacaine at a dose of 1 ml/kg gave a duration of action of 9.8 hours as compared to caudal bupivacaine alone being 5.2 hours. These patients with clonidine also had a longer duration of sedation 9.1 hours vs. 2.5 hours.<sup>22</sup> A recent study by Jamali compared plain bupivacaine 0.25% (1 ml/kg) with bupivacaine 0.25% (1 ml/kg) with 1/200,000 epinephrine or bupivacaine 0.25% (1 ml/kg) with 1 µg/kg of clonidine. Duration of analgesia was 16 hours in the clonidine group, 6 hours in the epinephrine group and 7 1/2 hours in the bupivacaine alone group.<sup>23</sup>

Constant compared a mixture of 1% lidocaine and 0.25% bupivacaine with 1/200,000 epinephrine (total 1 ml/kg) with the same mixture adding either 1 µg/kg fentanyl or 1.5 µg/kg of clonidine. None of the 9 children with clonidine needed any intraoperative narcotic while only 1/9 of the fentanyl and 5/11 of the local anesthetic alone needed intraoperative narcotics. Duration of action till first analgesic was 2 1/2 hours for local anesthetic alone and 3 1/2 hours for the fentanyl or clonidine patients.<sup>24</sup>

Caudal studies done with 1% lidocaine (10 mg/kg) with 1/200,000 epinephrine vs. 1% lidocaine (10 mg/kg) with clonidine 3 µg/kg, duration of action was 50% longer in the clonidine group and 3.5 x more patients in the clonidine group had no pain. There were no side effects hemodynamically or with sedation noted.<sup>25</sup>

In single shot caudal in children with procedures lasting 90-150 minutes patients receiving either clonidine 1.5 µg/kg or fentanyl 1 µg/kg added to 1 ml/kg of 0.25% bupivacaine with 1/200,000 epinephrine and 1% lidocaine in equal parts had equal efficacy - however the fentanyl group had undesirable side effects such as vomiting and transient oxygen desaturation. This led the authors to conclude clonidine may be the drug of choice to prolong duration of caudal anesthesia by single injection.<sup>26</sup>

In combination with ropivacaine for caudal blockade addition of clonidine 2 µg/kg to 0.1% ropivacaine (1 ml/kg) resulted in better postoperative analgesia than 0.2% ropivacaine alone (1 ml/kg). This combination was not associated with any significant degree of sedation or motor blockade.<sup>27</sup>

In ambulatory inguinal hernia repair patients caudal blockade with 1 µg/kg of clonidine added to bupivacaine 0.25%, 0.75 ml/kg had a significantly

longer duration of action (360 min) than bupivacaine alone (346 min) or with 1/200,000 epinephrine (300 min). Also less additional analgesic was used in the first 24 hours at home in the clonidine group. Increasing to 2 µg/kg of clonidine did not increase the duration of action (360 min), but resulted in fewer rescue interventions for pain. Bradycardia and respiratory depression were not observed but a mild hypotension was seen in the clonidine group. Conclusions were made that caudal use of clonidine 2 µg/kg was safe in pediatric ambulatory surgery patients, however patients were kept 6 hours postprocedure.<sup>5</sup> In ambulatory surgical patients clonidine 1 µg/kg may be the best dose to prolong analgesia and decrease possible side effects such as prolonged sedation.

However, adding 2 µg/kg of clonidine to a mixture of 1 ml/kg of 0.125% bupivacaine with 1/200,000 epinephrine gave no enhancement of postoperative analgesia compared to the epinephrine alone.<sup>28</sup>

Care must be used with caudal clonidine in neonates either term or premature. Two case reports have suggested clonidine may be responsible for apneic episodes in these patients.<sup>29,30</sup>

For continuous lumbar epidural with 2% lidocaine (8 mg/kg) either 1/200,000 (5 µg/kg) epinephrine or clonidine 2 µg/kg was added. The duration of action was twice as long in the clonidine group as the epinephrine group with no side effects.<sup>31</sup>

With continuous postoperative lumbar epidural (L4-L5) infusion (in pediatric patients age 1-4 years) after urogenital surgery clonidine, .08-.12 µg/kg/hr added to 0.08% ropivacaine (0.16 mg/kg/hr) gave better postoperative analgesia, increased time to first analgesic demand and reduced total number of doses of supplemental analgesia during the first 48 h after surgery as compared to infusion of ropivacaine 0.1%, 0.2 mg/kg/hr. Analgesia was improved without any signs of increased sedation or other side effects.<sup>32</sup>

### INTRATHECAL

Clonidine 2-3 µg/kg has been added to intrathecal bupivacaine in adults. It may not offer any advantage as far as analgesia but may add more sedation and a greater decrease in blood pressure.<sup>33</sup>

### DEXMEDETOMIDINE

Dexmedetomidine displays specific and selective alpha-2 adrenoreceptor agonism. It is 8 times more specific for alpha-2 adenoreceptors than clonidine and is currently indicated for sedation in the intensive care unit. It is currently available for intravenous use only however it has been successfully administered epidurally for postoperative analgesia in humans in clinical trials.

Given as an intravenous infusion at a dose of 1.0 µg/kg for 10 minutes and then 0.2-0.7 µg/kg/hr the distribution half life (t 1/2) was 9 minutes and elimination half life of 2 hours.<sup>34</sup>

## CENTRAL NERVOUS SYSTEM

This drug causes sedation and anxiolysis. After a loading dose of 1 µg/kg and a maintenance infusion of 0.2-0.7 µg/kg/hr extubated patients required 80% less midazolam than a control group.<sup>35</sup> It also decreases the MAC of isoflurane by 90% compared with placebo.<sup>36</sup>

## CARDIOVASCULAR SYSTEM

Mean arterial blood pressure decreased by 27% and heart rate decreased by 17% in patients receiving a bolus dose of dexmedetomidine 2 µg/kg.<sup>37</sup>

## RESPIRATORY SYSTEM

In adult males, dexmedetomidine 2.0 µg/kg increases carbon dioxide partial pressure (pCO<sub>2</sub>) by 4.2 mm Hg and decreases minute ventilation by 28% with minimal changes in ventilating frequency.<sup>38</sup>

## ANALGESIA

Dexmedetomidine reduced rescue analgesia (morphine) requirements by 50% compared with placebo in postsurgical patients requiring mechanical ventilation and sedation in the ICU.<sup>35</sup>

## USE IN THE PEDIATRIC PATIENT

### SEDATION AND ANXIOLYSIS IN INTUBATED PATIENTS

Dexmedetomidine infusion has been compared with midazolam infusion for sedation in intubated patients. A dose of 0.25 µg/kg/hr of dexmedetomidine provided equivalent sedation as compared to midazolam at 0.2 mg/kg/hr. The dexmedetomidine group had a lower baseline heart rate when compared to the midazolam group. There was a decreased need for changes in infusion rate and supplemental morphine use with dexmedetomidine. The midazolam group had more episodes of inadequate sedation.<sup>39</sup>

Two case reports of a 10 week old infant intubated for respiratory failure and a 14 year old adolescent post spinal fusion showed good results with and infusion of 0.25 µg/kg/hr. In the 14 year old patient who had not received sedation a loading bolus of 0.5 µg/kg was administered. Blood pressure and heart rate were lower and morphine needed postoperatively was limited to a single dose. The patient was weaned during continuation of the infusion and extubated 10 minutes after the infusion was discontinued. This shows the drug can be used as a bridge to extubation, decreasing the use of opioids and other sedatives that can cause respiratory depression.<sup>40</sup>

One caveat must be noted that a 5 week old infant who was receiving digoxin had episodes of severe bradycardia with a dexmedetomidine infusion and so this combination must be used carefully.<sup>41</sup>

## PREMEDICATION

Oral dexmedetomidine 2.6 µg/kg gave adequate sedation for acceptance of mask induction in 20-30 minutes after administration and may be an alternative for neurobehavioral disorder patients.<sup>42</sup> Also intranasal or transmucosal dexmedetomidine 1 µg/kg administered 45 minutes before surgery provided adequate sedation for premedication.<sup>43,44</sup>

## CONTROLLED HYPOTENSION

For spinal instrumentation and fusion a continuous infusion of dexmedetomidine can be combined with isoflurane (0.2-0.3%) in 50% nitrous oxide/oxygen and remifentanyl 0.2-0.3 µg/kg/min. Dexmedetomidine is initiated at 0.2 µg/kg/hr and can be increased to 0.5-0.7 µg/kg/hr to maintain a mean arterial pressure of 55-65 mm Hg. Heart rate also decreases.<sup>40</sup>

In many of these cases a direct acting vasodilator such as sodium nitroprusside, incardipine and fenoldopam is used for controlled hypotension. Disadvantages of any of these agents include reflex tachycardia and stimulation of the sympathetic nervous system especially with sodium nitroprusside with potential for rebound hypertension. Also interference with hypoxic pulmonary vasoconstriction (HPV) and cerebral vasodilation with the potential of increased intracranial pressure (ICP) is possible. The decrease in HPV is particularly important in patients undergoing anterior spinal fusion needing one lung ventilation. The induced bradycardia with dexmedetomidine avoids the need for beta blocker use.

## SEDATION FOR NONINVASIVE PROCEDURES

Koroglu et al<sup>45</sup> randomized 80 children (1-7 yrs of age) to dexmedetomidine or midazolam during MRI. Dexmedetomidine was administered as a loading dose of 1 µg/kg over 10 mins followed by an infusion of 0.5 µg/kg/hr, whereas midazolam was administered as a loading dose of 0.2 mg/kg followed by an infusion of 6 µg/kg/hr. The quality of sedation was better and the need for rescue sedation was less (8 of 40 vs. 32 of 40) with dexmedetomidine compared with midazolam.

A second study by Koroglu et al<sup>46</sup> randomized 60 children to dexmedetomidine or propofol during MRI. Dexmedetomidine was administered as a loading dose of 1 µg/kg over 10 mins following by an infusion of 0.5 µg/kg/hr, whereas propofol was administered as a loading dose of 3 mg/kg followed by an infusion of 100 µg/kg/hr. Although equally effective in providing sedation, induction time, recovery time, and discharge times were shorter with propofol. Adverse effects including hypotension and oxygen desaturation were more common with propofol.

Mason et al<sup>47</sup> presented data regarding dexmedetomidine for sedation in 62 children during radiologic imaging. Dexmedetomidine was administered as a loading dose of 2 µg/kg over 10 mins and repeated to achieve effective sedation, after which an infusion was started at 1 µg/kg/hr. The mean loading dose was 2.2 µg/kg, with 52 patients requiring only the initial

dose of 2 µg/kg. The time to achieve sedation was 9.9 + 2.4 mins (range 6-20 mins). Sinus arrhythmias were noted in ten patients (16%). Although HR and BP decreased in all patients, no treatment was necessary and no value was less than the fifth percentile for age. No changes were observed in end-tidal CO<sub>2</sub>, and no patient developed oxygen desaturation while breathing room air. Two patients manifested significant agitation during the administration of the loading dose and were switched to other sedative agents (propofol or pentobarbital).

### SEDATION FOR INVASIVE PROCEDURES

In a case report in an 11 year old for endoscopic gastrodeuodenoscopy, dexmedetomidine was administered in a bolus of 0.6 µg/kg followed by an infusion of 0.5 µg/kg/hr. Although being sleepy and unresponsive to verbal commands, with the introduction of the endoscope the patient became responsive and distressed. A significant level of sedation was not achieved, the infusion was discontinued and alternative sedation (midazolam and ketamine) was administered to complete the procedure.<sup>40</sup> Larger clinical trials are needed in children for use in these procedures.

In the first prospective evaluation of dexmedetomidine as the lone agent during an invasive procedure in infants and children, Munro et al<sup>48</sup> reported their experience with dexmedetomidine during cardiac catheterization. Following premedication with midazolam and the placement of intravenous access with the inhalation of sevoflurane, the inhalational anesthetic agent was discontinued and dexmedetomidine administered (1 µg/kg over 10 mins followed by an infusion of 1 µg/kg/hr titrated up to 2 µg/kg/hr as needed). The average maintenance infusion rate was 1.15 + 0.29 µg/kg/hr (range, 0.6-2.0 µg/kg/hr). Five patients (25%) moved during local infiltration of the groin, which did not require treatment or interfere with cannulae placement. Twelve (60%) patients received a propofol bolus during the procedure for movement, an increasing Bispectral Index number, or anticipation of a stimulus. No adverse hemodynamic or respiratory effects were noted.

Tosun et al<sup>49</sup> compared a dexmedetomidine-ketamine combination with a propofol-ketamine combination in 44 children (4 months to 16 yrs) with acyanotic congenital heart disease undergoing cardiac catheterization. Ketamine (1 mg/kg) and dexmedetomidine (1 µg/kg) were administered over 10 mins followed by an infusion of 0.7 µg/kg/hr of dexmedetomidine and 1 mg/kg/hr of ketamine. In the other arm of the study, propofol (1 mg/kg) and ketamine (1 mg/kg) were administered as the loading dose followed by an infusion of propofol (100 µg/kg/hr) and ketamine (1 mg/kg/hr). Supplemental ketamine (1 mg/kg) was given as needed. Although sedation was managed effectively with both regimens, patients sedated with ketamine-dexmedetomidine required

more ketamine (2.03 + 1.33 vs. 1.25 + 0.67 mg/kg/hr,  $p < .01$ ) and more supplemental doses of ketamine (10/22 vs. four of 22) and had longer recovery times (median time of 45 vs. 20 mins,  $p = .01$ ) than patients sedated with a propofol-ketamine combination. No clinically significant differences were noted in hemodynamic and respiratory variables.

### EMERGENCE AGITATION

A single dose of IV dexmedetomidine 0.3 µg/kg after induction and maintenance of anesthesia with sevoflurane anesthesia decreased emergence agitation with no adverse effects.<sup>50</sup> In addition, a 1 µg/kg dose of IV dexmedetomidine reduces emergence agitation after sevoflurane anesthesia in children undergoing MRI.<sup>51</sup>

### OPIOIDS

#### REMIFENTANIL

Remifentanyl hydrochloride is a new ultrashort-acting opioids metabolized by nonspecific plasma and tissue esterases. Alfentanil also has a short elimination half life but this has not equated to as rapid offset – particularly following infusions of this drug. In an initial abstract ten children age 2-12 had kinetics determined after 5 µg/kg of remifentanyl. Mean clearance was 58.7 ml/min-1 and elimination half life was 5 minutes.<sup>52</sup>

A multicenter study in 129 pediatric patients age 2-12 having strabismus surgery has been published. The study compared alfentanil maintenance of anesthesia with propofol, remifentanyl and isoflurane. Standards in the study included premedication with midazolam, halothane, N<sub>2</sub>O, O<sub>2</sub> induction (except for the propofol group who received 2.5 mg/kg of propofol for induction), vecuronium (0.1-0.2 mg/kg), atropine (10-20 µg/kg), ondansetron (100 µg/kg to a maximum of 4 mg) and acetaminophen suppositories (325-650 mg). Patients were then continued on one of the maintenance agents. Remifentanyl 1 µg/kg bolus followed by constant infusion of 1 µg/kg/min, alfentanil 100 µg/kg bolus followed by a continuous infusion of 2.5 µg/kg/min, propofol 200 µg/kg/min or isoflurane at 1 MAC. There was no difference in these groups between time to extubation, PACU times or hospital discharge times. However, there were significant differences in side effects. Patients who received remifentanyl had higher pain discomfort scores than those who received alfentanil or propofol. Patients anesthetized with alfentanil had a greater incidence of use of naloxone and a greater incidence of postoperative hypoxemia, compared with those anesthetized with remifentanyl. There was no difference in nausea and vomiting or hemodynamic profiles.<sup>53</sup>

The dose of remifentanyl that was chosen was 2 times the ED<sub>50</sub> for adults, but this dose was chosen because children usually have faster clearance rate

and variable volumes of distributions. Subsequently it has been noted that the pharmacokinetics are probably similar to adults. Even though the dose was well tolerated hemodynamically, the correct dose may be 0.5 µg/kg/min or lower. An infusion rate of 0.25 µg/kg/min has been suggested when using an inhaled agent.<sup>54</sup> Hypotension may be noted with larger infusion or bolus doses.

In pediatric patients undergoing dental restoration and extraction having a desflurane anesthetic supplemented by remifentanyl 0.2 µg/kg/min and 35 mg/kg acetaminophen rectally or acetaminophen alone the rate of vomiting was no greater in the remifentanyl group than the nonopioid. The quality of emergence and discharge times were also equal. Remifentanyl patients had a lower heart rate during surgery and may be useful in surgeries where tachycardia should be avoided.<sup>55</sup>

Remifentanyl is an effective analgesic in children undergoing major abdominal surgery when compared with epidural bupivacaine<sup>56</sup> and has been used alone with midazolam premedication and nitrous oxide for strabismus surgery in children.<sup>54,57</sup>

It appears that as in adults, because of remifentanyl's short duration of action, longer acting analgesics need to be used to supplement painful procedures. This may be a place for administration of nonsteroidal anti-inflammatory drugs during surgery to extend their effect of pain relief into the recovery phase.

Another use for remifentanyl may be in combination with propofol for anesthesia in patients undergoing cardiac catheterization, esophagogastrosocopy or having combined regional/general technique (eg axillary block). A mixture can be made where 10 mg/cc of propofol is combined with remifentanyl to have a concentration of 10 µg/cc of remifentanyl. Remifentanyl 0.5 mg can be combined with 50 cc of propofol or 0.2 mg of remifentanyl and 20 cc of propofol will give this concentration. The one infusion can administer 50-100 µg/kg/min of propofol and 0.05-.1 µg/kg/min of remifentanyl.

For lumbar puncture in children a dose of 30 mg/kg propofol plus 1.5 µg/kg remifentanyl was compared with 4.0 mg/kg propofol plus 0.5 µg/kg remifentanyl. The duration of apnea was higher in the 1.5 µg/kg remifentanyl group but recovery time decreased with the lower propofol dose.<sup>58</sup> Remifentanyl has been used for patients undergoing pyloromyotomy with similar hemodynamic and recovery variables and no new onset of postoperative pneumogram abnormalities or clinical respiratory depression. However, postoperative apnea did occur in both groups.<sup>59,60</sup>

A recurring problem with remifentanyl is acute opioid tolerance especially during infusion of remifentanyl for pediatric scoliosis surgery. More cumulative morphine consumption (30%) was seen in the remifentanyl group than the morphine control group in the initial 24 hours.<sup>61</sup> Adding a bolus of

ketamine 0.5 mg/kg followed by continuous infusion of 4 µg/kg/min of ketamine did not decrease morphine consumption in the first 72 hours after surgery.<sup>62</sup> Giving morphine 150 µg/kg before beginning the remifentanyl infusion also did not decrease the initial 24 hour morphine consumption.<sup>63</sup>

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# Mechanisms Leading to [CHRONIC] Post-Operative Pain: And ways to avoid it.

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**Learning Objectives:** The goal of this lecture is to present data on the incidence of clinical post-operative pain, discuss some of the known and speculative factors/mechanisms for this pain, and present data on current and potential future drugs for prevention or treatment of this condition.

## 1. WHEN DOES CHRONIC POST-OPERATIVE PAIN OCCUR?

Chronic post-operative pain often occurs after common surgical procedures, including thoracotomies (Dajczman et al., 1991; Karmarkar and Ho, 2004), breast surgery (Iu and Fine, 2005), cholecystectomy and herniorrhaphy (Tverskoy et al., 1990; Bay-Nielsen et al., 2001) (overall, cf. Perkins and Kehlet, 2000; Poobalan et al., 2003; Eisenach 2006a,b; Wilder-Smith et al., 2006). It is characterized by both resting and incident-related pain, the latter most often provoked by pressure or torsion as the patient twists and turns, ambulates or even just sits and breathes, contributing to morbidity and delaying or preventing a return to a full and active life (Macrae, 2001; Pavlin et al., 2002). The single factor that seems to be predictive of the duration and degree of prolonged (several months) or chronic (>6 mos) post-operative pain is the intensity of the acute post-operative pain reported by the patient (Katz et al., 1996; Ochroch and Gottschalk, 2005) which itself can be a response to a high degree of tissue/nerve injury and/or inflammation, or an indication of the individual patient's response to an unexceptional surgical procedure.

## 2. MODELS FOR POST-OPERATIVE PAIN

Several animal models and a few human surrogate models for post-operative pain have been developed. Animal models, exclusively on rodents, include **a.** skin incision (SI), of the plantar paw skin, sometimes with damage of the underlying muscle (Brennan et al., 1996; Wu et al., 2009), and incision of the hairy skin on the rat's back (Duarte et al., 2005), **b.** incision and retraction of the skin and muscles of the rat's inner thigh (SMIR; Flatters and Strichartz, 2006; Flatters, 2008), entrapping the saphenous nerve and **c.** thoracotomy with rib retraction (TRR, Buvanendran et al., 2004). Mechanical stimulation reveals heightened pain from these procedures that has distinctly different, procedure-dependent characteristics (Table 1): 1. for both SI procedures, elevated pain is present at the "primary" (1°) area near the incision, with some secondary (2°) allodynia at more distant sites, or 2. for SMIR, pain is characterized by a strong 2° allodynia, in the region innervated by the sciatic n., or 3. for TRR, persistent pain is characterized by profound and extensive 1° and 2° allodynia, rostral and caudal to the wound

site. These elevated pain conditions last various times, from 4-6 d for skin incision, with or without intentional muscle damage, ~4 wks for SMIR, and >6 mos for TRR. The latency from the time of surgery to the appearance of heightened pain also varies, with that from skin incision showing up as soon as 30min or less, from SMIR after ~3 d and from TRR after ~6 d. In addition, the percentage of operated animals that develops pain differs: near 100% for skin incision, 75-80% for SMIR and ~50% for TRR. The fact that fewer animals develop the more severe pains, and after a longer time after surgery, may reflect the complex combination of factors that are required for chronic pain to occur.

	Percent Occurrence	Induction Stage (latency)	Duration	Modality of Hyperesthesia	Nerve injury
Skin Incision (S.I.)	100%	1-4 hr	4-7 d	Mechanical, heat	yes
Skin Muscle Incision Retraction (SMIR)	75-80%	2-3 d	4-5 wks	Mechanical (2° location)	no
Thoracotomy with Retraction (TRR)	40-50%	5-6 d	>6 mos	Mechanical and Cold	yes

Table 1: Comparative features of three animal models for Post-Operative Pain.

## 3. DO GENETIC FACTORS ACCOUNT FOR THE LARGE VARIATION IN PAIN REACTIONS TO THE SAME PROCEDURE?

How much is due to neuropathic pain due to nerve damage? Although some authors have claimed that genetic factors are likely to account for the large variance in clinical chronic pain development after the same surgical procedures (Kehlet, et al., 2006), the animal data show that the same variance in behavior also occurs with heavily inbred rodent species, where genetic differences are much smaller. Furthermore, there is a widespread notion that chronic post-operative pain is largely neuropathic pain resulting from nerve injury during the surgery, but a recent neurological analysis of post-thoracotomy patients shows that only about half of the chronic pain can be classified as neuropathic (Steegers et al., 2008).

## 4. PERIPHERAL MECHANISMS THAT CONTRIBUTE TO CHRONIC PAIN.

**A. Soluble substances.** Chronic pain is probably initiated by relatively acute (0-24-48 h) pain caused

by local tissue damage, release of “pro-inflammatory” mediators combined with nerve trauma from surgical manipulations. It is likely that substances released from injured tissue at sites of incision/retraction are essential for establishing the prolonged excitability and neural discharge that drives central sensitization and chronic pain after surgery. Evidence for this hypothesis comes from post-incisional pain studies and from experiments on peripheral nerve activation during inflammation. In the paw incision model, treatments that reduced local **nerve growth factor (NGF)** levels reduced thermal but not mechanical hyperalgesia, whereas treatments that reduced free Tumor Necrosis Factor alpha (TNF- $\alpha$ ) affected neither modality (Zahn et al., 2004). NGF content and expression increases in the peri-incisional tissue, as early as 2-4 h after incision, and lasts for ~7d (Wu et al., 2007). Pain after paw incision also corresponds to an increase in H+ activity for up to 4d at the incision (Woo et al., 2004), a change that may account for some of the TRPV1-dependent changes in spontaneous activity from afferents at this incision site (Banik and Brennan, 2009; see **TRPV1**, below). These behavioral changes can be ascribed at least in part to peripheral responses, as spontaneous activity and hyper-responsiveness to cutaneous stimuli occur in excised skin-nerve preparations (Banik and Brennan, 2008).

Mechano-allodynia after hairy skin incision of the rat’s back is suppressed by inhibitors of **endothelin-A receptors** (ETA; Mujenda et al., 2007) for **endothelin-1** (ET-1; cf. Khodorova et al., 2009a for review). However, such inhibition occurs only when the inhibitor is given pre-operatively, during the induction stage (0-4h), implying that ETA receptors are important for induction, not for maintenance of allodynia. In other studies, the subcutaneous injection of micromolar [ET-1] in rats causes allodynia, which is prevented by pre-treatment with antagonists of NMDA-type **glutamate receptors** (Khodorova et al., 2009b); the later stage of this allodynia is selectively reversed by inhibitors of **TRPV1 receptors** and of **CGRP1 receptors** (Balonov et al., 2006; Khodorova et al., 2009b), implicating these receptors in the ET-1-triggered mechano-sensitivity. *Blockade of ETA receptors during the induction stage of post-incisional pain has no effect on primary mechano-hyperalgesia one day later, but totally prevents 2o allodynia measured 24 h after the incision, showing that those peripheral fibers that are activated by ET-1 serve a critical role in central sensitization after incision* (Mujenda et al., 2007).

Injection of 100-fold higher concentrations of ET-1 into the paw causes pain and activates C- and A delta- nociceptors (Gokin et al., 2001a), thus creating an afferent discharge and nociceptive input to the spinal cord that lasts for ~30min. Since ET-1 is synthesized and secreted by keratinocytes that are the major cells of the epidermis, extensive trauma to the skin, e.g., by retraction after incision, will release

a large quantity and ET-1 (Khodorova et al., 2009a) which can stimulate nociceptive fibers acutely and directly and, as its concentration falls, will continue to sensitize peripheral fibers to cause allodynia. We intend to measure ET-1 levels in tissues at surgical sites, and also ET receptors, both known to be increased after local injury (Klass et al., 2000).

**Glutamate and calcitonin gene related peptide (CGRP)**. Both of these substances are likely candidates to mediate an enhanced responsiveness of peripheral nociceptors, including that caused by ET-1. Glutamate plays an important role in hyperalgesia (Jackson et al., 1995) by participating in both central and peripheral pain transmission (Beirith et al., 2002). Ionotropic glutamate receptors are present on the peripheral terminals of small diameter primary afferents (Carlton et al., 1995; Coggeshall and Carlton, 1998; Kinkelin et al., 2000) and glutamate is released in the plantar skin following high threshold A delta- and C-fiber stimulation of the sciatic nerve (de Groot et al., 2000). Injection of glutamate and of agonists for ionotropic glutamate receptors into the normal rat hind paw (Beirith et al., 2002; Leem et al., 2001) results in acute mechanical hyperalgesia, while local, but not systemic, administration of the NMDA receptor antagonist MK-801 attenuates inflammatory mechanical hyperalgesia induced by Freund’s complete adjuvant (Leem et al., 2001). Peripheral metabotropic glutamate receptors also appear to contribute to post-incisional pain, since mechano-induced changes in weight-bearing were significantly prevented or reversed by , respectively, pre- or post-operative intra-plantar injections of an mGluR5 receptor antagonist (Zhu et al., 2005). In contrast, a local antagonist of AMPA/kainate type glutamate receptors was ineffective on paw incision-induced pain (Lee et al., 2006)

**B. Receptors and Channels. Changes in Na+ and K+ enhance neuronal excitability.** Impulse firing not only occurs immediately after incision (the “injury discharge” but also persists as spontaneous, ectopic firing from the injured tissue for hours and days afterwards. This hyperexcitability is due to changes in the ion channels that critically determine impulse threshold, notably, neuronal Na+ channels (Devor et al., 1993; Matzner and Devor, 1994,) particularly the nociceptor-expressed Na+ channels Nav1.7, 1.8, and 1.9 (Amir et al., 2006). In cultured neurons the expression of Na+ channels is increased by exposure to NGF (Toledo-Aral et al., 1995), which is known to be released from peripheral tissues by injury (see above). Both threshold and the propensity for repetitive firing are shaped by several types of K+ channels that are known to be down-regulated after procedures that result in hyperalgesia (Ishikawa et al., 1999; Kim et al., 2002; Rasband et al., 2001). And it is further noteworthy that **NGF** has been shown to rapidly modify the gating properties of the delayed-rectifier type of these channels as well as that of a

class of voltage-gated Na<sup>+</sup> channels in isolated rat DRG pain neurons.

There is evidence that TRPV receptors, including the classic **TRPV1, capsaicin receptor**, that is activated by chemicals in hot peppers, by H<sup>+</sup> that are elevated in the acidic environment of inflammation, and by supra-physiologic temperatures, are involved in a number of responses of skin to damage and inflammation. Mice that are deficient in TRPV1 have lowered hyperalgesic responses to inflammation, although normal heat sensation remains (Caterina et al., 2000). In biopsies of breast skin taken from women with breast pain, TRPV1 is elevated in cutaneous nerve fibers (Gopinath et al., 2005).

**Receptors in skin.** Activation of TRPV1 in isolated keratinocytes results in the up-regulation of COX-2, with a concomitant increase in PGE2 and in the release of IL-8, a pro-inflammatory interleukin (Southall et al., 2003). This illustrates the point that damaged non-neuronal tissue not only can contribute substances that will excite or sensitize local neurons, but themselves have receptors and pathways that engage in signaling pathways closely associated with pain sensation.

Relating these observations back to the release of soluble factors, nerve growth factor (NGF) increases TRPV1, acting through the trkA receptor (Zhang et al., 2005). In one analyzed pathway PI3Kinase is closely coupled to trkA, with downstream activated Src kinase ultimately binding to and phosphorylating TRPV1, followed by the protein's insertion into the plasma membrane. NGF, which is freed by injured tissues adjacent to peripheral neurons, also can be taken up and transported to sensory cell bodies in the DRG, where it stimulates the MAPKinase p38, leading to an increase in TRPV1 protein (but no mRNA) in these sensory neurons, 24h after injury or inflammation (Ji et al., 2002). So it appears that both local stores at neuron terminals and stores of TRPV1 in the cell soma can be recruited to enhance TRPV1 activity after injury or inflammation.

**C. Other peripheral mechanisms.** In addition to the actions of chemicals released by incision and trauma (retraction), there are physical actions that can sensitize peripheral nerve. Incision itself, in cutting local blood vessels, reduces blood flow and leads to **local ischemia** (Kim et al., 2007). The pressure from retractors pressing tissues against muscle or, particularly, bone (as in the TRR model), will almost certainly cause local ischemia and hypoxia. In isolated rat sensory neurons, moderate hypoxia has been shown to increase excitability (Gruss et al., 2006). **Stretch of nerve fibers** is known to induce action potentials, perhaps by altering the gating of voltage-sensitive Na<sup>+</sup> channels (Morris and Juranka, 2007), and **inflammation**, such as would occur at an incision, or in tissue after retractor-induced ischemia and reperfusion, induces mechano-sensitivity in peripheral nerves (Bove et al., 2003).

## 5. CENTRAL MECHANISMS CONTRIBUTING TO CHRONIC PAIN.

**A. Glial contribution to pain.** It has been increasingly apparent that spinal glial cells play an essential role in persistent pain sensitization (reviewed in DeLeo and Yeziarski, 2001; Watkins et al., 2001; Ji and Strichartz, 2004; see DeLeo et al., 2007). Spinal glial cells are activated by several different pain-inducing procedures, such as peripheral nerve injury (Garrison et al., 1991), paw incision (Wen et al., 2009), and inflammation (Ragahavendra et al., 2004). Intrathecal injection of glial inhibitors such as fluorocitrate, propentofylline, and minocycline have been shown to reduce pain sensitivity after inflammation and nerve injury. After their activation, spinal glial cells produce various inflammatory mediators, such as proinflammatory cytokines (e.g., IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ), NO, and PGE2, to increase spinal cord neuron sensitivity and enhance pain.

Accumulating evidence supports a role for spinal microglia in neuropathic pain, and it seems likely that identical processes will be involved in chronic post-operative pain. Nerve injury induces the expression of microglial markers (e.g. CD11b, TLR4, CD14) within several hours. Specifically, nerve injury upregulates several receptors, such as the chemokine receptors CCR2 and CX3CR1, ATP receptor P2X4, and Toll-like receptor-4 in spinal microglia. Blocking or deleting these receptors results in decreased neuropathic pain (Abbadie et al., 2003; Tsuda et al., 2003; Milligan et al., 2004; Verge et al., 2004; Tanga et al., 2005). A microglial inhibitor, minocycline, has been shown to prevent/delay neuropathic pain, but not to reverse established neuropathic pain.

Less is known about the role of astrocytes in pain regulation. But astrocytes are closely associated with synapses (Haydon, 2001). Astroglial activation is typically preceded by microglial responses (Kreutzberg, 1996). CFA inflammation increases the expression of microglial markers (e.g. Mac-1, TLR4, CD14) in a few hours, but elevates the expression of the astrocyte activation marker GFAP after several days. Microglial activation is known to cause astroglial activation. Further, astroglial activation in the spinal cord is more persistent than that of microglia in several different chronic pain states. Therefore, spinal astrocytes could play a role in the maintenance of chronic pain, due to their delayed and persistent activation characteristic. Intrathecal injection of an astroglial "toxin", alpha-amino adipate, suppresses nerve ligation-induced mechanical allodynia (Zhuang et al., 2006). We hypothesize that a very similar mechanism occurs during chronic post-operative pain, and that this astrocytes-selective drug will have a similar effect on SMIR- and TRR-induced pain.

**B. MAP kinase regulation of glial function and persistent pain.** Mitogen-activated protein kinases (MAPKs) play important roles in persistent pain sensitization by regulating intracellular signaling

and neural plasticity (reviewed in Ji and Woolf, 2001). The MAPKs family includes 3 major members: extracellular signal-regulated kinase (ERK), p38, and c-Jun N-terminal kinase (JNK) that represent 3 different signaling cascades. Interestingly, MAPKs are also activated in spinal cord glial cells after tissue and nerve injury and play important roles in regulating the synthesis and release of proinflammatory cytokines (reviewed Ji and Strichartz, 2004; Ji et al., 2009). For example, nerve injury induces a dramatic activation of p38 in spinal microglia, which plays a critical role in the development of neuropathic pain (Jin et al., 2003; Tsuda et al., 2004; Svensson et al., 2005). Wen et al. have recently shown that p38 activation in spinal microglia after paw incision also contributes to the development of post-operative pain (Wen et al., 2009; see Preliminary Studies, below). Nerve injury induces JNK activation selectively in spinal astroglia (Ma and Quirion, 2002; Zhuang et al., 2006), and this activation is important for the maintenance of nerve injury-induced mechanical allodynia (Zhuang et al., 2006). JNK is also persistently activated in spinal astrocytes after CFA-induced inflammation and contributes to inflammatory pain sensitization (Gao et al., 2007). In contrast, ERK is sequentially and only transiently activated in neurons, microglia, and astrocytes at different times of nerve injury, suggesting distinct role of microglial-ERK and astrocytic-ERK in the early- and late-development of chronic pain (Zhuang et al., 2005).

## 6. PHARMACOLOGICAL APPROACHES TO POST-OPERATIVE PAIN.

Patients have been variously responsive to the analgesic effects of pre-operative opioids, local anesthetics (neuraxial, peripheral n. block, or wound infiltration), NSAIDs and several less frequently used therapeutics (Wilder-Smith et al., 2003; Ong et al., 2005). Meta-analysis has shown that such “pre-emptive” treatments are, in general, inconsistently effective in reducing post-operative pain, with the exception of peri-operative i.v. lidocaine (see below). Both the initial discharge of local nerves caused by the incision (Yamamoto et al., 1993) and the later, delayed activation of impulses from peripheral nerve, that may be conducted by injured or uninjured fibers (Pogatzki et al., 2001; Hamalainen et al., 2002) probably contribute to the establishment of longer-lasting hyperalgesia, and there is little doubt that changes in the CNS, at least at the spinal cord (and probably also in the brain), are essential for the maintained chronic pain (Dirks et al., 2002; Kawamata et al., 2005; Kehlet et al., 2006).

*The differential ability of different drugs, applied at the incision site or delivered systemically, to prevent or reverse post-operative pain supports the concept of at least two stages of post-operative pain, an induction stage and a maintenance stage, which involve different mechanisms that occur at different locations.*

**A. Intravenous lidocaine.** The intentional intravenous delivery of lidocaine has been an effective method for reducing acute post-operative pain (Marret et al., 2008) and also for treating, with some success, existing neuropathic pains arising from various causes (Mao and Chen, 2000). Peri-operative infusions of lidocaine, starting shortly before abdominal surgery, cholecystectomy, or prostatectomy and extending to 1-3 hrs after surgery, have reduced self-reported pain scores (usually as visual-analogue scales, VAS) and post-operative analgesic (opioid) consumption, accelerated return of function and shortened hospital stays (Cassuto et al., 1985; Groudine et al., 1998; Koppert et al., 2004; Kaba et al., 2007). However, there have been no systematic, prospective studies of the effectiveness of i.v. lidocaine for the surgical procedures that frequently lead to chronic pain.

The effect of i.v. lidocaine on experimental pain in humans has been studied using infusion protocols like those for peri-operative administration. In a model of skin incision at the volar forearm, Kawamata et al. (2002) found that systemic lidocaine (delivered over 45 min in pre- and post-incisional periods), transiently suppressed 1° allodynia but persistently suppressed 2° allodynia. In the same study, i.v. lidocaine given 30 min after the incision was effective only during the drug administration period, with allodynia returning quickly after that. Using an almost identical dosing end-point (to give up to 3 ug/ml plasma), Koppert et al. (1998) found that the elevated pain that occurred during the repeated presentation of a skin pinch was prevented from developing by i.v. lidocaine restricted to the “test arm’s” circulation, whereas the pain threshold for heat stimulation was unaffected. These changes did not occur when the same dose of lidocaine was allowed to distribute within the entire circulation, showing that the site of action was peripheral and not central.

Animal studies confirm the pre-emptive actions of i.v. local anesthetics. Although systemic bupivacaine has little effect on the initial post-incisional primary mechanical allodynia and hyperalgesia at the incision site, on the hairy skin of the rat, it can suppress the later components of this pain and virtually abolish secondary allodynia and hyperalgesia (here collectively called secondary “hyperpathia”, elevated pain) (Duarte et al., 2005). This therapeutic action will last for the entire hyperpathic period, up to 7d after the incision, even though bupivacaine’s half-life in blood is <3 h, showing that the systemic drug is interfering with a key process early in the **induction stage** of post-operative pain. Identical delivery of bupivacaine 4-6 h after the incision, when the allodynia had reached a constant value and the **maintenance stage** of post-operative pain had been reached, had less than 0.5 the effectiveness in reversing both 1° and 2° allodynia, showing that the mechanisms and pathways for developing pain after

surgery are different from those for maintaining it. These results mirror the findings of Kawamata et al., (2002), who applied local lidocaine before or after experimental skin incision in humans. In that study, pre-incisional block prevented the development of 2° allodynia, but post-incisional block had no effect, implying that the initial afferent impulse activity was essential for causing the central sensitization that underlies 2° hyperesthesia, but was unnecessary for maintaining that sensitization.

A very similar result occurred when bupivacaine was delivered systemically around the time of experimental thoracotomy, such that 3 wks after the procedure those rats that received the local anesthetic were 70% less likely to show mechano-allodynia as those that received no bupivacaine (Shin et al., 2008). Changes in the activity of spinal wide dynamic range (WDR) neurons after skin incision (Kawamata et al., 2005) are transiently suppressed by systemic lidocaine and by its quaternary homologue, QX-314, which does not pass through the blood:brain barrier and so is restricted to peripheral sites. This suggests that some peripheral activity, perhaps other than impulse inhibition, is a factor in central neuron changes, although the role of WDRs in ongoing pain has not been established.

Mechano-allodynia after nerve constriction injury also can be strongly reversed by i.v. lidocaine (Araujo et al., 2003), and the duration of anti-allodynia long outlasts the plasma lifetime of lidocaine; days to weeks of prevention occur although the drug disappears from the circulation in a few hours. The timing of this therapeutic effect is not unlike that for surgical effects; when lidocaine is administered early after the nerve injury the persistent reversal of allodynia is ~75%, but the same dosing one week after injury results in almost none of the persistent effect (Araujo et al., 2003), implying that some virtually irreversible process has occurred in the intervening 5 days, one that precludes the salutary long-lasting action of lidocaine. We think that similar processes occur after surgery, so that peri-operative lidocaine is effective for suppressing post-operative hyperesthesia but delayed, post-operative lidocaine is not

**Is impulse blockade the mechanism for i.v. local anesthetic action?** Local anesthetic conduction block, e.g. by neuraxial administration, is far less clinically effective than i.v. lidocaine in providing pre-emptive relief of post-operative pain (Moiniche et al., 2002), and the lidocaine plasma concentrations that are reached are inadequate to block conduction of normal nerve impulses (Huang et al., 1997a). However, abnormal impulses, such as arise ectopically at sites of injury or inflammation, or at other locations of affected neurons, can be almost fully suppressed by such low lidocaine concentrations (Devor et al., 1992; Xiao and Bennett, 2008), as can abnormal repetitive impulses that result from an increased expression of atypically gating VGSCs on peripheral nerve fibers

(Khodorova et al., 2001; Persaud and Strichartz, 2002).

**B. Peripheral nociceptor blockade.** Peripheral nerve blockade during surgery is almost always accomplished with local anesthetics (LA). These drugs can be used safely and effectively to abolish sensation from peripheral locations, producing a somewhat selective block of small myelinated (e.g., A-delta) fibers and a significantly less potent block of C-fibers (Huang et al., 1997a; Gokin et al., 2001). Infiltration of a surgical area before an incision (Huang et al., 1997b; Kato et al., 2000) or of the wound after incision (Rosaeg et al., 1998; Gottschlak et al., 2003; Rowlingson and Rawal, 2003) can both be effective for suppressing acute post-operative pain. Evidence from other studies indicates that early afferent discharge is critical for establishing neuropathic pain after nerve injury (Xie et al., 2005). This is also likely to be so for post-incisional pain, where impulse blockade can be accomplished by the less fiber-selective blockade, by LA alone, and by the C-fiber specific blockade afforded by resiniferatoxin (RTX; Kissin et al., 2002) or by LAs plus capsaicin (Gerner et al., 2008). Both of these approaches take advantage of the specific expression of the TRPV1 (vanilloid) receptor on non-myelinated C-fibers to provide a selective blockade, and with RTX one already shown to prevent the short-term allodynia after paw incision (Kissin et al., 2005).

**C. Anti-inflammatory actions of local anesthetics.** Local anesthetics not only block Na<sup>+</sup> channels (and Ca<sup>2+</sup> and K<sup>+</sup> channels, as well as TRPV1 receptors and other ligand-gated receptors) (cf. Yanagidate and Strichartz, 2006a,b), they also disrupt the coupling between certain G proteins and their associated receptors (Li et al., 1995; Hollmann et al., 2004a, 2005). Through this action local anesthetics exert potent anti-inflammatory effects, particularly on neutrophil priming reactions (Hollmann et al., 2000, 2001). There are, in addition, a variety of other, anti-thrombotic and neuroprotective actions of intravenous local anesthetics (cf. Hollmann et al., 2004b for review) that are independent of Na<sup>+</sup> channel blockade but may account for many of the improvements in pain after surgery (Kaba et al., 2005, 2007).

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# For the Antiplatelets to Anticoagulants: Making Sense of the Coagulation Cocktails

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## INTRODUCTION

Anticoagulation is the basis of therapy for perioperative thrombosis, but also for patients with ischemic cardiovascular disease. In patients with an acute coronary syndrome, following percutaneous coronary interventions, or with an acute ischemic stroke, the rupture or injury of an atherosclerotic arterial plaque serves as a nidus for platelet aggregation and thrombus formation, which, in turn, may cause myocardial infarction, stroke, or death.<sup>1,2</sup> Activation and expression of the glycoprotein IIb/IIIa receptor (where fibrinogen binds) on platelets leads to platelet aggregation and thrombus formation.<sup>2</sup> When this receptor is activated, circulating fibrinogen binds to it and cross-links with adjacent platelets to create a platelet–fibrinogen matrix. Since platelets have a pivotal role in the pathogenesis of thrombosis after plaque rupture, antiplatelet agents including aspirin, thienopyridines (clopidogrel-Plavix), and the glycoprotein IIb/IIIa inhibitors, reduce adverse events that are associated with plaque rupture.<sup>3</sup> Fibrinolytic agents are only occasionally used in the current era with all the available catheter and pharmacologic agents available. As a result, patients often present for surgery with underlying hemostatic disorders because of preexisting preoperative anticoagulation or antiplatelet therapy.<sup>4</sup> Patients may also present receiving anticoagulation therapy for reasons that include atrial fibrillation, venous thrombosis prophylaxis, prosthetic valves, or for coronary artery disease. All therapies that prevent clot from forming in pathologic states, also interfere with normal hemostasis, an important mechanism to protect patients from exsanguination.<sup>5,6</sup>

Under normal circumstances, there is a complex and delicate equilibrium between blood cells, platelets, coagulation factors, natural inhibitors of coagulation, and the fibrinolytic system.<sup>7</sup> Surgical patients also develop additional acquired hemostatic changes that contribute to postoperative bleeding; causes that include activation of the coagulation, fibrinolytic, and inflammatory pathways.<sup>8</sup> Even healthy patients can develop massive hemorrhage and/or tissue injury following trauma, surgery, or in an obstetrical population.<sup>9</sup> Hemostasis is also a far more complex system than intrinsic and extrinsic hemostatic activation as taught in medical school.<sup>10,11</sup> Multiple factors are responsible for stopping bleeding including release of tissue factor, and generation of factor VIIa, platelet activation, and the complex

cellular and humoral amplification that follows.<sup>11-14</sup> The increasing use of low-molecular weight heparins (LMWH), pentasaccharide (fondaparinux), oral anticoagulants (warfarin and new oral antiXa inhibitors), platelet inhibitors (thienopyridines-clopidogrel, prasugrel or IIb/IIIa receptor antagonists), or direct thrombin inhibitors (r-hirudin, bivalirudin, argatroban), also may potentiate bleeding.<sup>15,16</sup> This review will focus on current pharmacologic therapies surgical patients may receive and therapeutic prohemostatic pharmacologic approaches that are used to treat or prevent bleeding.

## ANTICOAGULATION: HEPARIN, DERIVATIVES, AND THROMBIN INHIBITORS

Anticoagulation is based on inhibiting both thrombin activation and platelet activation.<sup>16-19</sup> Thrombin is a potent procoagulant that generates fibrin from soluble fibrinogen, activating factors V and VIII, and activating platelets.<sup>11</sup> Activated platelets adhere to injured vascular endothelia, express IIb/IIIa receptors, aggregate, and further increase generation of thrombin.<sup>20</sup> Because of the complex humoral amplification system linking both hemostatic and inflammatory responses, there are multiple pathways to produce thrombin and prothrombotic effects.<sup>5</sup> Anticoagulation is based on inhibiting both thrombin activation and platelet activation. Thrombin is a potent procoagulant that generates fibrin from soluble fibrinogen, activating factors V and VIII, and activating platelets. Activated platelets adhere to injured vascular endothelia, express IIb/IIIa receptors, aggregate, and further increase generation of thrombin. Current and future anticoagulants used to prevent clot formation will be considered.

## HEPARIN

Heparin, the most commonly used anticoagulant, is isolated from either porcine intestine or from beef lung where it is stored in the mast cell granules. Heparin is an acidic polysaccharide, with sulfate groups important in its anticoagulant activity. Unfractionated heparin is a diverse mixture of 3000 to 30,000 dalton fragments.<sup>21</sup> Heparin binds to antithrombin III (antithrombin or AT III) increasing the rate of thrombin-AT III complex formation, but also inhibits other steps in coagulation, through acceleration of the reactions between antithrombin and thrombin or factor Xa.<sup>21</sup> One of the advantages

of heparin anticoagulation is that it can be reversed immediately by removing heparin from AT III with protamine.<sup>22</sup> Unfractionated heparin is also an important cause of heparin induced thrombocytopenia.

In early 2008, reports of acute hypersensitivity reactions consistent with anaphylaxis seriously threatened our heparin supply.<sup>23</sup> A contaminant was identified as an unusual oversulfated form of chondroitin sulfate. The reason heparin is reversible is because similar to chondroitin sulfate, they both are glycosaminoglycans that contain highly charged molecular species that promote binding to basic molecules like protamine. The oversulfated chondroitin sulfate molecule that was a contaminant was demonstrated to activate inflammatory cascades including the kinin-kallikrein pathway, and the complement cascade to generate C3a and C5a, potent anaphylatoxins to produce an anaphylactic clinical syndrome.<sup>23</sup>

### **LOW-MOLECULAR-WEIGHT HEPARINS (LMWH)**

Like unfractionated heparin, low-molecular-weight heparins are glycosaminoglycans<sup>18</sup> Low-molecular-weight heparins are fragments of unfractionated heparin purified to a mean molecular weight of about 500018. Low-molecular-weight heparins have a longer half-life, and dose-independent clearance; the recovery of antifactor Xa activity approaches 100 percent, compared with about 30 percent with unfractionated heparin. The plasma half-life of low-molecular-weight heparins is longer than unfractionated heparin, ranging 2-4 hours after intravenous injection, and 3-6 hours after subcutaneous injection<sup>18</sup>. Commonly used LMWHs include enoxaparin and dalteparin.

### **SYNTHETIC XA INHIBITORS (FONDAPARINUX AND DANAPAROID)**

Fondaparinux is a synthetic antithrombotic agent with specific antiXa activity. Its pharmacokinetic properties allow for a simple, fixed-dose, once-daily regimen of subcutaneous injection, without the need for monitoring. Danaparoid is also a synthetic agent that although approved for use in the United States is not currently available, and used in Europe for treating heparin induced thrombocytopenia (HIT).

### **ORAL ANTICOAGULANTS INCLUDING NEW ORAL XA INHIBITORS**

Vitamin K antagonists (VKAs) (e.g., warfarin and its analogs) are the only oral anticoagulants currently available for clinical use. These agents inhibit II, VII, IX and X, key components of the hemostatic cascade, but also inhibit protein C and S. Warfarin has major limitations, including slow onset and offset, a narrow therapeutic window, and metabolism affected by diet, accompanying drugs, and genetic polymorphisms and requires careful monitoring.<sup>24</sup> Ximelagatran was the first oral anticoagulant, but was not approved in

the US because of organ toxicity. Rivaroxaban and apixiban are new oral anticoagulants in advanced stages of clinical development that are directed against the active site of factor Xa or thrombin, the enzymes responsible for thrombin generation and fibrin formation, respectively.<sup>24</sup> Rivaroxaban and apixaban target factor Xa, whereas dabigatran etexilate inhibits thrombin. Rivaroxaban is a small molecule directed against the active site of factor Xa. After oral administration, it is absorbed in the stomach and small intestine with a bioavailability of 60% to 80%. Peak plasma levels are achieved in 3 hours, and the drug circulates with a half-life of 9 hours<sup>24</sup>. Ximelagatran is an oral anticoagulant that has recently been withdrawn in Europe.

### **HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)**

Heparin-induced thrombocytopenia (HIT) is a serious, yet treatable, prothrombotic disease that develops in 1 to 3% of heparin-treated patients that increases their risk of thrombosis.<sup>25</sup> HIT is produced by a heparin-platelet factor 4 immunoglobulin G (IgG) antibody, and is associated with increased thrombotic morbidity and mortality cardiac surgery.<sup>25,26</sup> HIT should be suspected whenever the platelet count drops >50% from baseline after starting heparin (or sooner if there was prior heparin exposure) and/or new thrombosis occurs during, or soon after, heparin treatment, with other causes excluded. When HIT is strongly suspected, with or without complicating thrombosis, heparins should be discontinued and a non heparin alternative anticoagulant such as a direct thrombin inhibitor (argatroban) should be initiated immediately.<sup>25,27,28</sup> Despite their association with long-term adverse effects, circulating heparin-PF4 antibodies are transient. For cardiac surgery, bivalirudin has emerged as the agent most studied in this setting, for on or off pump surgery.<sup>29,30</sup> However, HIT is a prothrombotic disease that carries significant morbidity and mortality and requires immediate therapy.<sup>25</sup> The agents approved for use in HIT are the direct thrombin inhibitors based on current 2008 recommendations.<sup>28</sup>

### **PLATELET INHIBITORS**

In patients with myocardial ischemia and/or atherosclerotic vascular disease, inhibiting platelet activation is the basis of pharmacologic therapy.<sup>31</sup> Platelet inhibitors/antiplatelet agents should also be considered as anticoagulants, and potentially place the patient at risk for bleeding. The antiplatelet agents differ in their modes of action, potency, onsets of action, and indications. Aspirin irreversibly inhibits platelet cyclooxygenase and thromboxane A<sub>2</sub>, a platelet activator. Aspirin is a relatively weak antiplatelet agent.<sup>32</sup> Nonsteroidal anti-inflammatory drugs also reversibly inhibit cyclooxygenase. Aspirin, however, irreversibly alters the cyclooxygenase so that platelet pool is destroyed until effective replacement occurs from the bone marrow, however resistance

can occur<sup>33</sup>. More potent antiplatelet agents include clopidogrel (Plavix) and IIb/IIIa receptor antagonists (abciximab, tirofiban, eptifibatide). Clopidogrel is more potent than aspirin, and inhibits platelets by selectively and irreversibly binding to the P2Y<sub>12</sub> receptor to inhibit the adenosine diphosphate-dependent pathway of glycoprotein IIb/IIIa-receptor activation although resistance can occur.<sup>32,34,35</sup> Clopidogrel is the major agent used with the least knowledge available about how to manage these patients or monitor its effects.

Antiplatelet therapy with aspirin and clopidogrel is standard care following revascularization by percutaneous coronary intervention with stent insertion. This so-called dual therapy is recommended for up to 4 weeks after intervention for bare-metal stents and for 6-12 months after intervention for drug-eluting stents.<sup>31</sup>

Vincenzi noted a 45% complication rate and a mortality of 20% reported in patients undergoing noncardiac surgery after coronary artery stenting<sup>36</sup>. Discontinuation of antiplatelet drugs appeared to be of major influence on outcome. They prospectively evaluated 103 patients receiving stents within 1 year before noncardiac surgery. Antiplatelet drug therapy was not, or only briefly, interrupted. Heparin was administered to all patients. Of 103 patients, 44.7% developed complications after surgery; 4.9% of the patients died. All but two (bleeding only) adverse events were of cardiac nature. Most complications occurred early after surgery. The risk of suffering an event was 2.11-fold greater in patients with recent stents (<35 days before surgery) compared with percutaneous cardiac intervention more than 90 days before surgery.<sup>36</sup> The clopidogrel package insert suggests if a patient is to undergo elective surgery and an antiplatelet effect is not desired, it should be stopped 5 days before surgery. However, if patients bleed, therapy or monitoring its effects has not been established. Further, the risk compared to the benefit of stopping clopidogrel, need to be weighted against the risk of stent thrombosis, and the need for surgical intervention as well.

Another agent, prasugrel, was just approved this year.<sup>37</sup> The TRITON-TIMI 38 study of 13,608 patients with acute coronary syndromes compared prasugrel against clopidogrel, both in combination with aspirin, and found that, as prasugrel reduced the combined rate of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (12.1% for clopidogrel vs. 9.9% for prasugrel), but the rate of serious bleeding (1.4%, vs. 0.9% in the clopidogrel group) and fatal bleeding (0.4% vs. 0.1%).<sup>38</sup> Overall mortality did not differ between the two treatment groups. The advantage of prasugrel is increased potency and potentially a lower rate of "resistance", one of the potential problems for clopidogrel.<sup>35</sup> Despite clopidogrel use, adverse ischemic events including stent thrombosis is a serious clinical problem, and may represent response

variability and nonresponsiveness to clopidogrel (and aspirin) therapy based on ex vivo platelet function measurements.

## **PROCOAGULANT AGENTS**

Anesthesiologists are often called on to correct coagulopathy in patients who are actively bleeding despite transfusion and other therapies. Further, many patients may also have received any one or combination of the anticoagulant agents just reviewed. Therefore, clinicians must understand some of the potential procoagulant therapies available to reverse bleeding or anticoagulation therapy.<sup>39</sup> These agents include antifibrinolytics, protamine, desmopressin, fibrinogen, purified protein concentrates, recombinant factor VIIa [rFVIIa]), and topical hemostatic agents, and each will be considered separately<sup>40</sup>.

## **ANTIFIBRINOLYTIC AGENTS**

### **APROTININ**

Aprotinin is a broad-spectrum serine protease inhibitor that inhibits plasmin and other serine proteases.<sup>41</sup> In cardiac surgery, multiple randomized, placebo-controlled trials on aprotinin safety and efficacy reported aprotinin reduces reduces bleeding and the need for allogeneic transfusions.<sup>42,43</sup> However, over the past 3 years, articles from observational databases<sup>44-47</sup> and one randomized study<sup>48</sup> questioned the safety of aprotinin. Following publication of the Blood conservation using antifibrinolytics: A randomized trial in a cardiac surgery population (BART) study in *The New England Journal of Medicine*, Bayer Pharmaceuticals, the manufacturer of Trasyolol (aprotinin), notified the FDA of their intent to remove all remaining supplies of Trasyolol from hospital pharmacies and warehouses.<sup>49</sup> The FDA noted "because Trasyolol has been shown to decrease the need for red blood cell transfusions in patients undergoing coronary artery bypass surgery, future supplies of Trasyolol will continue to be available through the company as an investigational drug under a special treatment protocol. In November 2007, Bayer suspended the marketing of this drug until final results of the BART study became available. The BART study showed an increase in the risk of death with Trasyolol compared with aminocaproic acid and tranexamic acid, consistent with findings from other recent studies." As noted on their website, FDA is reviewing these data and will reassess the status and access to the product once the review is completed.

### **ANTIFIBRINOLYTIC AGENTS: EPSILON-AMINOCAPROIC ACID (EACA) AND TRANEXAMIC ACID (TXA)**

The two synthetic antifibrinolytic agents currently available include the lysine analogs EACA and TXA that competitively inhibits activation of plasminogen to reduce conversion of plasminogen to plasmin, an enzyme that degrades fibrin clots, fibrinogen, and

other plasma proteins, including the procoagulant factors V and VIII. Tranexamic acid also directly inhibits plasmin, but higher doses are required than are needed to reduce plasmin formation.<sup>39,50</sup> The lysine analogs have variable effects on reducing bleeding, especially EACA, and published safety data on these agents are limited. Most of the efficacy data for these agents are reported with TXA, and represent small studies or from meta-analyses of pooled previously published data. We reported a study of 100 patients undergoing CABG surgery, and noted that EACA significantly reduced chest tube drainage by 30% compared to the placebo group (EACA, 650 ± 261 mL; placebo, 940 ± 627 mL;  $p = 0.003$ ); however, it did not reduce the need for allogeneic blood transfusion.<sup>51</sup> Although meta-analyses of patients undergoing cardiac surgery suggests that lysine analogs decrease transfusion requirements and the rate of surgical reexploration from 4.7 to 1.9% (RR, 0.44; 95% CI; 0.22–0.90), these are not consistent finding.<sup>52</sup> In the Cochrane database, 18 trials of TXA (1,342 patients show a reduction in the RBC transfusion rate by a relative 34% (RR, 0.66; 95% CI; 0.54–0.81).<sup>53</sup> while there were only 4 trials of EACA (208 patients that do not demonstrate a reduction in transfusions (RR, 0.48; 95% CI; 0.19–1.19).<sup>53</sup> Antifibrinolytic agents have also been reported for blood conservation in orthopedic procedures.<sup>54</sup>

### PROTAMINE

Protamine is the only available therapeutic approach to reverse unfractionated heparin. Protamine is a polypeptide composed of nearly 70% arginine residues, and thus has a high pKa to reverse the acidic molecule heparin by forming a simple acid-base interaction.<sup>55</sup> Protamine and does not reverse low-molecular-weight heparin. Following administration, protamine rapid reverses heparin as noted by return of activated clotting times, but also with marked elevations plasma concentrations of prothrombin fragment 1.2, thrombin-antithrombin III complex, and fibrin monomer.<sup>56</sup> Protamine can cause adverse reactions including anaphylaxis, acute pulmonary vasoconstriction and right ventricular failure, and hypotension.<sup>55</sup> Patients with diabetes are at an increased risk for adverse reactions due to the presence of neutral protamine Hagedorn (NPH), which contains insulin and protamine, causing increased protamine sensitization.<sup>55,57,58</sup> Individuals reported at risk for protamine reactions include patients with vasectomy, multiple drug allergies, and prior protamine exposure.<sup>59</sup>

### DESMOPRESSIN

Desmopressin (DDAVP) is the V2 analog of arginine vasopressin that stimulates the release of ultralarge von Willebrand factor (vWF) multimers from endothelial cells.<sup>4,60-62</sup> vWF mediates platelet adherence to vascular subendothelium by functioning as a protein bridge between glycoprotein Ib receptors

on platelets and subendothelial vascular basement membrane proteins. DDAVP shortens the bleeding time of patients with mild forms of hemophilia A or von Willebrand disease.<sup>60,61</sup> Surgical patients who might benefit from use of DDAVP are not clear. DDAVP is administered intravenously at a dose of 0.3 mg/kg, and should be given over 15-30 minutes to avoid hypotension.<sup>63,64,65</sup> Most studies have not confirmed the early reported efficacy during complex cardiac surgery.<sup>66-68,63,65</sup> Mannucci noted there have been 18 trials of desmopressin in 1295 patients undergoing cardiac surgery that show a small effect on perioperative blood loss (median decrease, 115 ml).<sup>4,69</sup>

### RECOMBINANT COAGULATION PRODUCTS

Recombinant coagulation products are used to manage bleeding in patients with hemophilia, von Willebrand's disease (vWD), or acquired inhibitors to antihemophilic factor (e.g., AHF concentrates, factor IX concentrates, factor VIIa concentrate, factor IX complexes, anti-inhibitor coagulant complexes).<sup>50,70</sup> Recombinant activated factor VIIa (rFVIIa; NovoSeven®, Novo Nordisk) is approved for hemophilia patients with inhibitors to treat bleeding. Currently, rFVIIa is increasingly used off label as a universal prohemostatic agent in complex clinical situations for life threatening hemorrhage.<sup>71</sup>

Recombinant factor VIIa produces a prohemostatic effect by forming a complex with tissue factor (TF) that is expressed at the site of injury, and locally initiates hemostatic activation.<sup>12</sup> TF is a membrane-bound glycoprotein that is expressed on subendothelial cells after tissue injury and loss of endothelial protective mechanisms.<sup>72</sup> Circulating FVIIa accounts for nearly 1% of circulating FVII, and is inactive until bound with TF.<sup>12</sup> When rFVIIa is administered, it binds to TF that activates factor X to factor Xa, leading to the generation of thrombin (FIIa) and resulting fibrin formation and platelet activation.<sup>13</sup> Giving rFVIIa to patients with multiple hemostatic abnormalities may result in added thrombin generation both on the surface of activated platelets but also at the local site of injury.<sup>73</sup> Multiple publications report rFVIIa in surgical patients and cardiac surgical patients including a recent reported analysis of the clinical studies.<sup>71,74-76</sup> Other publications have reported the cessation of bleeding following major trauma with refractory hemorrhage and coagulopathy.<sup>77</sup> The therapeutic dose of rFVIIa in non hemophilia patients are not established.<sup>78</sup> More studies are needed to further evaluate dosing, safety and efficacy in perioperative use of rFVIIa. However, guidelines as reported by Goodnough<sup>78</sup> and Despotis<sup>79</sup> for off label use in patients with life threatening hemorrhages.

Controlled clinical trials report the incidence of thrombotic complications among patients who received rFVIIa was relatively low and similar to that among patients who received placebo.<sup>74</sup>

However, most case reports administering rFVIIa as rescue therapy include patients who have impaired coagulation, have received multiple transfusions, and are at a high risk for adverse events. The complex role that transfusion therapy has in producing adverse outcomes is increasingly being noted in the literature.<sup>80-82</sup> A report using the FDA MED Watch database noted thromboembolic events in patients with diseases other than hemophilia in whom rFVIIa was used off-label basis, and included 54% of the events as arterial thrombosis (e.g., stroke or acute myocardial infarction).<sup>83</sup> Venous thromboembolism (mostly, venous thrombosis or pulmonary embolism) occurred in 56% of patients. In 72% of the 50 reported deaths, thromboembolism was considered the probable cause. It is not clear to what extent the clinical conditions requiring the use of rFVIIa may have contributed to the risk of thrombosis.<sup>4</sup> Other major issues regarding rFVIIa include costs and dosing. This drug has also seen widespread use in battlefield conditions in Iraq.

### REVERSAL OF VITAMIN K ANTAGONISTS ASSOCIATED COAGULOPATHY

Prohemostatic agents are often needed to urgently reverse the anticoagulant effect of warfarin in the perioperative setting. Treatments available for reversal include vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), and rFVIIa.<sup>84</sup> Warfarin reversal is becoming a major indication for FFP in some hospitals.<sup>85</sup> PCCs were originally developed for repleting factor IX in hemophilia B, and contain standardized amount of FIX along with various amounts of other vitamin K dependent factors (prothrombin, FVII, FX, protein C and S).<sup>84</sup> PCCs are recommended in guidelines as primary treatment for reversal in patients with life-threatening bleeding and an elevated international normalized ratio (INR), and rFVIIa may be considered as an alternative.<sup>84,86</sup> Compared with FFP, evidence suggests PCCs offer quicker INR correction and improved bleeding control; they also have a lower infusion volume and are more readily available without cross matching.<sup>84,87-89</sup> Although there are historical concerns regarding potential thrombotic risk with PCCs, present-day PCCs are much improved.<sup>89</sup> Clinical data suggest that rFVIIa may provide similar benefits over FFP as PCCs; however, preclinical comparisons suggest that PCCs are more effective in correcting coagulopathy.<sup>89</sup> PCC are being investigated as a therapeutic alternative in this setting.<sup>84</sup>

### FIBRINOGEN

Fibrinogen is an under recognized coagulation factor critical for producing effective clot in surgical patients, and data supports it as a predictor of perioperative bleeding.<sup>9,90,91</sup> During the third trimester of pregnancy, fibrinogen levels are elevated to >400 mg/dL. Bleeding increases for each 100 mg/dL decrease

in fibrinogen level in parturients.<sup>92</sup> These clinical data highlight critical roles of fibrinogen in the prevention of excessive bleeding, thus adequate plasma levels (~ 200 mg/dL) need to be considered when treating life threatening bleeding. Fibrinogen can be replete by human plasma-derived fibrinogen concentrate; otherwise, fibrinogen-rich cryoprecipitate can be given (one unit per 10-kg increases fibrinogen by 50–70 mg/dL). In Europe, fibrinogen concentrates are available and cryoprecipitate is not used. A fibrinogen concentrate (RiaSTAP, CSL Behring) has just been granted licensing as an orphan drug for treating bleeding in patients with congenital afibrinogenemia or hypofibrinogenemia, but not for patients with dysfibrinogenemia. Data to support the approval came from a study of 15 patients with afibrinogenemia who received 70 mg/kg of fibrinogen concentrate and achieved a target level of fibrinogen expected to prevent bleeding. Plasma from 14/15 patients showed increased maximum clot firmness, a surrogate marker likely to predict clinical benefit of the drug.

### TOPICAL HEMOSTATIC AGENTS

Topical hemostatic agents are used extensively by orthopedic, neuro, cardiac, and vascular surgeons to promote hemostasis locally at the site of surgery and vascular. These agents can be classified based on their mechanism of action and include physical or mechanical agents, caustic agents, biologic physical agents, and physiologic agents. Gelatin sponges or Gelfoam<sup>®</sup> are composed of purified pork skin gelatin that increases contact activation to help create topical clot. Oxidized regenerated cellulose is also known as Surgicel or Oxycel that works like Gelfoam. Microfibrillar collagen is Avitene<sup>®</sup> and is collagen, which is derived from bovine skin. Collagen sponges, these come in a wide variety of different commercial forms, and are derived from bovine Achilles tendon or bovine skin.

One of the widely used agents is topical thrombin and ~1 million patients in the United States are treated with topical applications of thrombin yearly.<sup>93</sup> Bovine-derived thrombin until recently was the only topical thrombin available, and has the potential to induce robust immune responses following human exposure.<sup>93</sup> Reports include development of antibodies against thrombin, prothrombin, factor V, and cardiolipin that can cause severe postoperative bleeding to vascular bypass graft thrombosis.<sup>94,95</sup> Floseal<sup>™</sup> is bovine thrombin plus cross-linked gelatin granules mixed together. The problem with bovine thrombin is that antibodies form to this molecule and its contaminant proteins (factor V) that may contribute to hypersensitivity and coagulopathy due to antibody formation.<sup>93</sup> As a result, there are now purified human thrombin (purified from multiple donors) and a recombinant thrombin for RECOTHROM<sup>™</sup>.

## THE FUTURE

The potential for bleeding in surgical patients represents a growing problem for clinicians. The increasing use of anticoagulation agents creates a need for multiple pharmacologic approaches. The growing use of clopidogrel, the new agent prasugrel, and newer anticoagulants including the oral Xa inhibitors will continue to pose new paradigms and potential problems in managing surgical patients. Newer therapies including recombinant therapies provide clinicians with the ability to give key coagulation proteins to treat hemorrhage when standard therapies are ineffective. Additional novel therapeutic agents are also under investigation to replace aprotinin as a therapeutic agent.<sup>96,97</sup>

Suggested web sites:

Bleedingweb.com

HeparinInducedThrombocytopenia.com

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# Ultrasound in Regional Anesthesia

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## INTRODUCTION

Conventional nerve localization techniques for regional anesthesia rely on surface anatomical landmarks and tactile experience to estimate nerve location. A variety of useful endpoints that have been used to indicate needle to nerve proximity in clinical practice are: a subjective perception of arterial pulsation or fascial click; or more objectively, a sensory paresthesia response; or a motor response through electrical stimulation. These are essentially 'blind' techniques and work only by trial and error. Furthermore, these indirect indicators of needle to nerve contact have been shown to be less sensitive and reliable than one originally thought.<sup>1,2</sup> This may lead to multiple needle attempts, long induction time, procedure related pain, patient discomfort and post-block complications.

In contrast, ultrasound offers the benefits of visualizing all of the following in real time: relevant anatomical structures (nerve, vascular, muscular, bony and pleural structures), needle advancement, needle-nerve contact, and local anesthetic spread. Pre-block anatomical survey (neural and non neural structures) helps define the optimal site and path for needle insertion. Real time imaging guidance during needle advancement helps minimize random needle attempts and the number of moves to reach the target nerve. Observation of local anesthetic spread helps ensure sufficient local anesthetic is injected around the nerves to accomplish a successful blockade.

The technique and study of ultrasound-guided regional anesthesia (UGRA) involving peripheral nerve blockade (PNB) and neuraxial blockade (NB) are in evolution.<sup>3,4</sup> It is important to point out that there are artifacts and pitfalls associated with UGRA.<sup>5,6</sup> Needle visualization can be challenging.<sup>7</sup> The place of ultrasound in modern regional anesthesia practice is being defined. At the present time, practice guidelines and teaching curricula are being developed for proper training. Detailed description of UGRA techniques can be found on [www.usra.ca](http://www.usra.ca) website. Illustrations for this presentation are also taken from the same website.

The following is a brief description of UGRA techniques for some of the commonly performed PNBs and NBs in the adult population.

## NERVE IMAGING AND NEEDLING TECHNIQUE

In principle, high frequency transducers (e.g., 10–15 MHz) emit sound waves that offer high-resolution imaging of superficial structures (e.g., interscalene region 2-3 cm from the skin surface) but have low

tissue penetration. Low frequency transducers (e.g., 2–5 MHz), on the other hand, emit sound waves that allow for deeper tissue penetration (e.g., gluteal region > 5-6 cm deep) but have low image resolution. The field of view is influenced by the shape of a transducer. For example, a curved array transducer affords a wider field of view than a linear array transducer.

The two-dimensional anatomic views most useful for UGRA are the transverse and longitudinal views.<sup>3</sup> A transducer positioned perpendicular to the long axis of the nerve generates a cross sectional view of the nerve (also called transverse or short axis view). A transducer positioned parallel to the long axis of the nerve, on the other hand, generates a longitudinal view of the nerve. The transverse image of the target nerve is most commonly used for US-guided PNB. Generally speaking, a nerve is best visualized when the ultrasound beam is at 90° to the target. The impact of the angle of incidence of the ultrasound beam on image clarity is called anisotropy.

Nerves have varying degrees of echogenicity depending on nerve composition and the anatomic location in the body. For example, nerve roots and trunks of the brachial plexus in the interscalene and supraclavicular regions appear mostly hypoechoic (dark), whereas peripheral branches of the brachial plexus and the sciatic nerve are more hyperechoic (bright). Neural tissue is hypoechoic and connective tissue (e.g., epineurium and perineurium) is hyperechoic. A mixture of hypo- and hyperechoic tissues gives a nerve the "honeycomb" appearance.

Similar to nerve imaging, the needle can be visualized in a transverse view (when the probe is oriented perpendicular to the needle shaft) and ultrasound guided needle advancement in this orientation is called the out-of-plane (OOP) approach. The needle can also be imaged in a longitudinal view (when the probe is oriented in parallel plane with the needle shaft). Needle advancement in this way is called the in-plane (IP) approach. Both needling approaches may be utilized for UGRA and the choice is dependent on the operator's preference.

## CLINICAL PEARLS

- It can be technically challenging to locate the needle tip when the needle is inserted at a steep angle (> 45°) and when the target is > 4-5 cm deep. Injection of a small amount of fluid (1-2 mL) through the needle will create an image of tissue expansion on ultrasound. This method of needle tip localization is called hydrolocation.<sup>8</sup>



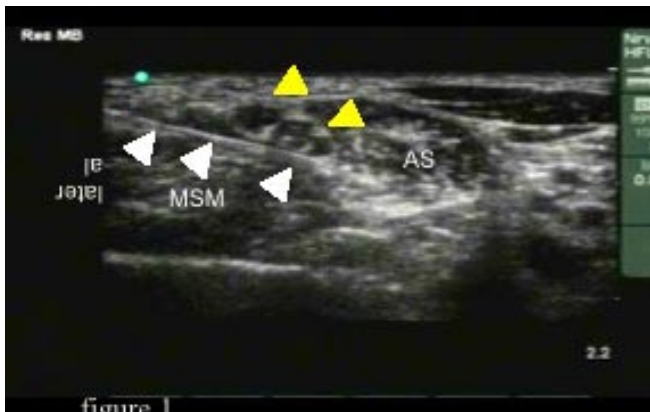
Dextrose 5% solution (a non-conducting medium) is injected if electrical stimulation is desired for nerve confirmation. Alternatively, saline or local anesthetic (conducting medium) can be injected if nerve stimulation is not required.

- The OOP needling approach may be preferred when the target is located deep because the needle to target distance is shorter with this approach than the IP approach.

## **BRACHIAL PLEXUS**

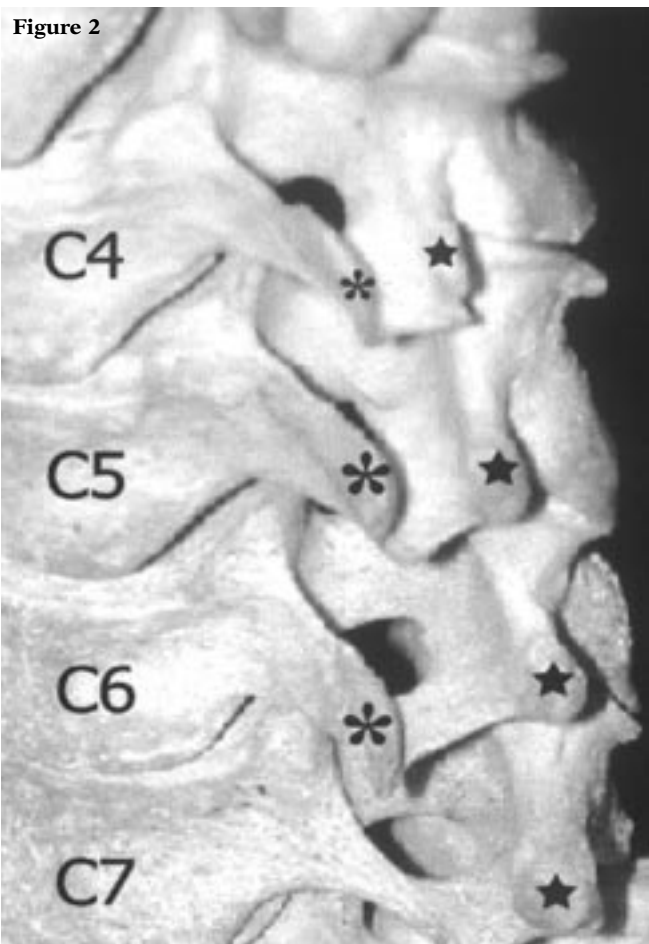
### **INTERSCALENE BLOCK**

Interscalene block is indicated for shoulder surgery.<sup>9</sup> A 10-12 MHz linear transducer is placed at the lateral aspect of the sternocleidomastoid muscle with the patient's head turned slightly to the contralateral side. In the axial oblique plane, the trachea, thyroid gland, carotid artery, internal jugular vein and the sternocleidomastoid muscle are visualized as superficial structures (from medial to lateral). Deep to the sternocleidomastoid muscle lie the anterior (ASM) and middle scalene muscles (MSM) which sandwich the roots/trunks of the brachial plexus in between (figure 1). Nerve structures (arrowheads) in this region are distinctly hypoechoic oval or round and the proximal nerve roots (e.g., C5) are located more superficially than the distal ones (e.g., C7).

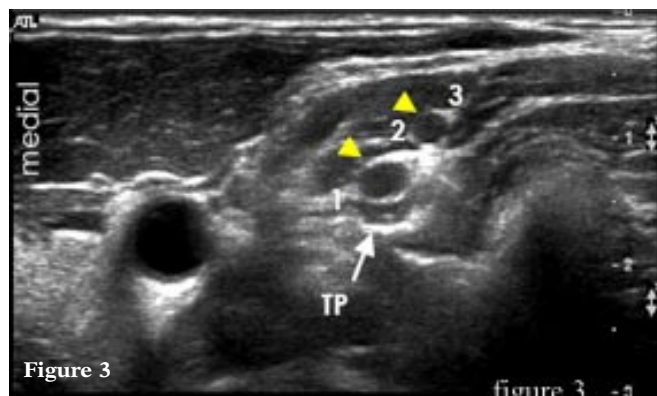


### **CLINICAL PEARLS**

- Nerve roots and their corresponding levels can be accurately identified by examining the shape of the transverse processes.<sup>10</sup> The transverse processes at and above C6 cast a bony shadow that is shaped like a "U", representing the anterior (\*) and posterior (★) tubercles (figure 2, taken from reference # 9). The C7 transverse process has a posterior tubercle (★) only.
- Another method of identifying the spinal level is visualization of the vertebral vessels which are generally visualized below C6.
- It is important to distinguish the C7 nerve root from the vertebral artery using Color Doppler if necessary. Both structures are hypoechoic and in close proximity to each other.



- With the IP (arrows in figure 1) or OOP approach, a 5 cm block needle is commonly used for this block. Block success is dependent on proper local anesthetic spread in the interscalene groove. Hydrolocation<sup>8</sup> and nerve stimulation techniques may be used to confirm needle to nerve contact.
- It is important to avoid local anesthetic injection immediately adjacent to the transverse process (TP) and the nerve root emerging from the neural foramen because of the risk of unintentional epidural or spinal anesthesia. As illustrated in figure 3, it is advisable not to inject at location # 1 since it is immediately next to the TP; injection at locations 2 and 3 is more appropriate.



### SUPRACLAVICULAR BLOCK

The supraclavicular block is indicated for upper limb surgery from the shoulder to the hand.<sup>11,12</sup> A 10-12 MHz linear transducer is placed in the supraclavicular fossa with the patient's head in the neutral position. In the coronal oblique plane (figure 4), the large anechoic subclavian artery (SA, lateral) and vein (medial) are visualized on each side of the anterior scalene muscle (SAM). Immediately lateral and posterior to the subclavian artery lie the trunks/divisions of the brachial plexus (arrowheads), which are visualized as a cluster of hypoechoic nodules. Deep to the subclavian artery and brachial plexus is the first rib (FR), often visualized as a hyperechoic line with a hypoechoic shadow below. The pleura, often visualized as a hyperechoic line with sliding movement during respiration and accompanying air artifact, can be found on each side of the first rib.

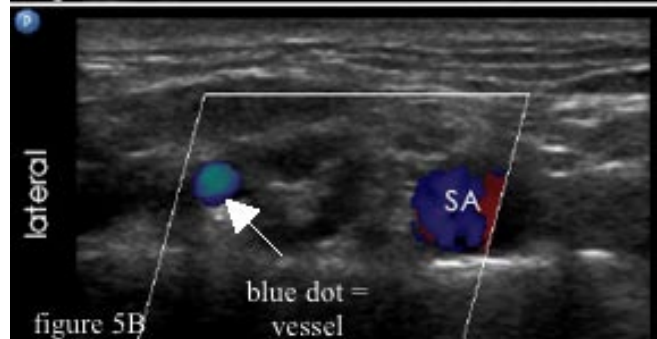


### CLINICAL PEARLS

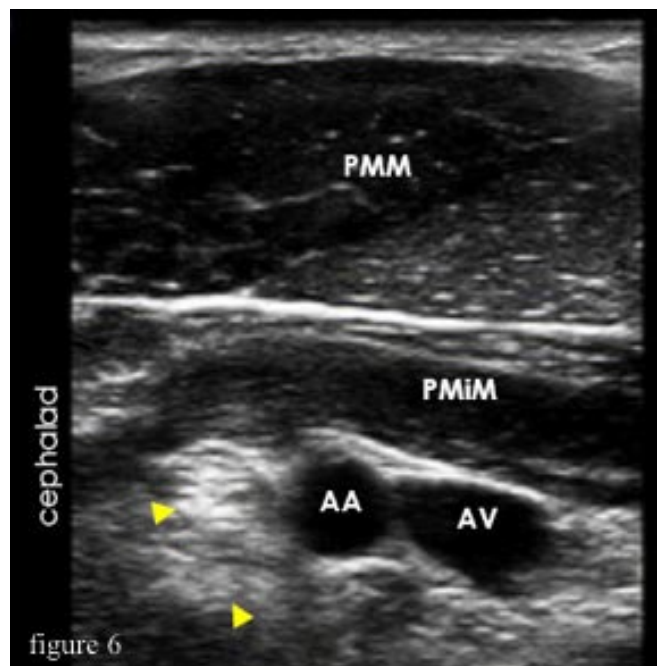
- The IP approach is generally recommended for supraclavicular block. Real time visual guidance to accurately localize the needle tip is mandatory throughout the time of needle advancement. A 5 cm 22 gauge needle may be inserted from the lateral or medial side of the transducer depending on the operator's preference.
- The technique of hydrolocation and hydrodissection is valuable for confirming needle tip location inside the supra-clavicular nerve compartment. Fluid spreading away from the plexus indicates needle tip outside the nerve compartment.
- The suprascapular artery or the transverse cervical artery in the transverse view (blue dot in figure 5B) also appears round and hypoechoic thus may be mistaken for nerve trunks or divisions (arrowheads, figure 5A). The use of Color Doppler is helpful to identify vessels.

### INFRACLAVICULAR BLOCK

The infraclavicular block is indicated for upper limb surgery from the arm to the hand.<sup>13</sup> A 10-12 MHz linear transducer is placed below the clavicle immediately medial to coracoid process in an average sized patient. For a patient with a higher BMI, a 4-7



MHz linear transducer may be required for deeper beam penetration. In the parasagittal plane (figure 6), the hypoechoic pulsatile axillary artery (AA) and collapsible axillary vein (AV) are visualized deep to the pectoralis major (PMM) and pectoralis minor (PMiM) muscles. The lateral and posterior cords (arrowheads) are often visualized as hyperechoic nodules located cephalad and posterior to the axillary artery, respectively. The medial cord may be visualized posterior to the artery or in between the artery and vein. When the transducer is angled medially, the pleura can be visualized deep to the vessels with a sliding lung sign during respiration.

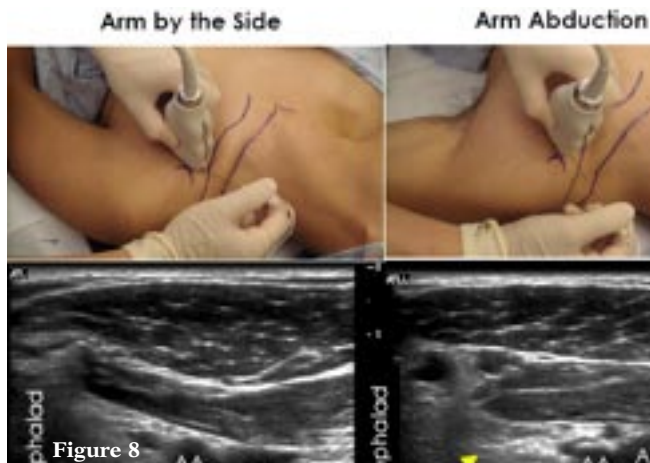


### CLINICAL PEARLS

- A 5-7 cm block needle is commonly inserted using the IP approach in the cephalad to caudad direction (arrows, figure 7). A larger bore 18 G needle is preferred when the cords are deep to facilitate visualization.

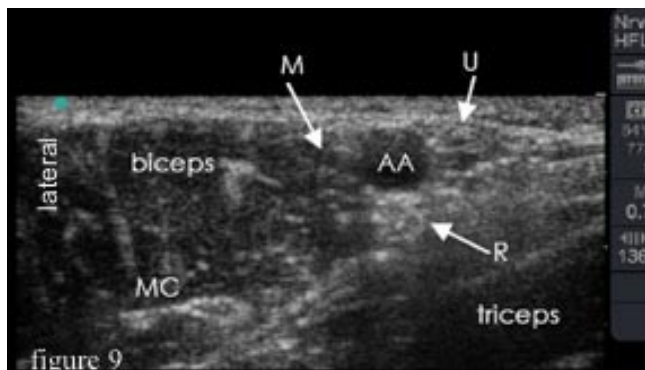


- It is recommended to place the needle tip and local anesthetic (LA) posterior to the axillary artery. A U shape spread of local anesthetic around the axillary artery has been shown to most consistently block all 3 cords (figure 7).<sup>14</sup>
- If the cords are not well visualized, consider abducting the arm to 90° which will stretch the brachial plexus and make it taut. This will bring the 3 cords closer together and enhance nerve visualization (figure 8).



### AXILLARY BLOCK

The axillary block is generally indicated for upper limb surgery from the elbow to the hand.<sup>15</sup> A 10-12 MHz linear transducer is placed in the distal axilla perpendicular to axillary crease with the patient's arm abducted to 90° and elbow flexed. In the transverse plane (figure 9), the hypoechoic pulsatile axillary artery (AA) and compressible vein(s) are visualized in a superficial location. The terminal branches of the brachial plexus at the axilla are hypoechoic and nodular with internal hyperechoic punctuations ("honeycomb" appearance). The median nerve (M) is typically situated lateral to the axillary artery, whereas the ulnar nerve (U) is medial and the radial



nerve (R) is often posteromedial to the axillary artery. The musculocutaneous nerve (MC) is often situated in the plane between the biceps and coracobrachialis muscles that are lateral to the axillary artery.

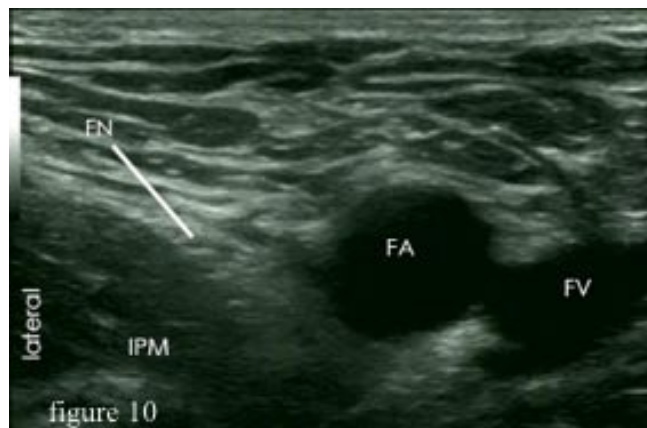
### CLINICAL PEARLS

- A 5 cm block needle may be inserted using an IP or OOP approach for this superficial block.
- A perineural injection technique around individual nerves is preferred over a perivascular technique to achieve consistent and complete block success.
- It is important to identify the axillary vein(s) during scanning and collapse the vein(s) during local anesthetic injection to avoid unintentional intravascular injection. An absence of fluid (hypoechoic) and/or tissue expansion during injection highly suggests an intravascular injection.

### LUMBOSACRAL PLEXUS

#### FEMORAL NERVE BLOCK

The femoral nerve block is generally indicated for surgical anesthesia and postoperative analgesia in the thigh and knee.<sup>16</sup> A 10-12 MHz linear transducer is placed transverse at or below the inguinal crease with the patient's leg in the neutral position. In the transverse plane (figure 10), the anechoic pulsatile femoral artery (FA) and compressible vein (FV) are visualized. At similar depth and lateral to the femoral artery, the femoral nerve (FN) is visualized as a hyperechoic linear or triangular structure superficial to the iliopsoas muscle (IPM).



**CLINICAL PEARLS**

- In some cases, the femoral nerve may be difficult to identify by ultrasound in the transverse scan because it can be thin and wide (nerve branching). It may also lie on top of the iliopsoas muscle at a distance from the femoral artery. The hyperechoic triangle immediately lateral to the femoral artery may not contain the femoral nerve thus nerve stimulation is a helpful confirmation tool.
- Accurate needle placement and local anesthetic (LA) injection is indicated by fluid expansion deep to the fascia iliaca (FI) which is imaged as a distinct hyperechoic line after injection (figure 11).

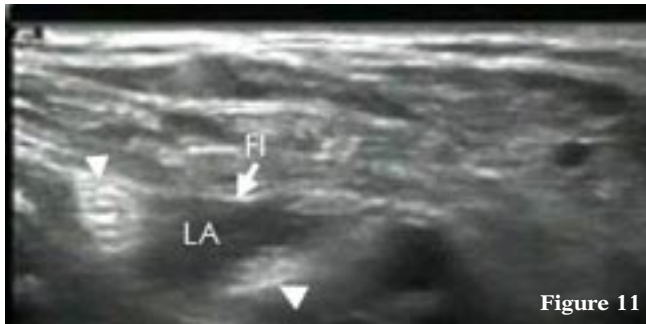


Figure 11

- A 5 cm block needle may be inserted using an IP or OOP approach for this superficial block. For continuous catheter placement, the IP approach (from lateral to medial) offers a number of potential advantages: 1) a subcutaneous tunnel is created during needle insertion; 2) the ease of needle contact with the posterior division of the femoral nerve immediately upon needle entry into the lateral side of the nerve compartment; and 3) the catheter can be securely positioned between the femoral nerve and the iliopsoas muscle.

**GLUTEAL SCIATIC NERVE BLOCK**

The gluteal sciatic nerve block is indicated for lower limb surgery at or below the hip often in combination with a lumbar plexus block.<sup>17</sup> A 2-5 MHz curved transducer is placed firmly on the buttock with the patient positioned semi-prone (Sims' position) with the hip and knee flexed. In the transverse view (figure 12), the sciatic nerve (arrowhead) is often



Figure 12

visualized as an elliptical hyperechoic structure deep to the gluteus maximus muscle (GMM) and superficial to the ischial bone (IB, a hyperechoic line with an underlying hypoechoic bony shadow). The nerve is usually found immediately lateral to the inferior gluteal artery (arrow, figure 13) and far lateral to the pudendal vessels (next to the ischial spine, IS).



Figure 13

**CLINICAL PEARLS**

- The sciatic nerve may be difficult to visualize in the transverse plane because of its shape (thin but wide). A longitudinal scan is recommended in this case since it has a higher probability to image successfully the width of the nerve in the longitudinal plane. Another useful hint is to trace the nerve from the popliteal crease cephalad in a patient lying prone.
- With the IP or OOP approach, a 8-12 cm block needle is often required to reach the deep seated sciatic nerve. It is useful to confirm needle tip location using the hydrolocation and/or nerve stimulation techniques.

**INFRAGLUTEAL SCIATIC NERVE BLOCK**

The infragluteal sciatic nerve block is indicated for lower limb surgery at or below the knee often in combination with a lumbar plexus block.<sup>18</sup> A 2-5 MHz curved transducer is placed in the inferior aspect of the buttock or caudal to the buttock, midway between greater trochanter of femur (GT) and ischial tuberosity (IT) with the patient positioned semi-prone. In the transverse plane (figure 14), the sciatic nerve (arrowhead) is visualized as a solitary hyperechoic elliptical structure deep to the gluteus maximus muscle (GMM), superficial to the quadratus femoris muscle (QFM) and in between two curvilinear hypoechoic bony shadows (the IT medially and the GT laterally).

**CLINICAL PEARLS**

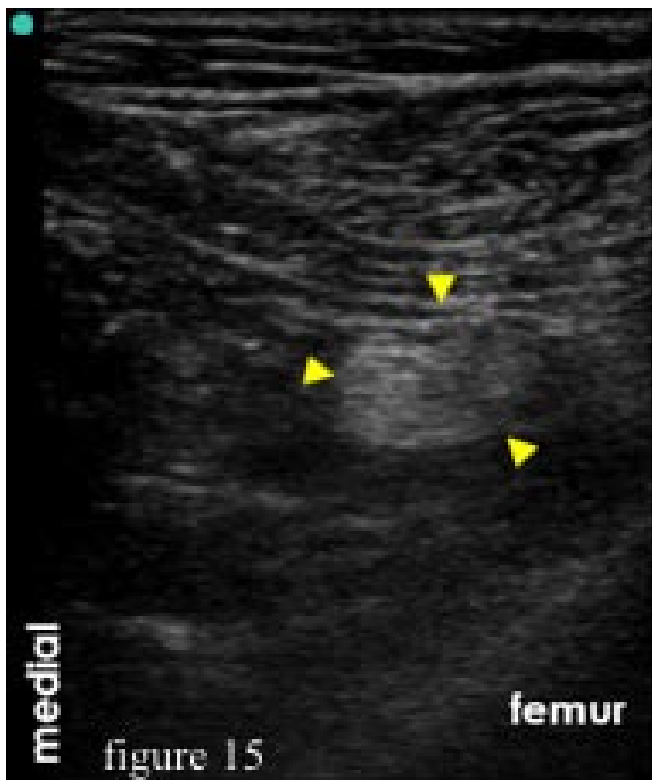
Similar to the gluteal region, the infragluteal sciatic nerve may be difficult to visualize in the transverse plane because it is thin and wide. Again a longitudinal scan may be useful to capture the width of the nerve in the longitudinal plane. Tracing the nerve from the popliteal crease cephalad is also a useful maneuver.



The sciatic nerve in the infragluteal region is often more superficial than in the gluteal region. A 8 cm block needle is often sufficient to reach the sciatic nerve. Again hydrolocation and nerve stimulation are useful techniques to confirm needle tip location whenever possible.

### POPLITEAL SCIATIC NERVE BLOCK

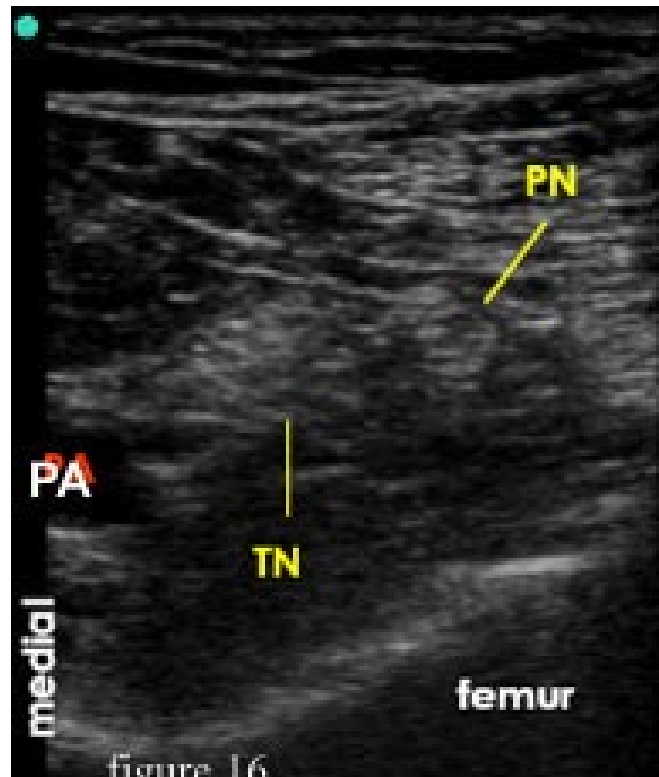
This block is indicated for lower limb surgery at or below the ankle with or without a saphenous nerve block.<sup>19,20</sup> A 4-7 MHz linear transducer is placed 7-10 cm cephalad to the popliteal crease with the patient positioned prone. In the transverse plane (figure



15), the hypoechoic pulsatile popliteal artery (PA) is visualized posterior (superficial) to the femoral bone and in the groove between the semitendinosus and semimembranosus muscles medially and the biceps femoris muscle laterally. The sciatic nerve (arrowheads) in this region is visualized as a hyperechoic round or oval shaped structure lateral to the artery.

### CLINICAL PEARLS

- To optimize a 90° angle of beam incidence, it is often necessary to angle the transducer caudally to enhance nerve visibility because the sciatic nerve travels more superficially as it approaches the popliteal crease.
- The sciatic nerve bifurcates at variable distance from the popliteal crease. It is best to scan the nerve cephalad and caudad and aim to block the nerve proximal to the point of bifurcation. Alternatively, the tibial (TN) and peroneal nerve (PN) components can be blocked individually after sciatic nerve bifurcation (figure 16).



- A 5-8 cm block needle is recommended for this procedure to contact the nerve on the medial and lateral sides (avoid hitting the nerve head on) before local anesthetic is injected circumferentially around the nerve to create the “donut” sign.

### TRUNK BLOCKS

#### TRANSVERSE ABDOMINIS PLANE

The transverse abdominis plane (TAP) block is indicated for pain control following bowel surgery<sup>21</sup> and cesarean section.<sup>22</sup> The anatomical basis of the TAP block was recently described<sup>23,24</sup> and local anesthetic injected bilaterally into the neurofascial plane between the internal oblique and the transversus abdominis muscles can block somatic abdominal wall neural afferents. The technique of ultrasound guided TAP block has been described for lower<sup>25</sup> and upper abdominal incisions.<sup>26</sup>

With the patient lying supine, a 10-12 MHz curved transducer is placed transverse in the anterior abdominal wall immediately superior to the iliac crest to identify the 3 abdominal muscle layers-external oblique (EOM), internal oblique (IOM) and transverses abdominis (TAM). Anterior branches of the lower thoracic and upper lumbar nerves are too small to be imaged.

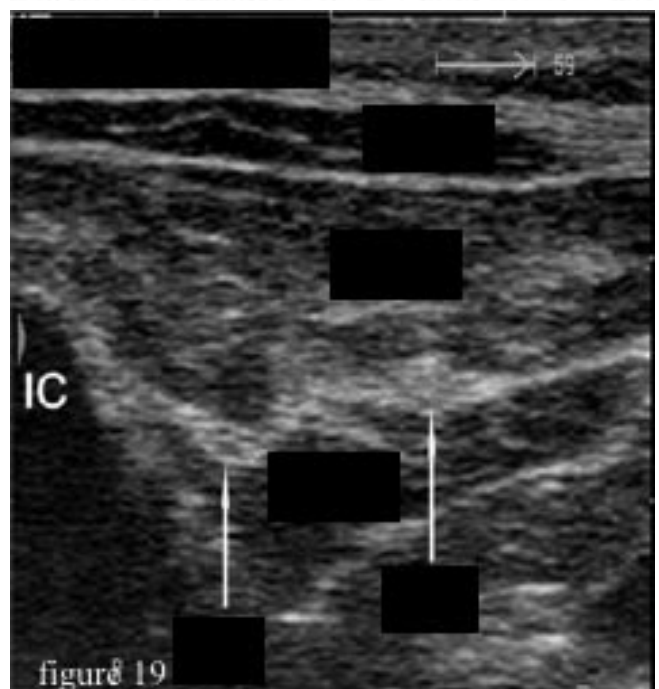
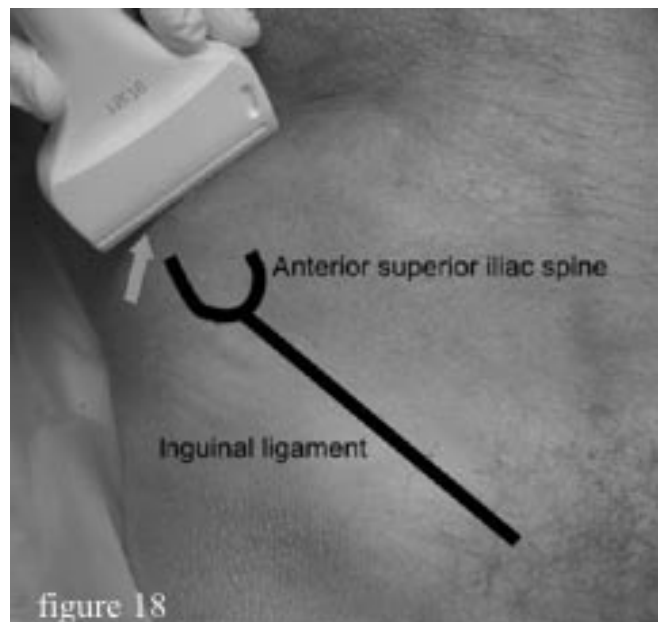
### CLINICAL PEARLS

- It is possible to visualize only 2 abdominal muscle layers above the iliac crest because the EOM has become an aponeurosis.
- When it is difficult to clearly identify the 3 muscle layers, it is useful to place the transducer in the midline anterior abdominal wall to first identify the rectus abdominis muscle before scanning laterally to see the EOM, IOM and TAM.
- A 9 cm 22 G spinal needle connected to an extension tubing is commonly used for this block. A long acting local anesthetic (LA) bolus (20-25 mL) is injected in the plane between EOM and TAM (figure 17).



### ILIOINGUINAL AND ILIOHYPOGASTRIC NERVES

The ilioinguinal (II)/iliohypogastric (IH) nerve block is indicated for analgesia following inguinal hernia<sup>27</sup> and lower abdominal surgery.<sup>28</sup> With the patient lying supine, a 10-12 MHz linear transducer is placed oblique (pointing at the opposite shoulder) and over the iliac crest (IC) as posterior as possible (figure 18, picture taken from reference #29) to image the II and IH nerves (often hypoechoic) as they emerge next to the iliac bone (figure 19, picture taken from reference #29).<sup>29</sup> The two nerves are sandwiched between the internal oblique (IOM) and transversus abdominis (TAM) muscles.



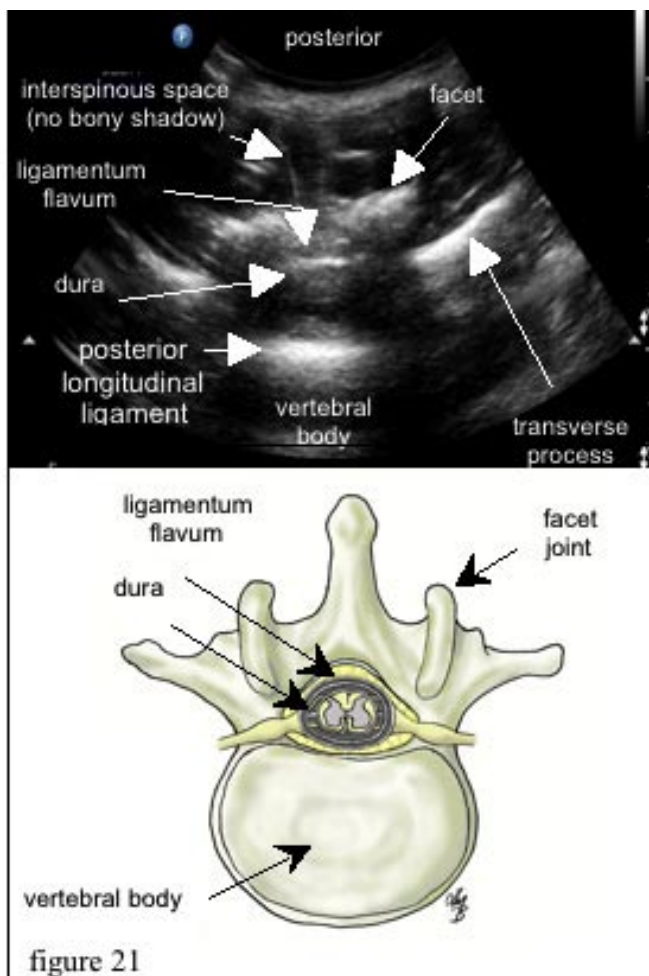
### CLINICAL PEARLS

- It is common to visualize the deep iliac circumflex artery in the same muscle plane as the II and IH nerves and the artery serves as an important landmark for nerve localization.
- Again a 9 cm 22 G spinal needle is commonly used for this block. A large volume local anesthetic (LA) bolus injection (20-25 mL) is required in the plane between EOM and TAM.
- Anesthesia may be incomplete during inguinal herniorrhaphy surgery because the genitofemoral nerve is not anesthetized.

## NEURAXIAL SPACE

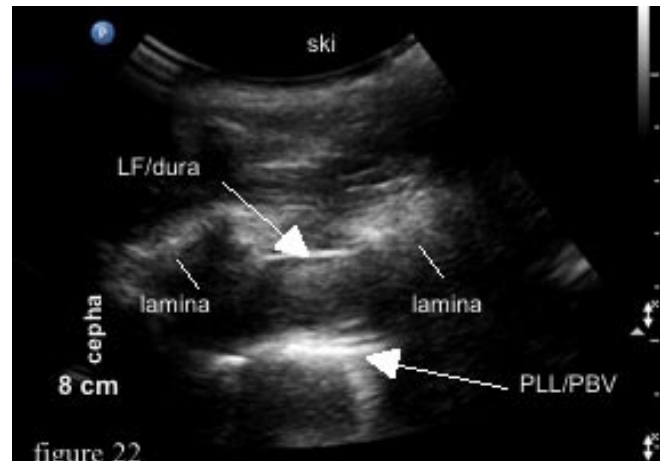
### EPIDURAL/SPINAL BLOCK

Ultrasound guidance is helpful to guide needle placement in obese patients with ill defined bony landmarks and patients with known abnormal spinal anatomy e.g., scoliosis,<sup>30</sup> previous laminectomy, previous bony fusion and instrumentation.<sup>31</sup> A 2-5 MHz curved transducer is placed transverse over the midline spinous process with the patient sitting and the trunk flexed to widen the interspinous space. In the transverse plane, the contour of the spinous process is identified as a superficial midline hypoechoic bony shadow. The lamina is visualized as a hyperechoic line anterolateral to the spinous process (figure 20). The transverse process is visualized also as a hyperechoic line but located more lateral and anterior to the lamina (figure 20). The location of the midline spinous process is marked on the skin at several spinal levels.



The transducer is then moved cephalad or caudad until the hypoechoic shadow of the spinous process has disappeared. This is the interspinous space for needle entry. The ligamentum flavum and dura can be visualized as 2 distinct hyperechoic lines (figure 21) although a single line representing the ligamentum flavum/dura complex is commonly seen

in elderly patients. The distance from the skin to the ligamentum flavum/dura complex is noted and the level of the interspinous space is marked by placing a mark laterally on each end of the transducer. Deep to the ligamentum flavum/dura complex, the posterior longitudinal ligament and the posterior border of the vertebral body are visualized most commonly as a single hyperechoic line (figure 21).



A paramechanical scan is also valuable for scanning the interspinous space through the paramechanical window (figure 22). This can further confirm the skin to ligamentum flavum/dura distance and assess the size of the interspinous space for needle access on the left and right sides. With the transducer placed in the longitudinal plane lateral to the spinous processes, the laminae of two contiguous vertebrae are often imaged as hypoechoic bone shadows (figure 22). The hyperechoic ligamentum flavum/dura complex (LF/dura, superficial) and the posterior longitudinal ligament/vertebral body complex (PLL/PBV, deep) are identified.



Ultrasound guided neuraxial block often involves a pre-block ultrasound scan prior to needle placement.<sup>32</sup> The midline spinous process (figure 23) and the interspinous space (figure 24) are marked on the skin at several levels. Real time ultrasound guidance is technically difficult because of the size and thickness of the transducer and requirement of more than one pair of hands. The intersection

between the posterior midline and the level of the interspinous space marks the site of needle insertion (figure 25). This is the midline transverse needle technique for neuraxial block.



Figure 24

After complete removal of the ultrasound gel (to avoid gel introduction into the neuraxial space) and skin sterilization and local anesthetic infiltration, an epidural needle is inserted using the loss of resistance technique or a spinal needle is inserted as indicated. The approximate depth of the epidural space can be estimated by the preceding ultrasound scans (skin to the ligamentum flavum/dura distance).



figure 25

### CLINICAL PEARLS

- A paramedian longitudinal scan can be used to count the spinal levels accurately. Starting caudally, the sacrum is imaged as a wavy continuous hyperechoic line (figure 26). The next bony structure cephalad is the L5 lamina and the interspinous space between L5 and sacrum is located. The transducer is then moved cephalad to image interspinous spaces at successive levels. Ultrasound imaging is a more accurate method of determining actual spinal levels than the palpation method.
- It is not always possible to visualize the ligamentum flavum/dura complex. Visualization

of PPL/PBVB alone indicates beam penetration through an interspinous space for needle access.

- Transducer angulation during midline transverse scan helps to estimate the size of the interspinous space and the angle of needle insertion.

### CONTINUOUS CATHETER TECHNIQUE

Real time ultrasound guidance during catheter placement is technically challenging because it requires 3 hands, one holding the transducer, one holding the needle and one advancing the catheter. For this reason, an assistant or alternatively the UltraStand transducer positioning system (<http://www.wellanmedical.com/ultrastand>) is required for the catheter procedure. Once the needle is positioned, it is the author's current practice to inject a fluid bolus (5-10 mL) to distend the perineural space (hydro-dissection) to facilitate catheter advancement. Saline or local anesthetic bolus is injected for a non stimulating catheter procedure and D5W is used for stimulating catheter insertion. Real time visualization of the catheter at the time of advancement is possible in the longitudinal scan<sup>33</sup> but it is technically challenging because accurate beam, nerve and catheter alignment is required. It is also challenging to accurately identify the catheter tip in its final location due to catheter coiling which gives the appearance of multiple hyperechoic dots. Because of these challenges, the best definitive confirmation of proper catheter position is visual detection of fluid spread around the target nerve during a bolus injection of fluid (5-10 mL of D5W, saline or local anesthetic) through the catheter (not the needle).<sup>34,35</sup>

### CLINICAL OUTCOME DATA

Preliminary data suggest that ultrasound may be a more reliable method of nerve localization than other existing methods e.g., nerve stimulation. However, more definitive data are required pending large scaled prospective studies. In particular, it is unclear at this time if ultrasound can decrease the incidence of accidental intravascular injection,<sup>36-39</sup> systemic local anesthetic toxicity and nerve injury.<sup>40</sup> It is important to recognize that the absence of fluid and/or tissue expansion at the time of local anesthetic injection is highly suggestive of an intravascular injection and ultrasound monitoring should continue throughout the injection, not only at the outset of the procedure.

A recent meta-analysis has concluded that block success, procedure time (one minute less), block onset time (29% shorter), block duration (25% longer) and vascular puncture are all in favor of ultrasound compared to nerve stimulation.<sup>41</sup> There are also other potential UGRA advantages in special circumstances. Ultrasound can confirm needle to nerve contact independent of nerve stimulation in subjects with pre-existing neuropathy,<sup>42</sup> without a limb,<sup>43</sup> anatomical anomalies<sup>44</sup> and bleeding



diathesis.<sup>45</sup> Accuracy of needle injection also demands a lower local anesthetic dose.<sup>46,47</sup> Most important of all, the novice can achieve greater success with UGRA than nerve stimulation.<sup>48</sup>

Below is a summary of randomized controlled trials of comparative studies between ultrasound and other techniques (data obtained from www.usra.ca website).

### ULTRASOUND (US) VS. NERVE STIMULATION (NS)

#### UPPER LIMB SURGERY

Author, Year Study Type	Surgery Block Type	Sample Size Local Anesthetic Stimulation endpoint US endpoint	Outcome Measures	Results US vs. NS *statistically significant
Casati <sup>49</sup> 2007 randomized, observer blinded	upper limb surgery axillary block	60 patients (30 per group) ropivacaine 0.75%, 20 mL NS threshold < 0.5 mA 4 nerve injection US endpoint = local anesthetic spread	1) # of needle passes 2) sensory block onset time 3) motor block onset time 4) surgical success 5) procedure related pain	1) 4* vs. 8 2) 14 min* vs. 18 min 3) same 4) same, 97% vs. 94% 5) less with US*
Chan <sup>15</sup> 2007 randomized, observer blinded	hand surgery axillary block	126 patients (62 in NS, 64 in US) 42 mL admixture of lidocaine 2% & bupivacaine 0.5% with epinephrine NS threshold 0.5 mA triple stimulation (median, ulnar and median nerves) ; proximal radial nerve stimulated response acceptable US endpoint = individual perineural injection	1) performance time 2) sensory block at 30 min 3) motor block at 30 min 4) success = complete pinprick anesthesia within 30 min in all 3 nerves 5) surgical anesthesia	1) 9 min* vs. 11 min 2) median n = 94% vs. 82% (p=0.06); ulnar n = 97%* vs. 83%; radial n = 86%* vs. 69% 3) same 4) 83%* vs. 63% 5) same, 95% vs. 86% (p=0.07)
Kapra <sup>50</sup> 2008 randomized, observer blinded	shoulder or upper arm surgery interscalene block	160 patients (80 per group) 20 mL ropivacaine 0.75% NS threshold < 0.5 mA single point stimulation; forearm or hand response US endpoint = individual perineural injection	1) block onset time 2) pinprick anesthesia at 30 min 3) motor block at 30 min 4) success = surgical anesthesia 5) time to first analgesic	1) 10 min* vs. 22 min 2) C8 and T1 blockade superior in US 3) median and ulnar nerve motor block superior in US 4) 99%* vs. 91% 5) 899 min* vs. 679 min

### ULTRASOUND VS. NERVE STIMULATION

#### UPPER LIMB SURGERY

Author, Year Study Type	Surgery Block Type	Sample Size Local Anesthetic Stimulation endpoint US endpoint	Outcome Measures	Results US vs. NS *statistically significant
Liu <sup>51</sup> 2005 randomized, observer blinded (?), reference not read	forearm and hand surgery axillary block	60 patients (30 per group) (double injection) 0.5 mL/kg 1.5% lidocaine with epinephrine	1) procedure time 2) success = blockade in all 7 sensory and motor nerves within 40 min 3) surgical anesthesia 4) adverse events (vascular puncture, paresthesia, hematoma)	1) 6.7 vs. 8.2 min* 2) same (73% vs. 70%) 3) same 100% 4) 0 vs. 20%
Macaire <sup>52</sup> 2008 randomized, observer blinded	endoscopic carpal tunnel release wrist block 1) median nerve 2) ulnar nerve	60 patients (30 per group) mepivacaine 1.5% 4 mL per nerve NS threshold = < 0.5 mA single point stimulation US endpoint = local anesthetic spread	1) performance time 2) onset time of complete sensory block 3) success = complete sensory block in 10 min	1) median n = 55 sec* vs. 100 sec (median); ulnar n = 57 sec* vs. 80 sec (median) 2) median n = 370 sec vs. 254 sec* (median); ulnar n = 367 sec vs. 241 sec* (in favor of NS) 3) success, same 93%
Marhofer <sup>53</sup> 2004 randomized, observer blinded	arm and forearm surgery infraclavicular block	40 pediatric patients (20 per group) ropivacaine 0.5%, 0.5 mL/kg NS threshold > 0.3 mA, 0.3 ms single point stimulation; distal motor response US endpoint = local anesthetic spread	1) block onset time 2) sensory block in 10 min 3) motor block in 10 min 4) block duration 5) procedure related pain	1) 9 vs. 15 min* 2) more complete for US 3) more complete for US 4) 384 min* vs. 310 min 5) 3* vs. 3.75/10
Sauter <sup>54</sup> 2008 randomized, observer blinded	hand or forearm infraclavicular block, lateral sagittal approach	80 patients (40 per group) mepivacaine 1.5% with epinephrine, 0.6 mL/kg NS threshold = 0.2 to 0.5 mA single point stimulation; distal nerve response (posterior or medial cord) US endpoint = local anesthetic spread	1) performance time 2) block onset time 3) the time until readiness for surgery 4) discomfort during the block 5) tourniquet pain (NRS) 6) success = analgesia or anesthesia of all five nerves distal to the elbow	1) 4.1 min vs. 4.3 min 2) 13.9 min vs. 13.7 min 3) same, 18.1 min 4) same, 1 (median) 5) 1 vs. 0.5/10 (median) 6) 95% vs. 85%

**ULTRASOUND (US) VS. NERVE STIMULATION (NS)  
UPPER LIMB SURGERY**

Author, Year Study Type	Surgery Block Type	Sample Size Local Anesthetic Stimulation endpoint US endpoint	Outcome Measures	Results US vs. NS *statistically significant
Marhofer <sup>16</sup> 1997	hip surgery  3-in-1 femoral nerve block	40 patients (20 per group)  0.5% bupivacaine, 20 mL  NS threshold = not specified  US endpoint = local anesthetic spread within fascial space	1) block onset 2) 2) block completeness in 1 h 3) block success	1) 16 min* vs. 27 min 2) better in US 3) same, 95% vs. 85%
Oberndorfer <sup>55</sup> 2007  randomized, observer blinded	lower extremity surgery  infragluteal or popliteal sciatic nerve block combined with femoral nerve + GA	46 children (23 per group)  levobupi 0.5%  NS threshold = 0.3 mA, 0.3 ms single point stimulation; plantar response  US endpoint = local anesthetic spread	1) block duration 2) local anesthetic volume for sciatic nerve block 3) local anesthetic volume for femoral block	1) 508 min* vs. 335 min 2) 0.2 mL/kg vs. 0.3 mL/kg 3) 0.15 mL/kg vs. 0/3 mL/kg
Perlas <sup>56</sup> 2008  randomized, observer blinded	foot or ankle surgery  popliteal sciatic nerve	74 patients (US 37 in US, 33 in NS, 4 incomplete assessment)  30 mL admixture of lidocaine 2% & bupivacaine with epinephrine  NS threshold < 0.5 mA single point stimulation; foot or toe response  US endpoint = local anesthetic spread	1) performance time 2) sensory block at 30 min 3) motor block at 30 min 4) success = complete pinprick anesthesia within 30 min in both tibial and common peroneal nerves 5) general anesthesia supplementation	1) 8.1 min vs. 8.3 min 2) TN = 89%* vs. 70%; CPN = 97%* vs. 82% 3) TN = 92%* vs. 70%; CPN = 100%* vs. 85% 4) Success = 89%* vs. 61% 5) 8% vs. 24% (NS)  TN = tibial nerve PN = peroneal nerve

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# New Insights on One-Lung Ventilation

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**Learning Objectives:** 1) To update practitioners on recent advances in our understanding of the physiology of one-lung ventilation. 2) To develop a plan to manage hypoxemia during one-lung anesthesia in a variety of clinical settings.

**Case Synopsis:** A 67 year old male with mild emphysema (FEV1 = 62% predicted) and no other significant co-morbidity is scheduled for a video-assisted (VATS) left upper lobectomy. After induction of general anesthesia and placement of a left-sided double-lumen tube (DLT) the patient is placed in the right lateral decubitus position and right one-lung ventilation (OLV) is commenced with a tidal volume of 6 ml/kg, respiratory rate 10/min and FiO<sub>2</sub> of 0.5 in air with sevoflurane 1MAC. After insertion of the VATS telescope the surgeon complains the lung is not well collapsed. What should the anesthesiologist do?

Improving lung collapse during OLV. The initial diagnostic maneuver is to re-assess the position of the DLT with a fiberoptic bronchoscope to ensure that the non-ventilated lung is adequately isolated from the ventilated lung and also that there is no lobar obstruction impeding collapse of the non-ventilated lung. Application of suction (e.g. -20cmH<sub>2</sub>O) to the lumen of the DLT to the non-ventilated lung will aid the elastic recoil of the lung and improve the rate of lung collapse to its closing capacity. Once the non-ventilated lung reaches its closing capacity, which is abnormally large in emphysema patients, further collapse depends on absorption of the trapped gas in the lung. If the non-ventilated lung contains poorly soluble nitrogen it will collapse slowly. To facilitate lung collapse, the non-dependent lung should be de-nitrogenated by ventilation with a FiO<sub>2</sub> of 1.0 for several minutes prior to the initiation of OLV! After the initiation of OLV, if the oxygenation remains stable, then air can be re-introduced to the gas mixture to decrease atelectasis in the ventilated (dependent) lung.

**Case Synopsis continued:** Eventually the left lung collapses sufficiently to allow surgery to proceed. During the first 30 min. of OLV the airway pressures (17/2 cmH<sub>2</sub>O), hemodynamic parameters (BP 120/70, HR 80) and end-tidal CO<sub>2</sub> (36 mmHg) remain stable. However there is a slow and persistent fall in the SpO<sub>2</sub> from an initial value of 99% to 90% in spite of increasing the FiO<sub>2</sub> to 1.0. What diagnostic and/or therapeutic maneuvers should be used?

After a recruitment maneuver of the ventilated lung and application of 5 cmH<sub>2</sub>O positive end-expiratory pressure (PEEP) to the ventilated lung the saturation continues to decline and is now 88%. The anesthesiologist suggests the use of continuous positive airway pressure (CPAP) to the non-ventilated

lung. The surgeon says that it may not be possible to continue with a VATS technique if CPAP is used and the operation will have to be converted to an open thoracotomy. Is there any other useful therapy for hypoxemia that can be used in this situation?

## MANAGEMENT OF HYPOXEMIA DURING OLV:

The incidence of hypoxemia (SpO<sub>2</sub> < 90%) during one-lung ventilation (OLV) with an inspired oxygen concentration (FiO<sub>2</sub>) of 1.0 has declined from levels of 20-25% in the 1970's to <10% today.<sup>2</sup> Several advances in thoracic anesthesia have aided this improved oxygenation. First, the routine use of fiberoptic bronchoscopy to position double-lumen tubes and bronchial blockers. Second, improved anesthetic techniques with lower doses of volatile agents.<sup>3</sup> And third, a better understanding of the pathophysiology of OLV.

**Etiology:** The major cause of hypoxemia is the shunt of de-oxygenated blood through the non-ventilated lung. Factors which influence this shunt are hypoxic pulmonary vasoconstriction (HPV), gravity, the pressure differential between the thoraces and physical lung collapse. HPV is inhibited by essentially all volatile anesthetics. Isoflurane seems to be less inhibitory than enflurane or halothane<sup>4</sup> and equivalent to sevoflurane or desflurane. Intravenous anesthetic techniques have not been shown to provide better oxygenation than the newer volatile anesthetics in <1MAC concentrations.

Manipulating the ventilating pressures and tidal volumes during one-lung anesthesia can improve the oxygenation for certain patients.<sup>5</sup> Some patients, particularly those with COPD, showed better oxygenation during OLV with pressure-controlled vs. volume-controlled ventilation.<sup>6</sup>

A third of the 25-35% shunt during OLV is due to ventilation-perfusion mismatch in the ventilated dependent-lung. Several factors under the control of the anesthesiologist can influence this dependent-lung shunt. An excess of intravenous crystalloids can rapidly cause desaturation of the pulmonary venous blood draining the dependent lung. Also, the use of nitrous oxide will lead to increased dependent-lung atelectasis since it causes greater instability of poorly ventilated lung regions than oxygen.

**Monitoring:** The risk of intraoperative hypoxemia is increased during OLV. Pulse oximetry is prone to malfunctions and does not give an early warning of the rapidly falling PaO<sub>2</sub> that occurs during OLV

before any change in saturation<sup>viii</sup>. Patients whose PaO<sub>2</sub> declines rapidly after initiating OLV are most likely to become hypoxemic. Side-stream spirometry permits on-line monitoring of pulmonary mechanics. This technology can provide an early warning of loss of lung isolation or accidental lobar obstruction. It may be possible to use this information to select the optimal ventilatory parameters for an individual patient during OLV.

**Prediction of Hypoxemia:** Several factors allow prediction of the risk of hypoxemia developing during OLV<sup>9</sup> (see Table 1). First, the side of lung collapse during OLV. The mean PaO<sub>2</sub> level is 70 mmHg higher for left vs. right thoracotomies. Second, patients with good preoperative spirometric pulmonary function tests tend to have lower PaO<sub>2</sub> values during OLV than patients with poor spirometry.<sup>10</sup> This may be related to auto-PEEP in patients with poor spirometry.<sup>11</sup> Other predictive factors include the A-aO<sub>2</sub> gradient during two-lung ventilation which correlates inversely with the PaO<sub>2</sub> during OLV. Also, hypoxemia occurs more frequently during OLV in the supine position<sup>12</sup> than the lateral position because there is not the increase of blood flow (approximately 10% increase) to the dependent (ventilated) lung due to gravity which is seen in the lateral position .

**TABLE 1: FACTORS INCREASING THE RISK OF HYPOXEMIA DURING ONE-LUNG VENTILATION:**

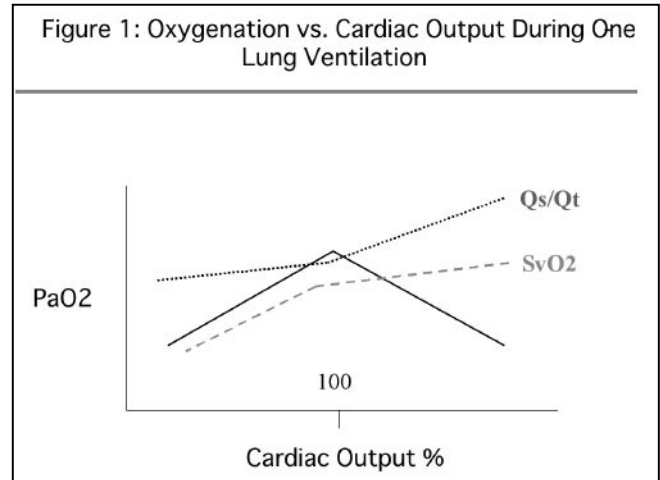
- High percentage of ventilation or perfusion to the operative lung on preoperative V/Q scan
- Poor PaO<sub>2</sub> during two-lung ventilation
- Right-sided surgery.
- Good preoperative spirometry (FEV1 or FVC)
- Supine (vs. lateral) patient position

**Treatment of Hypoxemia during OLV:** First, causes of hypoxemia such as malposition of an endobronchial tube or inadequate oxygen delivery should be ruled out. The use of the highest possible FiO<sub>2</sub> during OLV improves oxygenation. However, drugs such as Bleomycin, Mitomycin and Amiodarone, have been associated with pulmonary oxygen toxicity when a FiO<sub>2</sub> >0.4 was used intra-operatively for thoracic surgery.

Decreases in cardiac output during OLV decrease PaO<sub>2</sub> via a fall in mixed venous oxygen content since these patients have a large shunt.<sup>13</sup> Therefore, assure that the cardiac output is maintained. However, raising cardiac output beyond baseline tends to decrease PaO<sub>2</sub> as HPV is opposed by the passive increase in pulmonary arterial pressures (see Fig. 1).

CPAP to the non-ventilated lung has been used traditionally as the first-line of treatment for hypoxemia during OLV.<sup>14</sup> Useful increases in oxygenation can be achieved with 1-2 cm H<sub>2</sub>O levels of CPAP.<sup>15</sup> For maximal clinical efficiency CPAP must be applied to the inflated lung.<sup>11</sup> Even short periods of lung collapse impair the efficiency of CPAP since the opening pressure of atelectatic lung units exceeds 20

cmH<sub>2</sub>O. Because of the problems which re-inflation may cause at an in-opportune surgical moment, it is useful to predict which patients are most at risk of hypoxemia and to apply CPAP prophylactically at the onset of OLV. However CPAP to the non-ventilated lung can impede surgery during VATS procedures.<sup>16</sup>

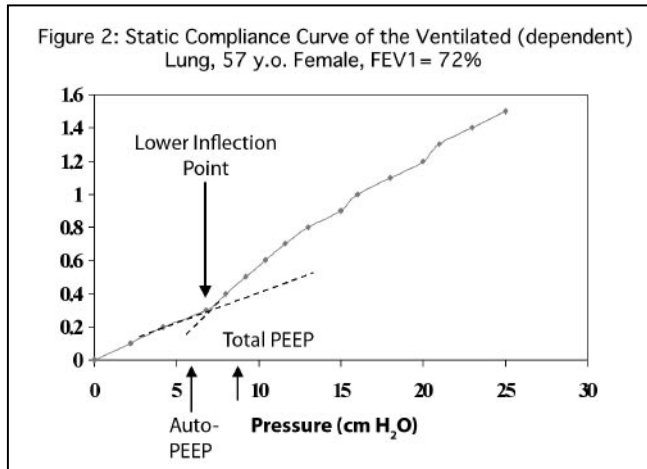


**Figure 1:** The effects of changes in cardiac output (C.O.) on arterial oxygenation (PaO<sub>2</sub>) during OLV. A decrease in cardiac output will lead to a decrease in shunt (Qs/Qt) as hypoxic pulmonary vasoconstriction (HPV) becomes more effective as pulmonary artery pressures fall passively. However the attendant decrease in mixed venous oxygen saturation (SvO<sub>2</sub>) as C.O. falls leads to a net decrease in PaO<sub>2</sub>. Conversely raising the C.O. above baseline (100%) with an inotrope leads to an increase in SvO<sub>2</sub> but also an increase in Qs/Qt and a net fall in PaO<sub>2</sub>. (Diagram based on data from Refs. # 4 & 13). During OLV it is very important to maintain C.O.

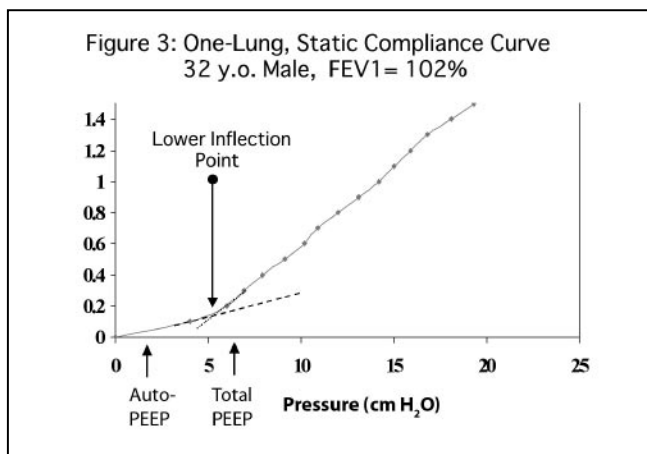
Added PEEP to the ventilated lung decreases PaO<sub>2</sub> in some groups of patients during OLV, particularly COPD patients who usually develop auto-PEEP during OLV. Some patients, often those with the poorest PaO<sub>2</sub> values, benefit from added dependent-lung PEEP. The beneficial effects of PEEP during OLV are related to changes in the end-expiratory dependent-lung volume and its static compliance curve.<sup>17</sup> The goal of ventilation during OLV is to maintain the volume of ventilated lung as closely as possible to its functional residual capacity (FRC), which is the lung volume at which the pulmonary vascular resistance is minimal (see Figs. 2 and 3).

Those patients most likely to benefit from PEEP to the dependent lung are patients with an increased A-aO<sub>2</sub> gradient (PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 300) in the lateral position during two-lung ventilation and a low level of auto-PEEP during OLV. Groups who can be expected to improve with PEEP are patients with healthy lungs on the side of thoracotomy (e.g. younger patients or esophageal surgery) or patients with low functional residual capacities (obese or pulmonary fibrosis). It is important to recruit the ventilated lung to eliminate atelectasis at the start of OLV and when PEEP is applied<sup>ii</sup>. The concept of individualizing ventilation parameters during OLV to accommodate individual patient differences in lung mechanical function and to maintain the ventilated lung as close as possible to its FRC is possibly the most important lesson that we have learned in the

past 20 years in thoracic anesthesia. Unfortunately the ventilators on modern anesthesia machines do not permit easy measurement of auto-PEEP or true total-PEEP so the application of PEEP during OLV is mainly on the basis of the clinician's best guess. As a personal guideline, I usually apply 5cmH<sub>2</sub>O PEEP to most patients during OLV with the exception of patients with moderate or severe COPD (FEV<sub>1</sub>/FVC ratio <70%) when I avoid added PEEP.



**Figure 2:** The static compliance (volume vs. pressure) curve of the dependent lung during OLV. During routine OLV this patient with mild COPD developed 6 cm H<sub>2</sub>O of auto-PEEP. The FRC estimated from the lower inflection point of the compliance curve was 7 cm H<sub>2</sub>O. The addition of 5 cm H<sub>2</sub>O PEEP via the ventilator raised the total PEEP to 11 cm H<sub>2</sub>O (the additive interaction of PEEP and auto-PEEP is not predictable, see ref. # 11). This increase of end-expiratory lung volume above FRC with PEEP raises the pulmonary vascular resistance of the ventilated lung and resulted in a decrease of PaO<sub>2</sub> during OLV. This is the common pattern seen when patients with COPD have PEEP added to the ventilated lung during OLV (Based on data from Ref. # 17).

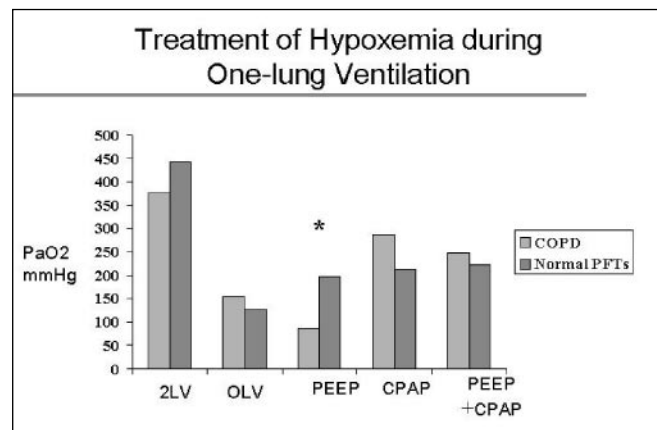


**Figure 3:** The compliance curve of the ventilated lung during OLV in a patient with normal pulmonary function. This patient developed 2 cmH<sub>2</sub>O auto-PEEP during standard OLV. The addition of 5 cmH<sub>2</sub>O PEEP via the ventilator raised the total PEEP to 7 cmH<sub>2</sub>O and by raising the end-expiratory lung volume closer to the FRC resulted in an increase of PaO<sub>2</sub> during OLV for this patient. This is the typical pattern of response with the addition of PEEP during OLV in patients with normal pulmonary function or in patients with restrictive (vs. obstructive lung disease). (Based on data from Ref. # 17).

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with healthy lungs on the side of thoracotomy (e.g. younger patients or esophageal surgery)<sup>18</sup> or patients with low functional residual capacities (obese or pulmonary fibrosis). It is important to recruit the ventilated lung to eliminate atelectasis at the start of OLV and when PEEP is applied.<sup>19</sup> **The concept of individualizing ventilation parameters during OLV to accommodate individual patient differences in lung mechanical function and to maintain the ventilated lung as close as possible to its FRC is possibly the most important lesson that we have learned in the past 20 years in thoracic anesthesia.**

Unfortunately the ventilators on modern anesthesia machines do not permit easy measurement of auto-PEEP or true total-PEEP so the application of PEEP during OLV is mainly on the basis of the clinician's best guess. As a personal guideline, I usually apply 5cmH<sub>2</sub>O PEEP to most patients during OLV with the exception of patients with moderate or severe COPD (FEV<sub>1</sub>/FVC ratio <70%) when I avoid added PEEP.



**Figure 4:** A comparison of the effects on PaO<sub>2</sub> of strategies to improve oxygenation during OLV in patients with COPD vs. patients with normal preoperative pulmonary function tests (PFTs) during thoracic surgery. 2LV= two-lung ventilation. PEEP= application of PEEP to the ventilated lung. CPAP = application of CPAP to the non-ventilated lung. PEEP + CPAP= the simultaneous combination of ventilated-lung PEEP and non-ventilated lung CPAP. \* Note that in patients with normal PFTs, PEEP improves PaO<sub>2</sub> during OLV while it decreases PaO<sub>2</sub> in COPD patients (Based on data from Refs. # 14 & 18).

During pneumonectomy, lung transplantation or in life threatening situations, the ipsilateral pulmonary artery can be compressed or clamped by the surgeon to transiently improve PaO<sub>2</sub>. Pulmonary artery balloon-tipped floatation catheters can be placed under fluoroscopic control prior to OLV and inflated to decrease regional pulmonary blood flow. High frequency jet ventilation (HFJV) to the operative lung provides superior oxygenation.<sup>20</sup> However, HFJV tends to increase the diameter of central airways and can impede surgery during pulmonary resections. HFJV is useful for non-pulmonary intrathoracic surgery.

Various pharmacological methods of modulating the unilateral pulmonary vascular tone such as prostaglandin E1 and nitric oxide (NO) are available. The combination of NO (20 ppm) to the ventilated lung and an intravenous infusion of almitrene (a pulmonary vasoconstrictor) can restore PaO<sub>2</sub> during OLV to levels close to these during two-lung

ventilation.<sup>21</sup> NO alone does not improve PaO<sub>2</sub> in the majority of patients during OLViii. However, there is a small minority of hypoxemic patients who benefit from NO. It is not yet clear how to identify these patients prospectively.<sup>23</sup>

Contradictory studies have been published on the use of combined thoracic epidural with general anesthesia and PaO<sub>2</sub> during OLV.<sup>24,25</sup> It is unlikely that thoracic epidural blockade per se has any significant effect on HPV or PaO<sub>2</sub> during OLV. However falls in cardiac output due to the sympathectomy of local anesthetic epidural blockade will decrease PaO<sub>2</sub> if not corrected.

The traditional use of large tidal volume (10 ml/kg ideal body weight) ventilation during OLV may not be the optimal anesthetic management. High airway pressures and volumes during OLV may be associated with injury to the non-operated lung.<sup>26</sup> This is particularly a concern in pneumonectomy patients who are prone to develop increased permeability in the residual lung.<sup>27</sup> Post-pneumonectomy pulmonary edema is related to the use of large tidal volumes during one-lung ventilation<sup>28</sup> and has a high mortality rate.<sup>29</sup> There is a trend to use lower tidal volumes and/or pressure-controlled ventilation during OLV particularly in COPD patients who tend to develop auto-PEEP<sup>30</sup> (see Table 2).

**Table 2: Individualizing One-Lung Ventilation**

		<u>Exceptions:</u>
<u>Tidal Volume</u>	5-6 ml/kg	Peak Pa/w <35 cmH <sub>2</sub> O Plateau Pa/w P<25
<u>PEEP</u>	Total 5 cm.	Not added if COPD
<u>FiO<sub>2</sub></u>	1.0	Add Air as tolerated
<u>Resp. Rate</u>	12	Mild hypercapnia accepted
<u>Mode</u>	Volume or Pressure Control Ventilation	Press Cont Vent COPD, Transplant, Pneumonectomy

**Table 2:** Pa/w= airway pressure. The peak and plateau airway pressures during OLV should be maintained at < 35 and 25 cmH<sub>2</sub>O respectively. With the use of smaller tidal volumes (5-6 ml/kg ideal body weight), most patients will require added PEEP during OLV. After a period (20-30 min.) of stable OLV with FiO<sub>2</sub> 1.0, air can be added to the gas mixture to decrease atelectasis in the ventilated lung. Mild hypercapnia = PaCO<sub>2</sub> < 60mmHg. Pressure control ventilation is recommended in patients at increased risk for lung injury such as COPD patients, lung transplantation and pneumonectomies.

**Summary:** Recent advances in anesthetic agents, equipment and monitoring for lung isolation and in techniques of one-lung ventilation have improved the safety and reliability of one-lung anesthesia for thoracic surgery. Also our understanding of the respiratory physiology of OLV has evolved. It is possible to identify in advance patients who will benefit from PEEP to the ventilated lung. Ventilation parameters should be individualized for each patient depending on the patho-physiology of the underlying lung disease. A strategy to avoid and treat hypoxemia during OLV is presented in Table 3. Steps 1-5 under

“Gradual Desaturation” should be considered for all patients.

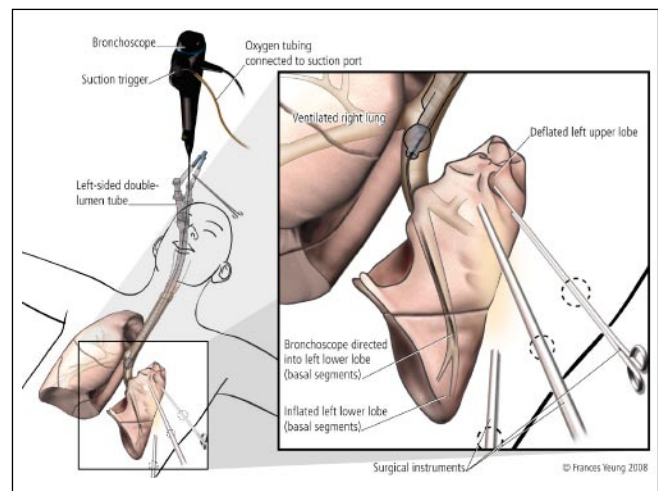
**Table 3: Management of Hypoxemia During One-Lung Ventilation:**

Severe or Acute desaturation: Resume two-lung ventilation, deflate the bronchial cuff of the double-lumen tube or blocker.

Gradual Desaturation:

1. Assure FiO<sub>2</sub> = 1.0
2. Check double-lumen tube or bronchial blocker placement with fiberoptic bronchoscopy
3. Optimize cardiac output
4. Recruit the ventilated lung
5. Apply PEEP 5cm H<sub>2</sub>O to ventilated lung (except COPD patients)
6. Apply CPAP 1-2 cm to the non-ventilated lung (after recruitment)
7. Partial ventilation of the non-ventilated lung:
  - i) Lobar/segmental re-inflation with fiberoptic bronchoscopy (see Fig. 5)
  - ii) Lobar collapse\*
  - iii) Whole lung oxygen insufflation
8. Intermittent re-inflation of the non-ventilated lung
9. Mechanical restriction of non-ventilated lung pulmonary blood flow

(\* Lobar collapse requires the placement of a bronchial blocker in the lobar bronchus of the lobe to be collapsed while ventilating the remaining lung. This can be a useful technique in patients having repeat pulmonary resections but the blocker needs to be placed during the initial intubation)



**Figure 5:** Treatment of hypoxemia during VATS. Oxygen 5L/min. from an auxiliary source is attached to the suction channel of a FOB and insufflated to recruit a segment of the non-ventilated lung distant from the surgical site with direct thoracoscopic observation. In this Figure, basal segments of the left lower lobe are recruited during a left upper lobe VATS surgery. (Reference: Ku M, et al. J Cardiothorac Vasc Anesth 2009, in press). This treatment can improve oxygenation during VATS and does not interfere with the exposure at the site of surgery. This would be a useful strategy in the case presented.

**QUESTIONS:**

**Question 1:** What is the incidence of hypoxemia during OLV for thoracic surgery?

- a) < 10%
- b) 10-20%
- c) 20-40%
- d) >40%

**Question 2:** Which of the following factors is associated with an increased risk of hypoxemia during OLV?

- Left-sided surgery
- COPD
- Increased A-aO<sub>2</sub> gradient during two-lung ventilation
- Lateral (vs. supine) position

**Question 3:** The initial treatment of acute severe desaturation during OLV should be?

- Fiberoptic bronchoscopy to verify tube/blocker position
- Resumption of two-lung ventilation
- Change to an intravenous anesthetic technique
- Apply PEEP to the ventilated lung

**Question 4:** Which of the following has not contributed to the decrease in the incidence of hypoxemia during OLV?

- Better understanding of the physiology of OLV
- The routine use of FOB to position double-lumen tubes and blockers
- Decreased inhibition of HPV by newer volatile anesthetics
- The use of thoracic epidural analgesia

**Question 5:** The addition of PEEP via the ventilator is most likely to cause a decrease in PaO<sub>2</sub> during OLV in which patient?

- A morbidly obese patient
- A child
- A patient with COPD
- A patient with pulmonary fibrosis

Answers: 1:a; 2:c; 3:b; 4:d; 5:c

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# Facilitating the Recovery Process: Fast-Track Anesthetic Techniques

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## INTRODUCTION

The concept of fast-track surgery as an approach to improving perioperative efficiency and throughput was introduced in the early 1990's.<sup>1</sup> Fast-track anesthesia represents an approach to improving perioperative efficiency by providing for a fast recovery from anesthesia, and thereby facilitating an early discharge from the hospital and more rapid resumption of normal activities of daily living after ambulatory surgery. The increasing popularity of minimally-invasive surgical techniques has allowed patients to undergo increasingly complex surgical procedures on an ambulatory and/or short-stay basis.<sup>2</sup> Therefore, fast-tracking implies implementation of a perioperative patient care paradigm that reduces the time to discharge home and resumption of activities of daily living after a wide variety of surgical procedures.

The role of the anesthesiologist has evolved from that of a physician primarily concerned with providing optimal surgical conditions and minimizing pain immediately after the operation, to that of a perioperative physician responsible for ensuring that patients with co-existing medical conditions are optimally managed before, during and after surgery.<sup>3,4</sup> The anesthesiologist plays a key role in fast-track surgery through their choice of preoperative medication, anesthetic agents and techniques, use of prophylactic drugs to minimize side effects (e.g., pain, nausea and vomiting, dizziness), as well as the administration of adjunctive drugs to maintain major organ system function during and after surgery. In addition to providing the best possible intraoperative surgical conditions, the ability to provide for a rapid emergence from anesthesia and avoid postoperative side effects and early complications is critically important for outpatients to meet the criteria for a fast-track recovery (Fig. 1).

## PREOPERATIVE PREPARATION

### PREOPERATIVE MEDICATION

When indicated, minimal amounts of preanesthetic medication are given primarily to provide sedation, reduce anxiety, optimize intraoperative hemodynamic stability, and decrease postoperative side effects without prolonging recovery from anesthesia.<sup>5</sup> Benzodiazepines remain the most commonly used premedicants (e.g., midazolam 10-20 µg/kg iv) because small doses can improve the perioperative fast-tracking process by reducing anxiety and anxiety-related complications, as well

as improving patient comfort and satisfaction.<sup>6</sup> With respect to improving surgical outcome, both the  $\beta$ -blockers and  $\alpha_2$ -agonists are increasingly popular adjuvants to fast-track anesthetic techniques because of their anesthetic and analgesic sparing effects.<sup>7-10</sup> Premedication with the  $\alpha_2$ -agonists, clonidine or dexmedetomidine, has been associated with a reduction in the use of opioid analgesics, postoperative nausea and vomiting (PONV), and intraoperative blood loss.<sup>10-12</sup> The inhibitory effects of these  $\alpha_2$ -agonists on the sympathoadrenergic and hypothalamo-pituitary stress response<sup>13</sup> facilitate glycemic control in type-2 diabetic patients<sup>14</sup> and reduce myocardial ischemia after surgery.<sup>15</sup>

Beta-blockers (e.g., atenolol, esmolol suppress surgery-induced increases in circulating catecholamines, and prevent untoward perioperative cardiovascular events in elderly patients undergoing non-cardiac surgery.<sup>7</sup> Evidence suggests that  $\beta$ -blockers are most effective in reducing cardiac events in surgical patients with pre-existing coronary artery disease.<sup>16-17</sup> Perioperative  $\beta$ -blockade improved hemodynamic stability during emergence from anesthesia and in the early postoperative period. The anesthetic and analgesic-sparing effects of  $\beta$ -blockers in the ambulatory setting also leads to a faster emergence from anesthesia and reduces postoperative side effects (e.g., PONV).

## PERIOPERATIVE HYDRATION

Ambulatory surgery has traditionally been performed after an overnight fast to ensure an empty stomach and minimize the risk of aspiration during the perioperative period. However, many studies have demonstrated that avoiding fasting-induced dehydration (e.g., allowing oral intake of clear liquids up to 2-3 hours before surgery and IV hydration before induction of anesthesia), is both safe and effective in reducing postoperative side effects.<sup>18-21</sup> Liberal (vs. restrictive) fluid administration during laparoscopic surgery also lead to improved patient outcomes.<sup>22-23</sup> Even obese patients without co-morbid conditions should be allowed to drink clear liquids until 2 hours before elective surgery procedures.<sup>19</sup> Preoperative administration of glucose-containing fluids, prevents postoperative insulin resistance and attenuates the catabolic responses to surgery while replacing fluid deficits.<sup>24-25</sup> However, effects of glucose-containing solutions on clinical outcomes including the length of the hospital stay, incidence of PONV, muscle strength and subjective well-being remains controversial.<sup>26-28</sup>

Perioperative hydration includes correction of preoperative dehydration due to fasting, bowel preparation, replacement of blood loss and insensible fluid losses during the maintenance period.<sup>29</sup> Liberal intraoperative fluid therapy was associated with reduced postoperative side effects (e.g., pulmonary dysfunction, dizziness, drowsiness, thirst and nausea/vomiting) and a shorter hospital stay after laparoscopic cholecystectomy.<sup>23</sup> Interestingly, liberal fluid administration leads to improved pulmonary function and significant hypercoagulability after fast-track knee arthroplasty.<sup>30</sup>

## **METABOLIC AND THERMOREGULATION**

Impaired glucose homeostasis during surgery can result in hyperglycemia.<sup>25</sup> Recent evidence suggests that even moderate increases in blood glucose may be associated with adverse outcomes, particularly in patients with cardiovascular, infectious and neurological diseases.<sup>31-32</sup> Use of glucocorticoid steroids (e.g., dexamethasone, methyl-prednisolone) as part of a fast-track anesthetic technique to reduce emetic symptoms and improve pain control may lead to transient postoperative hyperglycemia in diabetics.<sup>33</sup>

Perioperative hypothermia can have a wide range of detrimental effects which may include increased rates of wound infection, morbid cardiac events, blood loss, and even prolong the hospital stay.<sup>34-37</sup> Hypothermia can be reduced by using forced-air warming blankets and warming irrigation fluids in outpatients undergoing laparoscopic, arthroscopic and cytosopic procedures.<sup>38</sup> In addition, warmed and humidified insufflation gases may decrease postoperative pain and the need for opioid analgesics and antiemetic therapy after laparoscopic surgery.<sup>39</sup>

## **FAST-TRACKING ANESTHETIC TECHNIQUES**

### **LOCAL ANESTHESIA**

Infiltration of local anesthetics around a surgical incision should be a component of all fast-track ambulatory anesthetic techniques.<sup>40,41</sup> Local infiltration anesthesia alone provides adequate analgesia for superficial procedures (e.g., inguinal herniorrhaphy, breast and anorectal surgery, shoulder and knee arthroscopy), and is underutilized in clinical practice.<sup>42-44</sup> Patient comfort can be improved if IV sedation-analgesia is used to supplement local anesthetic infiltration, particularly when the local anesthesia is not completely effective.<sup>42,45</sup> However, use of IV adjuvants can also increase side effects (e.g., ventilatory depression, PONV).<sup>46,47</sup> The benefits of local wound infiltration in patients undergoing more invasive surgical procedures have not been as extensively studied. Although there is little evidence that “pre-emptive analgesia” involving local anesthetic injections at the surgical wound reduces the risk for developing persistent postoperative pain syndromes,<sup>48</sup> it does lessen intra- and postoperative

opioid requirements, as well as opioid-related side effects.<sup>49</sup>

Many studies have demonstrated improved analgesia, greater patient satisfaction with pain management, and reduced PONV and hospital stay with infusion of local anesthetic at the surgical incision site.<sup>50</sup> For example, patients receiving a continuous infusion of bupivacaine at the incision site not only experienced improved postoperative pain management, but were also able to ambulate earlier.<sup>51</sup> Infiltration of local anesthetic at portal sites and the gallbladder bed improves postoperative analgesia after laparoscopic cholecystectomy.<sup>52</sup> Compared with neuroaxial or general anesthetic techniques, local anesthetic infiltration techniques reduce the risk of postoperative urinary retention associated with anorectal surgery<sup>53</sup> and inguinal herniorrhaphy.<sup>47,54</sup> When used as the primary anesthetic technique, local anesthesia facilitates postanesthesia care unit (PACU) bypass, thereby reducing recovery costs (Tables 1 and 2).<sup>42,45,47,53,55</sup> Therefore, routine use of local analgesia at the surgical incision site(s) and in cavitory spaces is recommended for all ambulatory surgery procedures.

### **REGIONAL ANESTHESIA**

Intravenous regional anesthesia (IVRA), peripheral nerve blocks, and “mini-dose” neuraxial blocks are the most popular regional anesthetic techniques used for fast-track ambulatory surgery. Use of IVRA for hand surgery was associated with faster discharge and lower costs as compared with either general anesthesia or a peripheral nerve block.<sup>55</sup> As supplements to general anesthesia, peripheral nerve blocks (vs local infiltration) improve postoperative analgesia and reduce opioid-related side effects, thereby facilitating the fast-track recovery process.<sup>56</sup> For example, suprascapular block improves the recovery profile after arthroscopic shoulder surgery performed under general anesthesia,<sup>57</sup> but not after “open” surgery with an interscalene block.<sup>58</sup> As the primary analgesic technique, peripheral nerve blocks are associated with shorter discharge times, improved analgesia, and fewer side effects compared with general anesthesia for hand,<sup>56,59</sup> shoulder,<sup>60</sup> anorectal,<sup>53</sup> hernia repair,<sup>45-61</sup> and knee surgery.<sup>62</sup>

Although it is widely assumed that regional anesthesia offers advantages over general anesthesia with respect to speed of recovery,<sup>63</sup> a recent meta-analysis suggested that there were no significant differences in ambulatory surgery unit time.<sup>64</sup> However, use of continuous perineural catheters to administer local anesthetics can improve pain control and expedite hospital discharge after painful upper<sup>65</sup> and lower extremity<sup>66</sup> surgical procedures. In addition, the local analgesia can be continued at home after discharge.<sup>65-67</sup> These beneficial findings were confirmed in a recent multicenter trial which utilized patient-controlled perineural local analgesia as an alternative to IV patient-controlled analgesia

(PCA) with morphine.<sup>68</sup> A recent meta-analysis confirmed the advantages of a peripheral catheter technique over a parenteral opioid-based analgesic technique for extremity surgery.<sup>69</sup>

When central neuroaxis block techniques are used as a part of a fast-track regimen, it is important to select the most appropriate local anesthetic and adjuvant combination to avoid prolonged anesthetic effects that negatively impact on "readiness for discharge."<sup>44</sup> For instance, prolonging subarachnoid-induced analgesia with fentanyl rather than epinephrine avoids the prolonged time to micturition,<sup>70</sup> and reduces the time to discharge from the hospital.<sup>71</sup> As compared with conventional intrathecal doses of local anesthetics, use of so-called mini-dose lidocaine (10-30 mg), bupivacaine (3.5-7 mg), or ropivacaine (5-10 mg) spinal anesthetic techniques when combined with a potent opioid analgesic (e.g., fentanyl 10-25 µg or sufentanil 5-10 µg) can result in faster recovery of sensory and motor function.<sup>72,73</sup> When compared to a monitored anesthesia care (MAC) technique for ambulatory knee surgery, a mini-dose spinal technique involving lidocaine and fentanyl achieved comparable recovery times after knee arthroscopy.<sup>43</sup> For outpatient laparoscopic gynecologic surgery, this technique has also been reported to offer significant advantages over both conventional spinal and general anesthetic techniques.<sup>73,74</sup> However, surgical conditions may be inadequate for lower abdominal procedures, and postoperative side effects (e.g., pruritus, nausea) are increased due to the intrathecal opioid.<sup>43</sup>

Given that similar analgesia can be achieved using a perineural catheter technique (e.g., continuous femoral or popliteal nerve blocks) as with epidural local analgesia without the attendant risk of epidural-related complications (e.g., hematoma formation, abscesses, hemodynamic instability), peripheral nerve blocks would appear to be preferable for lower extremity surgery in the ambulatory setting. Therefore, the use of epidural analgesia for minimally-invasive ambulatory surgery has been discouraged (e.g., colectomy, nephrectomy, splenectomy, prostatectomy). Epidural anesthesia and analgesia for major laparoscopic surgery only facilitated recovery of bowel function when a traditional, non-accelerated perioperative care program was used.<sup>75</sup> However, a recent study in patients undergoing laparoscopy-assisted subtotal gastrectomy under combined epidural/general anesthesia experienced a fast early recovery and low incidence of urinary dysfunction.<sup>76</sup> Future advances in fast-track surgery techniques and perioperative use of peripheral mu-opioid antagonist,<sup>77</sup> will likely lessen the role of epidural analgesia.

### MONITORED ANESTHESIA CARE (MAC)

Compared with general endotracheal and central neuroaxis anesthetic techniques for superficial (non-cavitary) surgical procedures, MAC-based

techniques involving the use of local anesthesia via infiltration or peripheral nerve block in combination with and intravenous (IV) sedative-analgesic drugs can facilitate a fast-track recovery.<sup>46</sup> The simplest local anesthetic technique which provides adequate analgesia is recommended to minimize the risk of side effects and complications.<sup>78</sup>

Use of a MAC technique for inguinal hernia repair, anorectal and hand surgery was associated with a decreased incidence and severity of postoperative pain, reduced need for opioid-containing analgesics, less PONV, constipation, ileus, urinary retention, and other opioid-related side effects.<sup>45,53,55</sup> MAC techniques commonly involve the use of local anesthetic infiltration and/or peripheral nerve blocks using a mixture of lidocaine (2%) and bupivacaine (0.5%) or ropivacaine (0.5%) in combination with small doses of midazolam (1-3 mg IV) and a variable-rate propofol infusion (25-100 g•kg-1•min-1).<sup>79</sup> Increasingly, dexmedetomidine (0.5-1 g•kg-1) [80] and ketamine (75-150 g•kg-1)<sup>81</sup> are being used as alternatives to opioid analgesics like fentanyl (0.5-1 g•kg-1)<sup>82</sup> or remifentanyl (0.25-0.5 g•kg-1 boluses or 0.025-0.05 g•kg-1•min-1 infusion),<sup>83</sup> as part of a MAC anesthetic technique to reduce the ventilatory depression produced when combining a potent opioid analgesic with midazolam and propofol.<sup>83</sup> Respiratory depression due to "over sedation" and a lack of vigilance is the leading cause of serious patient injuries during MAC.<sup>47</sup>

Use of MAC techniques can facilitate a fast-track recovery after ambulatory surgery because these patients routinely bypass the PACU, and be discharged home earlier due to the low incidence of postoperative side effects. However, carefully intraoperative vigilance to avoid respiratory complications is mandatory to insure patient safety in the ambulatory setting. This is a major concern when sedation analgesic techniques are used in office-based outpatient plastic surgery.<sup>84,85</sup>

### GENERAL ANESTHESIA

Despite the obvious advantages of local, regional and MAC anesthetic techniques, many patients (and surgeons) still prefer general anesthesia because they are unaware of events during the operation. Propofol, 1.5-2.5 mg•kg-1, is clearly the IV induction agent of choice for fast-track anesthesia.<sup>86</sup> The less-soluble volatile anesthetics, desflurane (3-6%) and sevoflurane (0.75-1.5%) appear to offer advantages over propofol and isoflurane for maintenance of general anesthesia with respect to facilitating the early recovery process.<sup>87-90</sup> Nitrous oxide (50-70%) remains a popular adjuvant during the maintenance period because of its anesthetic and analgesic-sparing effects, low cost and favorable pharmacokinetic profile.<sup>91</sup> However, remifentanyl infusion (0.05-0.20 g•kg-1•min-1) is an increasingly popular alternative to nitrous oxide as an adjuvant to the less-soluble volatile anesthetics.<sup>92,93</sup>

The beta-blocking drugs (e.g., esmolol, labetalol) can be used as an alternative to short-acting opioid analgesics for controlling the transient, acute autonomic responses during surgery.<sup>94-96</sup> Whenever possible, a laryngeal mask airway should be used as an alternative to a tracheal tube.<sup>97</sup> If intubation is required, short (e.g., succinylcholine, mivacurium)<sup>98</sup> or intermediate-acting (e.g., cisatracurium, vecuronium, rocuronium) neuromuscular blocking drugs should be used.<sup>99</sup> A novel cyclodextrin compound, sugammadex,<sup>100</sup> is capable of facilitating a faster reversal of steroid-based, non-depolarizing neuromuscular blockers than either a combination of edrophonium-atropine or neostigmine-glycopyrrolate without anticholinergic side effects.<sup>101</sup> Use of this reversal agent may also lead to earlier tracheal extubation after surgery and reduce postoperative respiratory complications due to residual muscle paralysis.

Use of volatile agents (vs. propofol) for maintenance of anesthesia will increase PONV in the early postoperative period.<sup>102</sup> For patients receiving volatile anesthetics, the most cost-effective antiemetic prophylaxis technique consists of a combination of low-dose droperidol (0.625-1.25 mg IV) and dexamethasone (4-8 mg IV)<sup>103,104</sup> or methylprednisolone (125 mg IV).<sup>105</sup> If the patient is at increased risk for developing PONV, a 5-HT<sub>3</sub> antagonist (ondansetron 4 mg IV) should also be added as part of a multimodal antiemetic regimen.<sup>106</sup> The neurokinin-1 antagonists may play an increasingly important role in the management of emetic symptoms in the future. Use of non-opioid analgesics [e.g., non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, acetaminophen, 2-agonists, glucocorticoids, ketamine, and local anesthetics] as part of a multimodal analgesic regimen will minimize postoperative pain and opioid-related side effects.<sup>49,107</sup>

Use of short-acting anesthetic drugs and prophylactic drugs which minimize postoperative side effects, and avoiding surgical misadventures, will enhance the ability to fast-track patients after ambulatory surgery.<sup>108,109</sup> Although a majority of both adults and children can be fast-tracked after ambulatory surgery under general anesthesia, minimizing patient discomfort and anxiety during the perioperative period is critically-important in establishing a successful fast-track surgery program after all types of ambulatory surgery.<sup>95,108-110</sup> Finally, improving the titration of both IV and inhaled anesthetics by using cerebral monitoring devices (e.g., bispectral, entropy, cerebral state monitors) may also facilitate the fast-tracking process.<sup>111-114</sup> However, in spontaneously breathing (non-paralyzed) patients, the value of cerebral monitoring in facilitating the recovery process is questionable.<sup>115</sup>

## **POSTOPERATIVE CARE**

### **OPTIMIZING PAIN MANAGEMENT**

An observational study has confirmed that poorly controlled pain and associated nausea and vomiting can delay discharge after ambulatory surgery.<sup>116</sup> Improving postoperative pain control accelerates normalization of activities of daily living and functionality that may otherwise persist for weeks after an elective operation.<sup>117-119</sup> According to a recent systematic review by Liu and Wu<sup>120</sup> there is “insufficient evidence to conclude that analgesic techniques influence postoperative mortality or morbidity” due to the current low incidences of complications. However, excessive reliance upon opioids for perioperative analgesia contributes to acute opioid tolerance and hyperalgesia,<sup>121-123</sup> as well as dose-related opioid side effects [e.g., hypoventilation, sedation, nausea and vomiting, urinary retention, ileus] that delay hospital discharge and add to the cost of surgical care.<sup>50,122</sup> Although opioid infusions are frequently utilized both intravenously and epidurally, they do not always improve postoperative pain management due to the rapid development of tolerance,<sup>123</sup> and increased risk of ventilatory depression. Even if optimal pain control had no beneficial economic or physiological effects, efforts to assure optimal pain management may eventually be mandated by accrediting agencies as a basic human right.<sup>124</sup>

Multimodal (or “balanced”) analgesia involves the use of more than one modality of pain control to obtain additive (or synergistic) beneficial analgesic effects while reducing drug-related side effects.<sup>125</sup> Early fast-track studies demonstrated that these multimodal analgesic techniques can improve recovery and patient outcome after ambulatory procedures.<sup>126,127</sup> This approach is currently the standard practice in fast-track clinical care plans<sup>1,128</sup> because reliance on a single non-opioid analgesic modality such as non-steroidal anti-inflammatory drugs (NSAIDs) may not suffice to control severe pain, and reliance exclusively on opioids produces many undesirable side effects.<sup>107</sup> Use of partial opioid agonists (e.g., tramadol) is associated with increased side effects and patient dissatisfaction compared to both opioid and non-opioid analgesics.<sup>129</sup>

The concept of multimodal or “balanced” analgesia represents an approach whereby a combination of analgesics acting at different sites within the central and peripheral nervous system are administered in an effort to achieve more effective pain relief while minimizing opioid-related side effects.<sup>125</sup> Increasing numbers of more extensive and painful operations (e.g., laparoscopic adrenalectomy, nephrectomy and prostatectomy procedures, as well as laminectomy, shoulder and knee reconstructions, hip replacements, hysterectomy) are being performed minimally-invasively on an outpatient or short-stay basis.<sup>2,40,130</sup> Therefore, the use of multimodal

perioperative analgesic regimens involving both opioid and non-opioid analgesic therapies has assumed an increasingly important role in facilitating the recovery process and improving patient satisfaction in the future.<sup>49</sup> Pavlin et al.<sup>116</sup> confirmed the importance of controlling postoperative pain in order to facilitate recovery after ambulatory surgery. These investigators found that moderate-to-severe pain prolonged the recovery room stay by 40-80 min. Adjunctive use of local anesthetics and NSAIDs decreased pain scores and facilitated an earlier discharge home. Additional outcome studies<sup>106</sup> are clearly needed to validate the beneficial effect of these multimodal therapeutic approaches with respect to important recovery variables (e.g., resumption of normal activities [e.g., dietary intake, bowel function], return to work). Although many factors in addition to pain must be controlled in order to minimize postoperative morbidity and facilitate the recovery process (e.g., postoperative nausea and vomiting,<sup>131</sup> hydration status<sup>20-23</sup>), the adequacy of pain control remains a major concern of all patients undergoing elective surgical procedures,<sup>132</sup> as well as the healthcare providers responsible for their care.<sup>133</sup>

Opioid analgesics will continue to play an important role in the acute treatment of moderate-to-severe pain after surgical procedures. However, non-opioid analgesics will likely assume a greater role as “preventative” analgesics as the number of minimally-invasive (“key hole”) surgery cases continues to expand.<sup>2,40</sup> In addition to the local anesthetics, NSAIDs and COX-2 inhibitors, drugs like acetaminophen, ketamine, dextromethorphan, alpha-2 agonists, gabapentin, pregabalin and even magnesium will likely be more frequently utilized as adjuncts in the multimodal management of postoperative pain.<sup>49</sup> Interestingly, non-analgesics like the antiemetic droperidol<sup>134</sup> and the glucocorticoid steroids dexamethasone,<sup>135</sup> betamethasone<sup>136</sup> and methylprednisolone<sup>137</sup> appear to provide multiple beneficial effects with respect to controlling side effects in the postoperative period. Novel compounds like capsaicin (the active ingredient in chili peppers!) have been found to produce analgesic effects because of their ability to alter nociceptive input at peripheral nerve ending.<sup>138</sup> Other non-pharmacologic approaches involving a variety of acustimulation techniques may also be utilized more extensively as analgesic adjuvants in the future.<sup>139</sup>

Rather than advocating the more aggressive use of opioid analgesics,<sup>124,140</sup> use of analgesic drug combinations with differing mechanisms of action as part of a multimodal regimen will provide additive (or even synergistic) effects with respect to improving pain control, reducing the need for opioid analgesics, and facilitating the recovery process.<sup>130</sup> In a recently published critical assessment of multimodal analgesic regimens for laparoscopic surgery,<sup>141</sup> Bisgaard recommended that “opioids should only be used when these other non-opioid analgesic

techniques fail.” Although so-called “preemptive” analgesic techniques have been postulated to provide superior analgesia by preventing the establishment of central sensitization,<sup>140</sup> this approach does not appear to offer any clinically-significant advantages over common preventative multimodal regimens administered after the surgical procedure.<sup>142</sup> Safer, simpler, and less-costly analgesic drug delivery systems are still needed to provide cost-effective pain relief in the postdischarge period as more major surgery is being performed on an ambulatory basis.<sup>2</sup> A more aggressive multimodal strategy involving anesthesiologists, surgeons and nurses must be employed if we are going to improve surgical outcome for our patients in the future.<sup>1</sup> Newer non-opioid analgesics (e.g., NSAIDs, long-acting local anesthetics, capsaicin) and delivery systems (e.g., infusion systems on Q/I-flow) may further improve our ability to prevent moderate-severe pain and the need for opioid analgesics.<sup>140,143,144</sup>

Ideally, multiple non-opioids (e.g., NSAIDs, COX-2 inhibitors and gabapentin) could be combined to achieve more optimal pain relief and perhaps ultimately, an “opioid-free” environment.<sup>49,107</sup> Multimodal analgesia represents a key element for successful fast track surgery by minimizing postoperative pain, opioid-related organ dysfunction and facilitating the recovery process from anesthesia. Newer fast-tracking criteria recognize the importance of controlling pain and opioid-related side effects (e.g., PONV).<sup>145</sup>

## POSTOPERATIVE NAUSEA AND VOMITING

Despite the introduction of many new antiemetic therapies, the incidence of PONV remains high, occurring in up to 30% of all surgical cases (including both cardiac and neurosurgery) due to patient, anesthesia and surgery-related factors.<sup>146</sup> The major risk factors for PONV include female gender, non-smoker status, history of PONV or motion sickness, intraoperative use of volatile anesthetics and high-dose opioid techniques, as well as postoperative opioid analgesic use.<sup>147</sup> In adults, a multi-drug antiemetic prophylaxis strategy consisting of droperidol, dexamethasone<sup>148,149</sup> and a 5-HT<sub>3</sub> antagonist (ondansetron) is recommended for patients who present with two or more risk factors.<sup>150</sup> Recent studies suggest that non-traditional therapies (e.g., TD nicotine, topical capsaicin) may be useful additions to the traditional antiemetic drug therapies.<sup>151,152</sup> In addition to the administration of antiemetic drugs, multimodal strategies to reduce the risk of PONV include use of propofol and local anesthetic-based analgesic techniques, adequate hydration, as well as minimizing perioperative opioid use.<sup>153</sup> Use of cardiovascular drugs (e.g.,  $\beta$ -blockers,  $\alpha$ 2-agonists) to control transient acute autonomic responses to noxious surgical stimuli and non-opioid analgesics to reduce postoperative pain will minimize emetic symptoms.<sup>49,95,96</sup> In fact, a recent study

demonstrated advantages of the NSAID ketorolac compared to the glucocorticoid steroids with respect to preventing PONV.<sup>154</sup> Non-pharmacological techniques (e.g., acupuncture, acupressure and transcutaneous electrical nerve stimulation) can be useful adjuvants to standard antiemetic drugs when used after surgery.<sup>155-157</sup> Therefore, replacing fluid deficits, minimizing use of volatile anesthetics and nitrous oxide, opioid analgesics and reversal drugs, and utilizing propofol, multimodal antiemetic prophylaxis and non-opioid analgesic techniques are all important factors in preventing PONV.<sup>107</sup> In the future, practitioners should also consider incorporating alternative medical therapies into their treatment plan.<sup>131</sup>

### POSTOPERATIVE ILEUS AND CONSTIPATION

Postoperative ileus can cause discomfort and delay oral food intake, thereby prolonging convalescence and the length of the hospital stay.<sup>158</sup> The key elements in a multimodal fast-track strategy for preventing postoperative ileus include use of minimally-invasive surgical techniques, use of a peripheral acting mu-opioid receptor antagonist (e.g., alvimopan, methylnaltrexone), avoidance of a nasogastric tube, early oral feeding and ambulation, and opioid-sparing analgesic regimens.<sup>159</sup>

Rehabilitation paradigms which combine multimodal analgesia with oral feeding and mobilization have been found to decrease the duration of ileus.<sup>160</sup> In addition, there is evidence that reduced perioperative sodium administration and avoidance of fluid excess is associated with earlier return of bowel function after abdominal surgery,<sup>162</sup> and a decrease in the length of the hospital stay.<sup>162</sup> The results of recent clinical trials indicate that use of a peripheral mu-opioid receptor antagonists (i.e., alvimopan, methylnaltrexone) can facilitate the recovery of postoperative bowel activity and may reduce the time to hospital discharge after major surgical procedures.<sup>77,163,164</sup> Importantly, minimizing the use of opioid-containing oral analgesics after discharge reduces both constipation and PONV.<sup>165</sup>

### IMPLEMENTING A MULTIDISCIPLINARY APPROACH FOR FAST-TRACK RECOVERY

A common experience at ambulatory centers implementing fast-track surgery has been the challenge of changing long-standing surgical nursing care principles,<sup>166,167</sup> and this represents a major component of the "total care" package.<sup>168</sup> An intensified nurse-based preoperative patient education program is a crucial adjunct to improved fast-track anesthetic surgical care.<sup>109</sup> These programs need to focus on what is expected from the patient as an active participant in the recovery and rehabilitation process.<sup>169</sup> The provision of daily nurse care (i.e., clinical pathway) charts remains an important element in the fast-track recovery process. It is essential to secure daily tasks, and to establish programs to facilitate education

of new personal as every aspect of care must be carefully explained. Therefore, multidisciplinary team meetings before and after implementing fast-track ambulatory surgery are crucial to the overall success of the program.<sup>109</sup>

### CONCLUSIONS

Anesthesiologists play an important role in the implementation of fast-track ambulatory surgery programs as a result of their decisions regarding perioperative care. Understanding the importance of co-existing diseases and taking appropriate steps to minimize postoperative complications through appropriate use of preoperative medications, selection of the optimal anesthetic and analgesic techniques, and maintaining normal organ system function will lead to improved patient care at a reduced cost.<sup>170</sup> As more information become available, it should be possible to make recommendations for each of these steps on a procedure-specific basis as has been achieved for postoperative pain management.<sup>149</sup> Inadequately controlled pain is among the major factors contributing to delayed discharge and unanticipated hospital admissions after ambulatory surgery. Despite increased attention to minimizing pain and preventing PONV, these remain significant impediments to a fast-track recovery after ambulatory surgery.<sup>171,172</sup>

Future advances in fast-track surgery will require inter-disciplinary collaborations involving anesthetic, surgery and nursing care.<sup>173</sup> However, anesthesiologists are the ones who make the decisions regarding premedication, fluid management, anesthetic and adjuvant drugs, treatment of side effects, and pain management in the early postoperative period. Interventions to modify surgical stress responses are also performed by anesthesiologists and include perioperative use of beta-blockers, glucocorticoid steroids, administration of fluids, as well as control of stress-induced hyperglycemia by administering insulin.<sup>28,49,173</sup> The effective control of stress responses will likely prove to be advantageous with respect to improving patient outcome. Furthermore, an expansion of the anesthesiologists' interventions beyond the operating and recovery rooms may also be necessary in the future.

Perioperative anesthetic care should be considered as a multidisciplinary strategy to improve the management and outcome of patients undergoing surgery rather than a sub-speciality limited to one medical profession.<sup>174</sup> As a member of the multidisciplinary team, the decisions of the anesthesiologist have a direct impact on the ability to achieve a fast track recovery after ambulatory surgery. It has recently been reported that an anaesthesiologist led management team improved OR efficiency (resulting in a 48% reduction in "gap time" between cases in the same OR) when defined scheduling policies were supported by surgeons, nurses and hospital administrators.<sup>175</sup> In addition,

the implementation of a multidisciplinary approach to minimizing common postoperative side effects can lead to a reduced recovery room and hospital stay, as well as better pain control and patient satisfaction after surgery.<sup>176,177</sup>

In summary, anesthesiologists directly contribute to the fast-track process through the choice of appropriate anesthetic techniques for a given ambulatory surgical procedure. By encouraging the optimal use of multimodal analgesia, as well as in implementing novel techniques which can improve pain control and minimize side effects (e.g., PONV, ileus) after discharge, patients will be able to more rapidly resume their activities of daily living after ambulatory surgery.<sup>2,67,135,164</sup> The time is right for anesthesiologists to take a more active role as perioperative physicians in facilitating the recovery process after ambulatory surgery.

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# Anemia, Blood Transfusion, and Blood Conservation: Where Are We Now?

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The ability to transfuse blood is a critical factor in our ability to care for surgical and critically ill patients. This syllabus will review the risks and benefits of blood transfusion, available alternatives, and blood conservation strategies.

## RED BLOOD CELL TRANSFUSION

Approximately 15 million units of blood are collected annually in the United States; 14 million units are transfused, and the remainder expire and must be discarded. Surgical patients account for two-thirds of blood transfusions. To avoid critical blood shortages, institutional transfusion guidelines have become more restrictive. Recent studies have demonstrated that hemoglobin transfusion triggers are frequently in the range of 8 g/dL.

Red blood cell transfusion has two physiologic effects: increased intravascular volume and increased oxygen carrying capacity. Since blood is an expensive resource with significant risks, it should not be used simply as a volume expander. Normal subjects are able to tolerate significant decreases in hematocrit. The major goal of blood transfusion is to increase oxygen delivery to the tissues. Oxygen delivery is the product of oxygen content and flow (cardiac output). The viscosity of blood rises exponentially as the hematocrit increases over 30%. Theoretical calculations and animal studies demonstrate that oxygen delivery and tissue oxygen tensions are higher at a hematocrit of 30% than at 40% and do not decrease below normal values until hematocrit is below 20%. Anemia increases cardiac output by increasing stroke volume without affecting heart rate. The critical oxygen delivery required to prevent anaerobic metabolism is 8-10 ml/kg/min, which corresponds to a hemoglobin of 4 g/dL (hematocrit of 12%). Volunteers and healthy patients tolerate acute hemodilution to 5 g/dL with no major adverse effects (Weiskopf). In Jehovah's Witnesses who underwent surgery and refused transfusion, no deaths occurred at hemoglobin levels above 7 g/dL. Lower hematocrit values on cardiopulmonary bypass increase the risk of renal failure, stroke and impaired psychomotor development (Karkouti; Jonas). Habib demonstrated that both anemia during cardiopulmonary bypass (hematocrit below 24%) and red blood cell transfusions were associated with increased renal dysfunction in patients undergoing coronary revascularization.

The ability to tolerate decreased hemoglobin may be compromised in many patients. The required increase in stroke volume is dependent

upon maintenance of intravascular volume, so hypovolemia (a common occurrence in the setting of acute blood loss) results in inadequate oxygen delivery and tissue ischemia. Second, anemia may limit the ability to increase oxygen consumption when needed. Rivers et al. demonstrated decreased mortality among patients with sepsis using an early goal-directed therapy strategy that included blood transfusion when central venous oxygen saturation was below 70%. Third, unlike most tissues, the oxygen extraction ratio for the myocardium is already 50% so that decreased oxygen delivery results in ischemia rather than in an increase in extraction ratio. Thus, adequate coronary perfusion during anemia requires coronary vasodilation. In patients with coronary disease, perioperative ischemia increases as the hematocrit decreases below 28%. In a retrospective study of Medicare patients with acute myocardial infarction, Wu et al. demonstrated that mortality decreased when patients whose initial hematocrit was below 33% received blood transfusion. In their analysis of the subgroup of ICU patients with ischemic heart disease, Hébert et al. (2001) demonstrated a trend towards increased mortality with a hemoglobin transfusion trigger of 7 compared to 10 g/dL. However, in patients with acute coronary syndrome, Rao et al. (2004) suggested increased mortality with transfusion. Cardiac surgery studies have consistently demonstrated adverse outcomes in patients receiving transfusions (Gerber).

## RISKS OF BLOOD TRANSFUSION

In the past, the risks of blood transfusion emphasized the transmission of infectious diseases, particularly hepatitis B (HBV) and C (HCV) and HIV. These risks have dramatically decreased with sensitive serologic testing, nucleic acid testing, use of volunteer donors, and allowing self-exclusion of donors. The risk of viral transmission is now estimated at 1/7,800,000 for HIV, 1/1,935,000 for HCV, and 1/220,000 for HBV. Transfusion of blood from a patient seropositive for cytomegalovirus (CMV) to an immunosuppressed patient seronegative for CMV may result in acute CMV infection. Additional infectious risks include malaria, syphilis, trypanosomiasis, Yersinia, West Nile virus, human herpesvirus-8 and possibly Creutzfeldt-Jacob disease.

Although the risks of viral transmission are extraordinarily low, there are other significant risks, including a 1/100 risk of minor allergic reaction, 1/500,000 risk of anaphylactic reaction, and 1/500,000 risk of fatal hemolytic reaction. This last

complication results from administering the wrong unit to the wrong patient. Repeated transfusion may result in the development of antibodies which make cross-matching more difficult and increase the risk of minor transfusion reactions. Graft-versus-host disease has been described in which transfused donor lymphocytes survive and attack the recipient's tissues. TRALI (transfusion-related acute lung injury) is now the leading cause of death related to blood transfusion (Marik, 2008). Although the reported incidence is 1/5,000, the majority of cases are not reported. The classic description of TRALI involves acute onset and rapid resolution of non-cardiogenic pulmonary edema, normally due to antileukocyte antibodies in the donor plasma. Classic TRALI occurs with transfusion of red blood cells, fresh frozen plasma, and platelets. Delayed TRALI has a similar presentation to acute respiratory distress syndrome, is common in critically ill patients, and may be related to lipid mediators or cytokines in the donor blood. Chaiwat recently reported that in trauma patients each unit of packed red blood cells transfused during the first 24 hours increased the risk of ARDS by 6% and hospital mortality by 5%.

Recent studies have emphasized the effect of allogeneic transfusions in increasing bacterial infection rates and producing long-term immunosuppression. The concept of transfusion-induced immunomodulation was originally demonstrated in renal transplant patients with improved graft survival in recipients who had received multiple blood transfusions from unrelated donors. The mechanisms by which blood transfusions produce long-term immunosuppression likely involve exposure to allogeneic cells (lymphocytes, red blood cells) and proteins. Blood transfusion does decrease natural killer (NK) cell cytotoxicity and the helper to suppressor T-cell ratio.

Animal studies suggest that transfusion-induced immunosuppression enhances tumor growth. Most clinical studies demonstrate increased recurrence rate and shorter survival in patients transfused during tumor surgery. However, transfused patients are usually sicker or have more extensive tumor involvement than non-transfused patients, so conclusions remain controversial. Studies have demonstrated a higher tumor recurrence rate in patients receiving allogeneic blood compared to patients receiving only autologous blood.

Studies which have attempted to control for the effects of factors such as shock, hemorrhage, and surgical procedure consistently demonstrate an effect of allogeneic transfusion on perioperative infection rates. In a meta-analysis of 20 studies, Hill et al. demonstrated an odds ratio of 3.45 for postoperative bacterial infection. Taylor et al. reported that transfused ICU patients sustain rates of nosocomial infection that are nearly triple that of non-transfused patients. For each unit of PRBCs administered, the odds of developing nosocomial

infection increased by a factor of 1.5. The role of leukoreduction in decreasing perioperative infection or other transfusion-related complications remains controversial (Vamvakas; Watkins). A before-and-after analysis (Hébert, 2003) of universal prestorage leukoreduction in Canada suggested a small decrease in mortality in ICU patients.

### HEMOGLOBIN TRANSFUSION TRIGGER

Hébert et al.(1999) examined the issue of transfusion triggers in the ICU. Patients were randomized if they developed a hemoglobin below 9 g/dL within 72 hours of admission. In the liberal transfusion group, hemoglobin was maintained above 10 g/dL, and in the restrictive transfusion group hemoglobin was maintained above 7 g/dL. The restrictive policy decreased transfusion requirements by 54%, from 5.6 to 2.6 units per patient, and avoided blood transfusion in 33% of patients. There were strong trends towards decreased 30 day, hospital and ICU mortality, and there were significant decreases in 30 day mortality in patients with APACHE II scores 20 and in patients under 55 years of age. Mortality was not affected by transfusion strategy in patients with cardiovascular disease, but there was a trend towards increased mortality with the restrictive strategy in patients with severe ischemic heart disease. These data suggest that for the majority of ICU patients a hemoglobin transfusion trigger of 7 g/dL can decrease the frequency of blood transfusion while not increasing and possibly even decreasing mortality. A systematic review by Carson et al. of six randomized trials involving 1780 patients similarly demonstrated decreased transfusion requirements and a strong trend towards decreased mortality with lower transfusion triggers. In a systematic review of 42 observational trials, Marik and Corwin noted that 42 of the studies demonstrated that the risks exceeded the benefits.

### AGE OF BLOOD.

Blood that has been collected and stored has a limited shelf life. Parameters that change during storage include increased RBC membrane fragility (decreased deformability), decreased 2,3-DPG levels (impairing O<sub>2</sub> delivery), decreased pH, decreased RBC viability, and increased inflammatory cytokines. In a study of patients admitted to an ICU with sepsis, Purdy et al. described increased mortality related to the administration of older blood. Koch recently reported an increased incidence in long-term complications among cardiac surgery patients receiving blood stored for more than 14 days compared to blood stored for 14 or less days. Marik and Sibbald demonstrated that splanchnic perfusion (assessed by gastric tonometry) routinely decreased when patients were transfused with RBCs stored for more than 15 days. The authors postulated that the poorly deformable RBCs present in older stored blood produced microcirculatory obstruction. A more

recent study using blood which was leukoreduced at the time of donation did not demonstrate this adverse effect (Walsh). Two ongoing trials should provide a definitive answer to the issue of age of blood. The Red Cell Storage Duration and Outcomes in Cardiac Surgery trial is randomizing patients undergoing cardiac surgery to blood stored for less than 14 days versus more than 20 days. The Age of Blood Evaluation (ABLE) trial is randomizing ICU patients to blood stored for less than 8 days or to control leukoreduced blood.

### **ANEMIA IN THE CRITICALLY ILL**

The CRIT study in the United States (Corwin, 2004) and the ABC study in Western Europe (Vincent, 2002) examined current transfusion practices in the ICU. In the CRIT study, ICU patients had an initial hemoglobin of  $11.4 \pm 2.4$  g/dL, the anemia progressed throughout the ICU stay, 44% of patients received a blood transfusion while in the ICU, transfused patients received an average of  $4.6 \pm 4.9$  units, and the average pre-transfusion hemoglobin was  $8.6 \pm 1.7$  g/dL. RBC units were on average 21 days old. Patients who were in the ICU for longer periods of time were more likely to be transfused. Patients who received blood transfusions had longer time on mechanical ventilation, ICU stay, and hospital stay. Mortality was higher in transfused patients, even after matching for the propensity for being transfused. The results in the ABC study were almost identical to the CRIT study. The average initial hemoglobin was  $11.3 \pm 2.3$  g/dL, 37% of patients received a blood transfusion while in the ICU, the average pre-transfusion hemoglobin was  $8.4 \pm 1.3$  g/dL, and transfusion was associated with increased mortality (18.5% vs. 10.1%), both on logistic regression analysis (odds ratio of 1.37) and after propensity score matching. In contrast to the CRIT and ABC trials, the recent SOAP trial in Western Europe suggested decreased mortality related to blood transfusion, possibly reflecting the use of leukoreduced blood (Vincent, 2008).

### **ERYTHROPOIETIN**

Erythropoietin administration decreases blood transfusions when administered preoperatively in surgical patients. The etiology of anemia in critically ill patients involves a blunted erythropoietin response, similar to that seen in anemia of chronic disease. The utility of erythropoietin therapy to decrease transfusion requirements in critically ill patients was studied in three trials by Corwin et al. In the first trial, patients were randomized to receive placebo or human recombinant erythropoietin at a dose of 300 units/kg for 5 days followed by every other day dosing. Erythropoietin decreased transfusion from 3.8 to 2.1 units per patient over the 42 day study. In the second study, the erythropoietin dose was changed to 40,000 units subcutaneously weekly for up to four doses. Erythropoietin therapy decreased transfusion from 3.0 to 2.4 units per patient over the 28 day study.

However, our third erythropoietin trial (Corwin, 2007) did not demonstrate any decrease in transfusion requirements (4.5 vs. 4.3 units). There was a trend towards decreased mortality in the patients receiving erythropoietin, especially in the trauma patients. Erythropoietin increased the incidence of thrombotic events in patients not receiving pharmacological prophylaxis for deep venous thrombosis.

### **BLOOD MANAGEMENT TECHNIQUES.**

Techniques to decrease allogeneic blood use in surgical patients include acceptance of a lower hemoglobin, perioperative erythropoietin, autologous blood transfusion (preoperative autologous donation, acute normovolemic hemodilution, intraoperative or postoperative blood salvage), and the use of blood substitutes. Attempts to decrease blood transfusion are most successful when a combination of strategies is used. For patients requiring intensive care, blood loss from phlebotomy for diagnostic testing accounts for a significant proportion of blood transfusions. Phlebotomy volume was 41 ml/day in the ABC trial. Phlebotomy losses can be decreased by using a closed arterial sampling system, point-of-care diagnostic testing, pediatric tubes, and limiting the frequency of phlebotomy. This approach can decrease transfusion requirements by over 50%.

### **PREOPERATIVE AUTOLOGOUS DONATION (PAD)**

PAD involves the donation of one or more units of blood prior to surgery. Blood is usually donated at weekly intervals, with the last donation being at least 4 days prior to surgery. The donated blood is not separated into components so that there are few viable platelets and coagulation factors at the time of transfusion. Many studies have shown limited efficacy with PAD. Patients who donate blood as part of PAD do not have adequate time for red blood cell production to raise hemoglobin back to the pre-donation level. Thus, they require autologous transfusion at less blood loss than if they had not participated in PAD. In addition, the autologous blood which is transfused has been stored for several weeks and will therefore function less well. The costs of PAD involve an expensive collection process, with the majority of units being unused and either wasted or inappropriately administered. Estimates are that the cost of PAD is between \$235,000 and over \$23 million per quality-adjusted year of life saved. The efficacy of PAD may be enhanced by the use of erythropoietin which both allows additional units to be obtained and helps restore hemoglobin to baseline values before surgery.

### **ACUTE NORMOVOLEMIC HEMODILUTION (ANH)**

ANH is a blood conservation measure which involves intraoperative removal and storage of whole blood prior to surgical blood loss. ANH is frequently divided into limited (target hemoglobin 9-10) or extreme (target hemoglobin 7). In general, the blood

removed for ANH is replaced by crystalloid or colloid and is stored at room temperature for up to 6 hours. In contrast to PAD blood, ANH blood has functional platelets and coagulation factors with normal 2,3-DPG levels in the red blood cells. ANH blood must be collected under strict sterile conditions and can develop bacterial contamination.

The safety and efficacy of ANH are controversial. A simplified model assumes that during ANH the blood is removed at a hematocrit which is an average of the pre-ANH and the post-ANH hematocrit. Thus, if  $H_{init}$  is the initial hematocrit and  $H_{fin}$  is the final or desired hematocrit, then the volume of blood to be removed ( $V$ ) is given by the equation  $V = EBV \times (H_{init} - H_{fin}) / H_{ave}$  where  $EBV$  is the estimated blood volume and  $H_{ave}$  is the average of  $H_{init}$  and  $H_{fin}$ . For example, for a 70 kg man with an initial hematocrit of 40% and a desired final hematocrit of 30%, 1400 ml blood (almost 3 units) can be removed for ANH. The overall savings from ANH are small. In the absence of ANH, the patient would have required transfusion after 1400 ml blood loss (assuming one desires to maintain a hematocrit of 30%). With ANH, the patient will require reinfusion of the ANH blood as soon as any blood loss occurs. The only savings which occur are that the 1400 ml ANH blood has a hematocrit of 35% so that it can replace 1633 ml of subsequent blood loss at a hematocrit of 30%. Thus, removal of 3 units of ANH blood would be required to prevent the transfusion of less than half a unit of allogeneic blood. A recent study by Jarnagin et al. randomized 130 patients undergoing major hepatic resection to ANH or no ANH. Despite a median removal of 2,250 ml of blood for ANH, the average blood savings was only 0.29 units and did not reach statistical significance. A meta-analysis of studies of ANH demonstrated little benefit in studies which used well-defined transfusion protocols.

### **INTRAOPERATIVE BLOOD SALVAGE (IOBS)**

IOBS involves scavenging and re-transfusing lost blood. Scavenged blood has significant hemolysis, activated coagulation products (such as fibrin degradation products and tissue plasminogen activator) and inflammatory mediators, and no viable platelets or coagulation factors. Administration of scavenged blood usually involves a processing system which washes the blood with saline until the non-cell fraction is clear. IOBS is effective in decreasing allogeneic blood transfusion and is cost-effective compared to blood transfusion in cases requiring at least two units of blood transfusion. The red blood cells have normal 2,3-DPG levels and survival. However, recovery of the red blood cells is frequently only 50% due to hemolysis during suction, so results are therefore limited (Takagi).

### **BLOOD SUBSTITUTES**

Blood substitutes are often termed oxygen carriers because they do not replace the coagulation and

other functions of blood. The ideal blood substitute should deliver oxygen to the tissues, expand plasma volume, not require compatibility testing, have a long shelf-life at room temperature, have a long intravascular duration, be devoid of immunologic effects, and be inexpensive. Unfortunately, no such blood substitute is yet available. The two major types of blood substitutes are the stroma-free hemoglobin solutions and the perfluorocarbons.

### **STROMA-FREE HEMOGLOBIN SOLUTIONS**

With the exception of the use of recombinant hemoglobin, hemoglobin solutions are made by lysing red blood cells (human or animal), removing the red blood cell membranes and intracellular contents, and treating the resulting hemoglobin solution to remove and inactivate infectious agents. Because hemoglobin is a relatively stable compound, it can be sterilized (similar to albumin). Since intravascular hemolysis during major transfusion reactions results in shock, DIC, and renal failure, it was initially assumed that hemoglobin solutions would be toxic. However, the adverse effects of intravascular hemolysis are due to red blood cell stroma (membrane fragments) rather than the hemoglobin. Initial attempts to develop clinically useful hemoglobin solutions were limited by manufacturing problems, particularly stromal and endotoxin contamination. Although these problems have been solved, major problems continue to exist.

### **LIMITATIONS OF STROMA-FREE HEMOGLOBIN SOLUTIONS AS BLOOD SUBSTITUTES**

In the absence of modification, the hemoglobin tetramer rapidly dissociates into dimers (one and one subunit) and monomers which are rapidly filtered by the kidney and can produce renal failure. This problem has been addressed by covalently linking the dimers into tetramers and linking the tetramers into polymers. However, the half-life of most solutions remains under a day so that repeated doses may be necessary. Hemoglobin solutions contain large amounts of hemoglobin. Although hemoglobin is a normal protein, the source (bovine) or the preparation (cross-linking) results in a protein which may result in allergic-type reactions. The ferrous iron in hemoglobin rapidly oxidizes to form methemoglobin. Inside the red blood cell, methemoglobin reductase prevents the accumulation of methemoglobin. However, in stroma-free hemoglobin solutions, progressive oxidation can occur. Attempts have been made to modify the hemoglobin molecule to prevent oxidation. Hemoglobin can degrade to produce heme and free iron, which may result in free radical production. The red color of hemoglobin in plasma may cause problems with laboratory tests, particularly liver enzymes, bilirubin, and amylase.

A major problem with hemoglobin solutions has been inactivation of endogenous nitric oxide by hemoglobin. Nitric oxide is a potent endogenous vasodilator. Nitric oxide avidly binds to the heme iron

in hemoglobin and is thereby inactivated. Inhibition of endogenous nitric oxide results in vasoconstriction. Administration of hemoglobin solutions can produce systemic and pulmonary hypertension, coronary vasoconstriction, and decreased organ blood flow. Hemoglobin solutions may result in inhibition of nitric-oxide mediated gastrointestinal effects with nausea, vomiting, ileus, dysphagia, and pancreatitis. The nitric-oxide binding effects of hemoglobin solutions are magnified by the extravascular penetration of the small hemoglobin molecule. Companies have investigated the effects of altering the cross-linking site so as to interfere with nitric oxide binding and the use of polymerization to prevent penetration of the hemoglobin into the tissues.

Hemoglobin solutions which have come close to clinical use include diaspirin cross-linked hemoglobin (DCLHb), HBOC-201, Hemolink, and Polyheme. DCLHb, a diaspirin cross-linked tetramer, was produced from expired human blood. Although several studies demonstrated decreased blood transfusion with the use of DCLHb, other studies demonstrated worsened neurologic outcome in patients with acute ischemic stroke (Saxena) and increased mortality in patients with traumatic hemorrhagic shock (Sloan). HBOC-201 (Hemopure) is a glutaraldehyde polymerized bovine hemoglobin. It is now marketed for veterinarian use as Oxyglobin. It has a dose-dependent half-life of 8–23 hours. Polyheme is made by polymerization of hemoglobin extracted from expired human donor blood. In a randomized study of 714 trauma patients, mortality with Polyheme was 13% compared to control mortality of 10%. In a recent meta-analysis of 16 trials, Natanson et al. demonstrated increased mortality and increased rate of myocardial infarction with hemoglobin solutions, and an editorial recommended that these products are not safe for testing in elective surgical patients (Fergusson).

## PERFLUOROCARBONS AS BLOOD SUBSTITUTES

Perfluorocarbons are chemically inert hydrocarbons where fluorine atoms have been substituted for the hydrogen atoms. They have a high solubility for oxygen and carbon dioxide. In 1966, Clark and Gollan demonstrated that rodents could survive immersed in oxygenated perfluorocarbon solutions. In contrast to red blood cells and hemoglobin solutions where oxygen binds to hemoglobin, transport of oxygen in perfluorocarbons involves oxygen dissolved according to Henry's law. Thus, oxygen content linearly increases with arterial oxygen tension, and almost all the dissolved oxygen is delivered to the tissues (since mixed venous oxygen tension is much lower than arterial tension). Perfluorocarbons have limitations as blood substitutes, including a short half-life, dose-related thrombocytopenia, and a flu-like syndrome. In 2001, Alliance suspended enrollment in a phase 3 cardiac surgery trial of perflubron due to an increased incidence of stroke in the treatment arm.

## SUMMARY

Studies of the risks of blood transfusion have highlighted the need to avoid transfusion whenever possible. Accepting a lower hemoglobin transfusion trigger and using a multifaceted approach has made "bloodless surgery" a realistic possibility for the majority of patients (Shander).

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# Perioperative Care for the Patient with Renal or Hepatic Disease

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Patients with renal or hepatic disease present a challenge to anesthesiologists because these conditions imply abnormal handling of anesthetic agents, as well as multiorgan system dysfunction, general debility and specific problems associated with replacement therapy and transplantation. Moreover, in situations of hepatic or renal insufficiency, anesthesia and surgery may themselves precipitate acute failure.<sup>1-11</sup>

## **SYSTEMIC MANIFESTATIONS**

### **CHRONIC RENAL FAILURE**

#### **FLUID AND ELECTROLYTE BALANCE:**

##### **EDEMA, HYPERKALEMIA.**

- Metabolic acidosis, hyperkalemia and congestive heart failure are well controlled by dialysis. Anuric patients: only fluid loss is insensible, 500 mL/ day. Polyuric chronic renal failure (CRF): urine output appears normal, but concentrating ability is absent and fluid loss quickly results in hypovolemia.
- Most patients have a moderate compensated anion gap acidosis but with a depleted buffer base ( $\text{HCO}_3^-$  15–18 mEq/L). Shock, diarrhea, or hypercatabolism quickly result in profound metabolic acidosis.
- Acute hyperkalemia: catabolic stress, acidosis, potassium-sparing diuretics, red cell transfusion, or potassium replacement. A pH decrease of 0.1 can increase potassium by 0.5 mEq/L.
- Hypermagnesemia (muscle weakness, increased susceptibility to muscle relaxants), hypomagnesemia (arrhythmias), hyperphosphatemia (renal osteodystrophy) and hypophosphatemia (increased susceptibility to muscle relaxants, difficult ventilatory weaning, central nervous system dysfunction).

#### **CARDIOPULMONARY PROBLEMS:**

##### **HYPERTENSION, ATHEROSCLEROSIS.**

- Pericarditis, hemorrhagic pericardial effusion: rare, usually well controlled by regular dialysis.
- Systemic hypertension is prevalent and left ventricular hypertrophy and even asymmetric hypertrophy are not uncommon. Associated hyperlipidemia predisposes to accelerated atherosclerosis.
- Anemia and arteriovenous shunts cause a hyperdynamic circulation with fixed low systemic vascular resistance, and impaired circulatory

reserve with poor tolerance of myocardial ischemia or sepsis.

- The risk of postoperative pulmonary edema, atelectasis, and pneumonia is increased, and abdominal distention from peritoneal dialysis further compromises ventilation.

#### **HEMATOLOGIC CHANGES: ANEMIA, PLATELET DYSFUNCTION.**

- Normochromic, normocytic anemia (Hct 25–28%): decreased erythropoietin, red cell survival and chronic blood loss (gastrointestinal [GI] tract, labs). Compensation requires increased cardiac output and 2,3-DPG (impaired by hypophosphatemia).
- Uremic coagulopathy (blood urea nitrogen .60–80 mg/dL): defective endothelial release of von Willebrand's factor and factor VIII [VWF-VIII]. Platelet function is abnormal, and the Ivy bleeding time prolonged .15 min (normal: 3–8 min).

#### **NUTRITIONAL-METABOLIC PROBLEMS:**

##### **MALNUTRITION, INFECTION.**

- Hyperglycemia, hypertriglyceridemia and protein malnutrition (kwashiorkor, hypoalbuminemic malnutrition) are common.
- Hypoalbuminemia: dietary protein restriction, albuminuria and/or losses via continuous peritoneal dialysis (10–40 g/day protein). Low colloid oncotic pressure promotes interstitial and pulmonary edema; functional residual capacity and ventilatory reserve are decreased.
- Resistance to infection is decreased, especially nosocomial and opportunistic infections at shunt or peritoneal catheter sites. Wound dehiscence, fistulas, and bedsores occur as a consequence of depleted lean body mass and the catabolic effects of uremia.

#### **GASTROINTESTINAL PROBLEMS:**

##### **UREMIC ENTEROPATHY.**

- Anorexia, hiccups, nausea and vomiting (hallmarks of acute uremia) and delayed gastric emptying increase the risk of regurgitation and aspiration.
- Mucosal inflammation, ulceration, and bleeding may occur in any portion of the GI tract. Peptic ulcer disease occurs in up to 25% of patients with CRF despite regular dialysis.
- High incidence of hepatitis B and C (anicteric, carrier state) in patients on chronic hemodialysis.

**NEUROPSYCHIATRIC COMPLICATIONS:  
ENCEPHALOPATHY AND NEUROPATHY.**

- Central nervous system manifestations range from subtle personality changes to drowsiness, asterixis, myoclonus, and seizures. Major surgery, GI bleeding or infection may precipitate acute encephalopathy.
- Distal sensorimotor neuropathy is an important indication for dialysis.
- Autonomic neuropathy can predispose to delayed gastric emptying, silent myocardial ischemia, orthostatic hypotension, and impaired circulatory response to anesthesia.

**CHRONIC LIVER DISEASE****FLUID AND ELECTROLYTE BALANCE:  
REFRACTORY EDEMA AND ASCITES.**

- Hypoalbuminemia + portal hypertension = ascites + intravascular hypovolemia.
- Secondary hyperaldosteronism (salt and water retention, potassium loss) results in hypokalemic metabolic alkalosis, generalized edema (anasarca), and progressive ascites.
- Ascites causes decreased functional residual capacity, atelectasis, and hypoxemia. Venous return and renal blood flow are decreased. Spontaneous bacterial peritonitis occurs in approximately 10% of patients.
- Edema and ascites are resistant to loop diuretics, which exacerbate intravascular hypovolemia and hypokalemia and worsen hepatic perfusion. The aldosterone antagonist spironolactone is effective but its onset/offset is slow (2–3 d) and in acute renal insufficiency it can provoke acute hyperkalemia.

**GASTROINTESTINAL PROBLEMS:  
PORTAL HYPERTENSION, VARICES,  
AND JAUNDICE**

- All patients have potential for active viral hepatitis (A, C, D).
- Anorexia, hiccups, nausea and vomiting; delayed gastric emptying: increased risk of regurgitation and aspiration. Exacerbated by severe ascites (abdominal pressure).
- Major risk of hemorrhage from esophageal and/or gastric varices (portal hypertension).
- Increased risk of peptic ulcer disease—differentiate bleeding from varices.

**RENAL PROBLEMS: HEPATORENAL  
SYNDROME.**

- Hepatorenal syndrome: obstructive jaundice (total bilirubin .8 mg/dL) or hepatic failure result in portal endotoxemia, intense renal vasoconstriction (vasomotor nephropathy).
- Prerenal syndrome: oliguria with low urine sodium (10 mEq/L), progressive azotemia.

- Blood urea nitrogen low even with GI bleeding or acute renal failure: failure of arginine cycle (converts urea to  $\text{NH}_3$ ).

**CARDIOPULMONARY PROBLEMS:  
HYPERDYNAMIC CIRCULATION, HYPOXEMIA.**

- Hyperdynamic circulation with fixed low systemic vascular resistance. Arteriovenous (AV) shunts in skin (nevi, erythema), GI tract, lung: impaired circulatory reserve with hypovolemia, sepsis, or myocardial ischemia.
- Hepatopulmonary syndrome: hypoxemia (AV shunts), atelectasis, pulmonary hypertension.
- Increased risk of postoperative pulmonary edema, atelectasis, pneumonia.
- Alcoholic cardiomyopathy, arrhythmias (6 thiamine deficiency).

**HEMATOLOGIC CHANGES: FACTOR VII  
DEFICIENCY, THROMBOCYTOPENIA.**

- Factor VII deficiency—prolonged PT (impaired synthesis, vitamin K absorption).
- Thrombocytopenia: hypersplenism in portal hypertension, bleeding, disseminated intravascular coagulation. Factor V deficiency (acute marker after orthotopic liver transplantation)
- Dysfibrinogenemia (fibrinogen level may be normal).
- Macrocytic anemia (alcohol-induced bone marrow suppression).

**NUTRITIONAL-METABOLIC PROBLEMS:  
HYPOGLYCEMIA, MALNUTRITION,  
INFECTION.**

- Hypoglycemia in acute hepatic failure or end-stage liver disease (failure to synthesize glycogen).
- Protein-malnutrition, catabolic effects of hepatic failure: depleted lean body mass, hypoalbuminemia, low colloid oncotic pressure.
- Nosocomial and opportunistic infections, wound dehiscence, fistulas and bedsores.

**NEUROPSYCHIATRIC COMPLICATIONS:  
ENCEPHALOPATHY AND NEUROPATHY.**

- Hepatic encephalopathy: Grade 1: confabulation, constructional apraxia; Grade 2: drowsiness, asterixis, confusion; Grade 3: stupor; Grade 4: coma.
- Fulminant hepatic failure: coma with acute cerebral edema.
- Precipitating factors: hypovolemia (excessive diuresis), alkalosis, GI bleeding, surgery, infection.
- Alcohol-induced encephalopathy (thiamine deficiency): Wernicke's encephalopathy (oculomotor palsy, cerebellar ataxia), Korsakoff's psychosis (amnesia, confabulation).

## **PHARMACOLOGIC EFFECTS OF RENAL AND HEPATIC FAILURE**

Most IV anesthetic agents are lipid-soluble and nonionized and undergo hepatic biotransformation to active or inactive water-soluble metabolites, which are then excreted in the bile or the urine. Lipid insoluble, highly ionized drugs (mostly muscle relaxants) are directly excreted by the kidney. Renal and hepatic disease alter anesthetic and parenteral drug clearance by several mechanisms: decreased blood flow (drug delivery), increased unbound free fraction of highly protein-bound drugs (hypoalbuminemia or acidosis), and decreased enzymes and transport processes that irretrievably remove the drug from the blood.

The duration of action of many drugs administered by bolus or short-lived infusion is dependent on redistribution, not elimination. Their loading doses may not require to be decreased unless unbound free fraction is increased or there is known to be a greater pharmacodynamic effect. However, maintenance doses can accumulate and should be reduced accordingly.

Both liver and renal disease alter drug pharmacodynamics even if pharmacokinetics are not changed. Patients are often debilitated, with depleted lean body mass. Respiratory depression is much more likely with opioid or volatile anesthetic agents: consider reducing all drug dosages by 25%–50%.

### **DRUGS INDEPENDENT OF LIVER AND RENAL FUNCTION FOR ELIMINATION**

Enzymatic or spontaneous breakdown in the blood. Accumulation is unlikely, but altered pharmacodynamic responses should be anticipated. (e.g., succinylcholine, remifentanyl, atracurium and cisatracurium, esmolol.)

### **DRUGS WITH INCREASED UNBOUND FRACTION IN HYPOALBUMINEMIA**

Increased free or active fraction. Doses should be decreased 20%–50%, depending on the degree of hypoalbuminemia. (e.g., thiopental, methohexital, diazepam.)

### **DRUGS PREDOMINANTLY DEPENDENT ON HEPATIC BIOTRANSFORMATION**

Avoid or decrease dosage in hepatic failure. (e.g., all benzodiazepines, all opioids, nondepolarizing muscle relaxants, except atracurium, cisatracurium.)

### **DRUGS PREDOMINANTLY DEPENDENT ON RENAL ELIMINATION**

Avoid or decrease maintenance dose in CRF (loading doses remain unaltered). (e.g., gallamine, metubine, digoxin, penicillins, cephalosporins, aminoglycosides, vancomycin, cyclosporin A.)

## **DRUGS PARTIALLY DEPENDENT ON RENAL ELIMINATION**

Decrease maintenance doses by 30%–50% or titrate carefully to effect. (e.g., anticholinergic, cholinergic agents, pancuronium, pipecuronium, vecuronium, rocuronium, doxacurium, milrinone, amrinone, phenobarbital, aprotinin, aminocaproic acid, tranexamic acid.)

### **DRUGS WITH ACTIVE METABOLITES THAT ARE RENALLY ELIMINATED**

Drugs that may exert a prolonged effect in CRF despite rapid hepatic biotransformation of the parent compound. They should be avoided, or have their maintenance doses decreased by 30%–50% or titrated carefully to effect. (e.g., morphine [m-3-glucuronide, m-6-glucuronide, normorphine], meperidine [normeperidine], diazepam [oxazepam], midazolam [l-hydroxy midazolam], pancuronium [3-hydroxypancuronium], vecuronium [desacetylvecuronium], sevoflurane, enflurane [fluoride], sodium nitroprusside [thiocyanate].)

## **PERIOPERATIVE MANAGEMENT**

### **CHRONIC RENAL FAILURE PREOPERATIVE EVALUATION AND PREPARATION.**

- In evaluating the patient, note the etiology of CRF (i.e., 6 systemic disease), urine output, type of dialysis, and most recent treatment. Look for physical signs of systemic complications (anemia, left ventricular hypertrophy, congestive heart failure, neuropathy, sepsis, malnutrition) and examine shunt sites and/or CAPD catheter site for infection.
- Relevant lab studies include Hct, complete blood count, electrolytes (total CO<sub>2</sub> if arterial blood gases impracticable), blood urea nitrogen, creatinine, Ivy bleeding time, electrocardiogram, and chest radiograph.
- Human recombinant erythropoietin: normal Hct; —risk of hypertension, thrombosis.

### **PREOPERATIVE PREPARATION.**

- Hemodialysis: schedule day before surgery to avoid acute fluid and electrolyte shifts.
- Continuous ambulatory peritoneal dialysis: continue until time of surgery (assess abdominal girth).
- Preoperative blood transfusion is indicated only to treat acute blood loss or for patients with cardiopulmonary disease undergoing major surgery with Hct >28%.
- Transfuse during dialysis to avoid fluid overload and hyperkalemia.
- Platelet dysfunction (bleeding time .15 min despite platelet count >.100 k/mm<sup>3</sup>), should be corrected before major surgery with deamino-8-darginine vasopressin (0.3 mg/kg over 20

min), which stimulates endothelial release of VWF-VIII, or with cryoprecipitate (10 U), which contains VWF-VIII.

- Labile or symptomatic hypertension must be controlled before elective surgery. Patients on longterm clonidine or guanabenz should receive a clonidine transdermal patch to prevent rebound hypertension.

#### OPERATIVE PREPARATION.

- Minimize sedative or opioid premedication, provide aspiration prophylaxis (anticholinergic, H2- blocker, metoclopramide, sodium bicitrate).
- Use universal and aseptic precautions throughout.
- Avoid BP cuffs or arterial catheters on arm with arteriovenous fistula or shunt, and avoid urinary catheter in anuric or oliguric patients.
- Invasive hemodynamic monitoring is indicated if large fluid shifts are anticipated, or with sepsis or cardiopulmonary insufficiency.
- Avoid pressure or stretch on fistula sites, bony prominences, joints. Patients with sensory neuropathy may not complain of positional discomfort. Renal osteodystrophy = fragile bones and joints.
- Use active warming devices (e.g., forced-air convection blanket) to prevent hypothermia.
- Consider intraoperative hemodialysis (CPB).

#### ANESTHESIA.

- Regional anesthesia is not contraindicated if coagulopathy is corrected, but there is increased risk of hypotension (autonomic neuropathy) and infection. When sympathetic block wears off after surgery, sudden increase in systemic vascular resistance could precipitate pulmonary edema.
- For general anesthesia, use aspiration precautions (e.g., head up, rapid sequence, cricoid pressure).
- Preoxygenate and give adequate fluid load (250-1000 mL) before induction.
- Succinylcholine is not contraindicated in CRF if serum potassium is  $<5.0$  mEq/L and the patient has been dialyzed within the last 24 h. Avoid pancuronium and pipecuronium.
- After tracheal intubation, increase minute ventilation to compensate for chronic metabolic acidosis.

- Keep maintenance fluids to a minimum but fully replace fluid losses.
- Nephrotoxicity is a theoretic possibility with enflurane (fluoride) or sevoflurane (Compound A).
- Anticipate labile BP: hypotension (deep anesthesia, fluid losses, positional changes) or hypertension (inadequate anesthesia). Beta-blockers or calcium blockers are helpful.
- Anticipate hyperkalemia (b-blockers), arrhythmias, and potential for digoxin toxicity.

#### POSTOPERATIVE CARE.

- Anesthetic emergence may be delayed, and complicated by vomiting, aspiration, hypertension, persistent neuromuscular blockade, respiratory depression, or pulmonary edema.
- CO<sub>2</sub> retention in chronic metabolic acidosis: acute acidosis, hyperkalemia.
- If in doubt, a short period of postoperative mechanical ventilation allows controlled emergence, avoids reversal agents, and facilitates evaluation of neurologic and ventilatory function before extubation.
- Restrict maintenance fluid, replace sequestration or overt losses. Anticipate and treat hyperkalemia.
- For severe uremia, use hemodialysis. Hemodynamically unstable: consider peritoneal dialysis.
- CVVH/D: Large volume removal with hemodynamic stability, requires heparinization.

#### CHRONIC LIVER DISEASE

##### PREOPERATIVE EVALUATION.

Note the Child-Pugh Classification of Preoperative Risk in Liver Disease (Table 1).

##### PREOPERATIVE PREPARATION.

- Acute viral hepatitis, Child's C: postpone elective surgery (high morbidity and mortality).
- Ascites: discontinue spironolactone 3-4 days preoperatively, cautiously drain tense ascites.
- Correct prolonged PT with parenteral Vitamin K and/or fresh-frozen plasma. Refractory PT = severe liver damage.

Table 1. Child-Pugh Classification of Preoperative Risk in Liver Disease

	A (minimal risk)	B (moderate risk)	C (severe risk)
Serum bilirubin (mg/dL)	<2	2-3	>3
Serum albumin (g/dL)	>3.5	3-3.5	<3
PT (sec > control)	1-4	4-6	>6
CNS (coma grade)	Normal	Confused (1-2)	Coma (3-4)
Ascites	None	Easily controlled	Poorly controlled
Nutrition	Excellent	Good	Poor

PI = prothrombin time; CNS = central nervous system.

- Treat and remove precipitating factors of encephalopathy: protein restriction, lactulose, neomycin.
- Acute GI bleeding: 1) fluid resuscitation, transfusion, correction of coagulopathy; 2) establish diagnosis (varices versus peptic ulcer); 3) options for continued bleeding include endoscopic sclerotherapy, Sengstaken-Blakemore tube (6 tracheal intubation), vasopressin infusion, emergency decompression.
- TIPPS (transjugular intrahepatic portosystemic shunt): relieves ascites, improves renal function. Risk of endotoxemia, pulmonary edema, encephalopathy.

#### OPERATIVE PREPARATION.

- Omit oral premedication except for aspiration prophylaxis. If necessary, give small doses of IV sedation in induction room or operating room under direct observation.
- Use universal precautions and asepsis throughout. All staff should have hepatitis B vaccine.
- Indications for invasive monitoring as for CRF, but it should be remembered that these patients are at very high risk of perioperative acute renal failure (hepatorenal syndrome) and intravascular volume status is difficult to assess because of ascites and anasarca.
- Considerations for positioning and avoidance of hypothermia are as for CRF. Tense ascites adds an additional degree of difficulty. Anesthesia.
- If BP and cardiac output are maintained, regional anesthesia preserves hepatic blood flow. However, coagulopathy and ascites limit its application.
- Drug handling is extremely variable. Alcoholics may require large loading doses, but have delayed elimination and emergence. Decrease doses of all sedative agents in severe liver disease.
- Preoxygenate and fluid load before anesthetic induction. Use aspiration precautions as for CRF.
- Succinylcholine OK, but duration could be prolonged with severe liver dysfunction. Metabolism of atracurium and cisatracurium is independent of liver function.
- All volatile anesthetic agents and hypercarbia decrease hepatic blood flow. All opioids may accumulate. Propofol remains relatively short acting in cirrhosis.
- Anticipate hypoxemia (ascites, shunting), bleeding (coagulopathy), oliguria (vasomotor nephropathy).
- Renal protection (?): dopamine, furosemide infusion, fenoldopam.
- Avoid excessive volume loading (CVP .10 mm Hg); can induce acute hepatic congestion. Fluid restrictive approach during hepatic resection may decrease venous oozing.

#### POSTOPERATIVE CARE.

- Anesthetic emergence may be delayed and complicated by vomiting and aspiration, hypotension, respiratory depression, and acute respiratory failure.
- Extubate trachea when patient is fully awake to reduce risk of aspiration.
- If in doubt, a short period of postoperative mechanical ventilation allows controlled emergence, avoids reversal agents, and facilitates evaluation of neurologic and ventilatory function before extubation.
- Potential postoperative problems include bleeding, oliguria, encephalopathy, acute respiratory failure, sepsis, wound dehiscence, and acute hepatic failure.

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